Regimen Monograph

A - Regimen Name

FOLFIRI+CETU Regimen

Folinic Acid (Leucovorin)-Fluorouracil-Irinotecan-Cetuximab

Disease Site

Gastrointestinal
Colorectal

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

First-line treatment of EGFR-expressing metastatic colorectal cancer in patients with wild-type KRAS with an ECOG status of 0-1..

Cetuximab is not indicated in mCRC patients with RAS mutant tumours (exon 2, codons 12, 13; 3, codons 59, 61; or 4, codons 117, 146) or in tumours with unknown mutation status. Assessment of RAS mutation status should be performed prior to treatment using a validated test.

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B - Drug Regimen

Cetuximab (Loading Dose):

cetuximab	400 mg /m²	IV	Week 1 ONLY

(This drug is not currently publicly funded for this regimen and intent)

***Cetuximab (Maintenance Dose*):**

cetuximab	250 mg /m²	IV	Week 2 and then weekly thereafter

(This drug is not currently publicly funded for this regimen and intent)

OR

Alternative Q2 Weeks Dosing for Cetuximab:

cetuximab	500 mg /m²	IV	Day 1, every 2 weeks

(This drug is not currently publicly funded for this regimen and intent)

In combination with:

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	2400 mg /m²	IV continuous infusion over 46 hours (single dose)	Start on 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 thus 400 mg/m^2. Some studies specified the dose of leucovorin as 200mg/m^2 in the l-isomer (active) formulation.

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C - Cycle Frequency

REPEAT EVERY 14 DAYS

Until disease progression or limited by drug toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Other Supportive Care:

Also refer to CCO Antiemetic Summary

Cetuximab:

An H1 antagonist (e.g. 50 mg of diphenhydramine IV) is recommended with each dose of cetuximab. Premedication with an intravenous corticosteroid prior to the first dose may be used.

Irinotecan:

- Unless contraindicated, atropine 0.25-1mg IV/SC may be given for cholinergic adverse effects (early diarrhea)
- Prophylactic atropine may be considered in patients experiencing cholinergic symptoms
- 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.

Fluorouracil (5-FU):

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

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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.

Dosage with toxicity

CETUXIMAB

Dose modifications for infusion reactions:

Grade	Action	Next cycle
Grade1-2 infusion reaction	↓ infusion rate by 50% (5mg/min maximum)	Use antihistamine
Grade 3 or 4 infusion reaction	Discontinue immediately	Discontinue
Pneumonitis	Hold and investigate	Discontinue if confirmed
Keratitis	Hold and refer to ophthalmologist	Consider discontinuation

Dose modifications for skin toxicities:

Grade 3 or 4 Rash	Action	Outcome	Cetuximab
1st occurrence	Delay infusion 1 to 2 weeks	Improvement	Continue at 250mg/m^2
		No improvement	Discontinue
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce: 200mg/m^2
		No improvement	Discontinue
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce: 150mg/m^2
		No improvement	Discontinue
4th occurrence OR any occurrence of SJS/TENS	Discontinue		

FOLFIRI

Patients should not be retreated with irinotecan until recovery from GI toxicity (without loperamide for at least 24 h) 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

Toxicity Grade	At the start of subsequent cycles[1, 2]
Hematologic	
Grade 1	No change
Grade 2	No change
Grade 3	↓ 1 dose level
Grade 4 or febrile neutropenia	↓ 2 dose levels
Diarrhea	
2-3/day > pre-treatment	No change
4-6/day > pre-treatment	No change
7-9/day > pre-treatment	↓ 1 dose level
≥ 10/day > pre-treatment	↓ 2 dose levels

1 Relative to the starting dose used in the previous cycle.
2 Patients should not be retreated until GI toxicity resolved (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

The safety and efficacy of cetuximab have not been studied in patients with hepatic impairment. No dose adjustment required for leucovorin. OMIT leucovorin if 5-FU is omitted.

Transaminases	Bilirubin	Irinotecan	Fluorouracil
	1-1.5 X ULN	Consider ↓	No change
> 3 X ULN*	2-4 X ULN	Omit	No change
	> 4 XULN	Omit	Omit
* or 5 X ULN with liver metastases			

Renal Impairment

The safety and efficacy of cetuximab have not been studied in patients with 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

No dosage adjustment is required for cetuximab. Elderly patients receiving irinotecan may be at increased risk of diarrhea and should be monitored closely. Consider reducing the irinotecan starting dose in patients aged 70 and older.

