Regimen Monograph

A - Regimen Name

FOLFIRI Regimen

Folinic Acid (Leucovorin)-Fluorouracil-Irinotecan

FOLFIRI+BEVA Regimen

Folinic Acid (Leucovorin)-Fluorouracil-Irinotecan-Bevacizumab

Disease Site	Gastrointestinal Colorectal Small bowel and appendix
Intent	Palliative
Regimen Category	**Evidence-Informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.
Rationale and Uses	Treatment of metastatic colorectal, small bowel or appendiceal cancer
Supplementary Public Funding	**bevacizumab** New Drug Funding Program (Bevacizumab (Biosimilar) - Metastatic Colorectal, Small Bowel, or Appendiceal Cancer) (NDFP Website)

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B - Drug Regimen

Different bevacizumab products are **not interchangeable**.

irinotecan	180 mg /m²	IV over 90 minutes	Day 1
leucovorin[1]	400 mg /m²	IV over 120 minutes concurrently with irinotecan	Day 1
fluorouracil ***THEN***	400 mg /m²	IV bolus, after leucovorin	Day 1
fluorouracil[2] ***with or without:***	2400 mg /m²	IV continuous infusion over 46 hours only	Start on Day 1
bevacizumab[3, 4]	5 mg /kg	IV over 90 minutes for initial dose	Day 1

Irinotecan and leucovorin may be infused at the same time by using a y-connector, but not in the same bag, then fluorouracil.

[1]Commercially available form is d,l-racemic. Some studies specified the dose of leucovorin as 200mg/m² in the l-isomer form. Since only the l-isomer is active in the racemic form, thus the dose is doubled.

[2] Dose may be escalated to 3000 mg/m² if toxicity ≤ grade 1 during the first two cycles.

[3] If tolerated, next infusion can be given over 60 minutes; can thereafter be given over 30 minutes as maintenance dose. Alternative administration rates have been described by Mahfoud et al and Reidy et al, but these have not been approved by Health Canada.

[4] Sequence of administration: Bevacizumab has been given prior to chemotherapy in several phase III clinical trials.

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C - Cycle Frequency

REPEAT EVERY 14 DAYS

Until evidence of disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Other Supportive Care:

- Irinotecan:
- Unless contraindicated, atropine 0.25-1mg IV/SC may be used for cholinergic adverse effects (early diarrhea)
- Diarrhea (abdominal cramp = diarrhea) may be severe and delayed with irinotecan; use loperamide 4mg at the onset of diarrhea, then 2mg q2h until patient is diarrhea-free for 12 hours
- Patients with ileus, fever or febrile neutropenia should receive antibiotics

- 5FU:
- May advise patients to suck on ice chips during bolus injection of 5FU, to reduce stomatitis

Also refer to CCO Antiemetic Summary

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Patients should be tested for DPD deficiency before starting treatment with fluorouracil. Refer to the DPD Deficiency Guidance for Clinicians for more information.

In patients with unrecognized DPD deficiency, acute, life-threatening toxicity may occur; if grade 2-4 acute toxicity develops, treatment should be stopped immediately and permanent discontinuation considered based on clinical assessment of the toxicities.

Refer to bevacizumab drug monograph for additional details on bevacizumab.

Dosage with toxicity

See general recommendations for hematologic toxicity.

FOLFIRI

Patients should not be re-treated with irinotecan until recovery (to baseline) from GI toxicity (without

loperamide for at least 24 hours) has occurred, platelets ≥ 100 x 10^9/L, and ANC ≥ 1.5 x 10^9/L. All dose adjustments should be based on the worst preceding toxicity.

Patients with ileus, fever or febrile neutropenia should receive antibiotics.

Do not use in patients with ECOG PS of 3 or 4, nor in patients with moderate or severe increases in bilirubin.

Consider a reduction in the starting dose described below for elderly patients (≥ 70 years), patients with prior abdominal or pelvic irradiation, patients with a poor performance status (ECOG of 2), patients with mild increases in bilirubin (including Gilbert's syndrome), patients homozygous for UGT1A1*28 allele or patients with a history of myelosuppression with previous treatment.

Suggested Dose Levels:

Regimen	Drug	Starting dose (mg/m^2)	Dose level -1 (mg/m^2)	Dose Level -2 (mg/m^2)
FOLFIRI	Irinotecan	180	150	120
	Leucovorin infusion	400	No change	No change
	5-FU bolus	400	320	240
	5-FU infusion (start day 1 over 46h*)	2400	2000	1600

* This 5-FU dosing is not approved by Health Canada, but has been used in some phase III trials.

Dosage with Toxicity:

Dose Adjustments for Irinotecan in Combination with Fluorouracil:

Worst Toxicity Grade from Previous Cycle	**At the start of subsequent cycles[1, 2] (FOLFIRI)**
Hematologic	
Grade 1	No change
Grade 2	No change
Grade 3	reduce by 1 dose level
Grade 4 or febrile neutropenia	reduce by 2 dose levels
Diarrhea	
Grade 1: 2-3/day > pre-treatment	No change
Grade 2: 4-6/day > pre-treatment	No change
Grade 3: 7-9/day > pre-treatment	reduce by 1 dose level
Grade 4: ≥10/day > pre-treatment	reduce by 2 dose levels
Other Non-hematologic toxicities (excludes alopecia, anorexia and fatigue). For mucositis/stomatitis, decrease 5FU only.	
Grade 1	No change
Grade 2	Hold until ≤ grade 1, no change in dose
Grade 3	Hold until ≤ grade 2, reduce by 1 dose level
Grade 4	Hold until ≤ grade 2, reduce by 2 dose levels
[1] Relative to the starting dose used in the previous cycle. [2] Patients should not be retreated until GI toxicity resolved to baseline (without loperamide for at least 24 h), platelets ≥ 100 x 10^9/L, and ANC ≥ 1.5 x 10^9/L. If no recovery after a 2-week delay, consider discontinuing treatment.	

Hepatic Impairment

No dose adjustment required for leucovorin. OMIT leucovorin if 5FU is omitted.

Transaminases	Bilirubin	Irinotecan	5FU
	1-1.5 X ULN or Gilbert's	Consider ↓	No change
> 3 X ULN*	2-4 X ULN	Omit	No change
	> 4 XULN	Omit	Omit
* or 5 X ULN with liver metastases; consider investigating for reversible causes such as biliary obstruction and reevaluate after stent			

Renal Impairment

No dose adjustment required for leucovorin.

Creatinine Clearance (mL/min)	Fluorouracil (% previous dose)	Irinotecan (% previous dose)
>60	No change	No change
30-60	No change	Caution; no data available
<30	Caution; consider dose ↓	Caution; no data available

Dosage in the elderly

Consider reducing starting dose for patients ≥ 70 years. Monitor patients ≥ 65 years closely.

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F - Adverse Effects

Refer to irinotecan, leucovorin, fluorouracil (± bevacizumab) drug monograph(s) for additional details of adverse effects

The following adverse effects table is related to **FOLFIRI+BEVA**:

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Myelosuppression ± infection, bleeding (may be severe) • Nausea, vomiting • Fatigue • ECG changes (asymptomatic) • Alopecia (generally mild) • Abdominal pain • Anorexia, weight loss • Diarrhea (may be severe)	• Hypertension • Proteinuria • Headache • ↑ LFTs • Constipation • Mucositis • Cholinergic symptoms • Conjunctivitis and / or tearing	• Rash / dry skin • Insomnia • Venous thromboembolism • Rhinitis • Dizziness • Musculoskeletal pain • Cough, dyspnea • Cardiotoxicity • Hand-foot syndrome • Dyspepsia • Flushing • Dysphonia • Edema	• Arterial thromboembolism • Hypersensitivity • Delayed wound healing / dehiscence • GI perforation, ulceration, obstruction • Fistula, organ perforation • Ataxia / acute cerebellar syndrome • Bradycardia • Confusion • Dysarthria • Arrhythmia • Extrapyramidal or cortical dysfunction • Hemolysis • Leukoencephalopathy • Necrotizing fasciitis • Optic neuritis, oculomotor disturbance, tear duct fibrosis • Osteonecrosis of jaw and other • Pancreatitis • Pneumonitis • Pulmonary hypertension • Radiation recall reaction, photosensitivity • Renal failure • RPLS / PRES • Thrombotic microangiopathy

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G - Interactions

Refer to irinotecan, leucovorin, fluorouracil drug monograph(s) for additional details

Refer to bevacizumab drug monograph for additional details on bevacizumab.

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H - Drug Administration and Special Precautions

Refer to irinotecan, leucovorin, fluorouracil drug monograph(s) for additional details

Different bevacizumab products are **not interchangeable**.

Refer to bevacizumab drug monograph for additional details on bevacizumab.

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I - Recommended Clinical Monitoring

Refer to bevacizumab drug monograph for additional details on bevacizumab
Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- CBC, electrolytes, liver & renal function tests; baseline and before each cycle
- Clinical toxicity assessment (including diarrhea, infection, dehydration, stomatitis, nausea and vomiting, fatigue and cardiac effects); at each visit
- Close monitoring of above parameters in elderly patients and patients who are receiving pelvic radiotherapy.

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Blood glucose, especially in patients with diabetes; baseline and regular

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J - Administrative Information

Approximate Patient Visit	
FOLFIRI	3 hours
FOLFIRI+BEVA	First cycle: 4.5 hours; Second cycle: 4 hours; Subsequent cycles: 3.5 hours
Pharmacy Workload **(average time per visit)**	
FOLFIRI	37.403 minutes
FOLFIRI+BEVA	43.916 minutes
Nursing Workload **(average time per visit)**	
FOLFIRI	61.667 minutes
FOLFIRI+BEVA	75.333 minutes

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K - References

Bevacizumab, fluorouracil and irinotecan drug monographs, Cancer Care Ontario.

André T, Louvet C, Maindrault-Goebel F, et al: CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. GERCOR. Eur J Cancer 35:1343-1347, 1999.

Clinical Practice Guidelines in Oncology (NCCN Guidelines). Colon Cancer. Version 3.2015. NCCN.org

Douillard JY, Cunningham D, Roth AD et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomized trial. The Lancet, March 2000; 355: 1041-47.

Hurwitz H, Fehrenbacher L, Novotny W et al. Bevacizumab plus irinotecan, fluorouracil and leucovorin in metastatic colorectal cancer. N Engl J Med. 2004; 350: 2335-42.

Mahfoud T, Tanz R, Mesmoudi M, et al. Bevacizumab 5 or 7.5 mg/kg in Metastatic Colorectal Cancer Can Be Infused Safely Over 10 Minutes. J Gastrointest Cancer. 2011 Jan 4. [Epub ahead of print]
Reidy DL, Chung KY, Timoney JP, et al. Bevacizumab 5 mg/kg can be infused safely over 10

minutes. J Clin Oncol. 2007;25(19):2691-5.

National Comprehensive Cancer Network. Colon Cancer (Version 2.2017). https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed June 30, 2017.

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Sobrero A, Ackland S, Clarke S, et al. Phase IV Study of Bevacizumab in Combination with Infusional Fluorouracil, Leucovorin and Irinotecan (FOLFIRI) in First-Line Metastatic Colorectal Cancer. Oncology 2009; 77: 113-9.

Tournigand C, André T, Achile E, 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.

Van Cutsem E, Rivera F, Berry S, et al. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study. Ann Oncol 2009; 20: 1842-7.

Zaanan A, Costes L, Gaauthier M et al. Chemotherapy of advanced small-bowel adenocarcinoma: a multicentre AGEO study. Ann Oncol 2010; 21: 1786-93.

PEBC Advice Documents or Guidelines

- Continuous versus Intermittent Chemotherapy Strategies in Inoperable, Advanced Colorectal Cancer
- Strategies of Sequential Therapies in Unresectable, Metastatic Colorectal Cancer Treated with Palliative Intent
- The Role of Primary Tumour Location in the Selection of Biologics for the Treatment of Unresectable Metastatic Colorectal Cancer

April 2023 Updated DPD deficiency information in the Dose Modifications section and fluorouracil antidote information in the Other Notes section.

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L - Other Notes

Diarrhea can be severe, with either immediate or delayed onset. Patients must be instructed in the use of Loperamide as treatment for diarrhea, and must have a supply of this drug upon starting Irinotecan treatments.

Antidote for Fluorouracil Overdose:

Uridine triacetate is a prodrug of uridine and is a specific antidote for treating fluorouracil overdose or severe early onset toxicities. If available, consider administering as soon as possible (i.e. within 96 hours) for suspected overdose. If not available, treatment is symptomatic and supportive.

For usage approval and supply, contact Health Canada's Special Access Program (SAP) (Phone: 613-941-2108. On-call service is available for emergencies). Uridine triacetate (Vistogard®) is supplied by its manufacturer in the United States (Wellstat Therapeutics).

The recommended dosing and administration for **uridine triacetate** in patients ≥18 years is:

- 10 grams (1 packet of coated granules) orally every 6 hours for 20 doses in total, without regards to meals.
- Granules should not be chewed. They should be mixed with 3 to 4 ounces of soft foods such as applesauce, pudding or yogurt.
- The dose should be ingested within 30 minutes of preparation, followed by at least 4 ounces of water.
- Refer to the prescribing information on dose preparation for NG-tube or G-tube use.

Additional resources on the management of fluorouracil infusion overdose:

- Management of Fluorouracil Infusion Overdose Guideline (Alberta Health Services)
- Management of Fluorouracil Infusion Overdose at the BCCA - Interim Guidance (BC Cancer Agency)

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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