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F - Adverse Effects

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

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Rash (may be severe) • Fatigue • Increased LFTs (may be severe) • Nausea, vomiting • Anorexia • Alopecia • Abdominal pain • Constipation • Diarrhea (may be severe) • EKG changes	• Neuropathy • Cough, dyspnea • Hypomagnesemia • Infection (may be severe) • Headache • Mucositis • Insomnia • Myelosuppression +/- bleeding, infection (may be severe) • Nail disorders	• Hand-foot syndrome • Dizziness • Musculoskeletal pain • Paronychia • Infusion reaction • Mood changes • Rhinitis • Dry mouth • Edema • Somnolence	• Arterial / venous thromboembolism • Arrhythmia • Cardiotoxicity • GI obstruction / perforation • Hypersensitivity • Pancreatitis • Pneumonitis • Renal failure • Keratitis, optic neuritis • Tumour lysis syndrome • Hemolysis

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G - Interactions

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

- Additive skin toxicity may occur when cetuximab is given in combination with radiation
- Monitor drug levels and toxicity with phenytoin
- Monitor INR levels and toxicity with warfarin
- Azole antifungals are contraindicated with irinotecan (discontinue one week before the first dose of irinotecan)
- Avoid concomitant use of strong CYP3A4 inhibitors and inducers with irinotecan
- Avoid concomitant use of prochlorperazine, turmeric and azatanavir with irinotecan

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H - Drug Administration and Special Precautions

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

Administration:

Cetuximab:

- Do not shake or further dilute the solution.
- DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.
- Transfer undiluted solution into an empty Viaflex bag or an empty syringe, if using a syringe pump.
- Administer the undiluted solution via a low protein binding 0.22-micrometer in-line filter. Piggybacking to the patient's infusion line, infuse initial loading dose over 2 hours, and maintenance dose over 1 hour (maximum rate 10 mg/min). (May require infusion at slower rate in those who experienced infusion reactions).
- Prime administration line with drug solution before infusion and may use NS to flush line at the end of infusion.
- A 1-hour observation period is recommended following each cetuximab infusion. Longer observation periods may be required in those who experienced infusion reactions.
- Should not be mixed or diluted with other drugs.
- Discard any unused portion left in a vial 12 hours under refrigeration or 8 hours at room temperature, as the product contains no preservatives.

Irinotecan:

- Mix in 500mL bag (D5W-preferred or NS) in a concentration range between 0.12 to 3 mg/mL; infuse IV over 90 minutes
- Do not refrigerate admixtures in NS (may result in precipitation)
- Avoid freezing irinotecan and its admixtures since this may result in drug precipitation.
- Do not admix with other drugs
- Protect from light
- Prior to the initial irinotecan treatment, patients should be given a sufficient supply of loperamide and instructed on its appropriate use.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during irinotecan treatment

Leucovorin:

- Doses ≤100mg may be given by IV push through sidearm of free flowing IV (5% Dextrose, Normal Saline or 2/3-1/3). The injection must not exceed 160mg/min of leucovorin (due to calcium content).
- May be mixed in 50mL Normal Saline or 5% Dextrose minibag (doses up to 500mg) or 100mL minibag (doses >500mg) or in 100mL fluid in graduated administration set (5% Dextrose, Normal Saline or 2/3-1/3); Give over 15 minutes.
- Leucovorin should not be mixed in the same infusion as 5-fluorouracil as a precipitate may form.

- Keep refrigerated; protect from light.

Fluorouracil:

- IV PUSH OR INTERMITTENT INFUSION:
- Slow push through sidearm of free-flowing IV (5% Dextrose, Normal Saline)
- May be mixed in 50mL minibag (NS or D5W); infuse over 15 min.
- Protect from light.
- IV CONTINUOUS INFUSION:
- Continuous infusion using CADD infusion pump, or similar device
- Infuse through central venous access device, if available
- Infusion volume and duration depend on protocol.
- Protect from light
- Infuse through patent peripheral venous catheter, if infusion for only 3-5 days; Inspect peripheral infusion sites daily and replace if evidence of irritation or extravasation
- Incompatible with doxorubicin, epirubicin, diazepam, methotrexate and cytarabine; line must be flushed between administrations of fluorouracil and these agents

Contraindications:

- Patients with known hypersensitivity to cetuximab, murine protein or any components of the product or FOLFIRI regimen
- Treatment of colorectal cancer in patients with K-RAS mutations or K-RAS unknown status
- Patients with ECOG performance status of 3 or 4
- Patients with moderate to severe hepatic dysfunction
- Patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- Avoid FOLFIRi in patients with hereditary fructose or glucose-galactose or lactose intolerance
- Avoid the use of live or live attenuated vaccines
- Leucovorin should be avoided in the treatment of pernicious anemia or vitamin B12 deficiency anemias
- Leucovorin contraindicated for intrathecal use
- Patients with depressed bone marrow function (prior pelvic irradiation / marrow infiltration)
- Patients with potentially serious infections

Other warnings/precautions:

- Patients with a history of, or pre-existing keratitis, dry eyes or contact lens use
- Patients with poor performance status, or cardiopulmonary disease are at increased risk of severe hypersensitivity
- Elderly patients, patients with poor performance status (= 2), limited marrow reserve, 3rd space accumulation, Gilbert's syndrome and patients with reduced UGT1A1 activity may be more susceptible to the toxic effects of irinotecan; they should be carefully monitored and dose reduction considered
- Use fluorouracil with extreme caution in patients who have undergone recent major surgery, with renal or hepatic impairment, widespread bone marrow involvement, or are suspected to have DPD deficiency. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- This regimen is not recommended for use in pregnancy. Adequate contraception should be

used by both sexes during treatment, and for at least **6 months** after the last dose.
- Breastfeeding is not recommended.

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I - Recommended Clinical Monitoring

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, liver and renal function tests; baseline and at each visit
- Electrolytes, including serum magnesium, potassium and calcium; baseline, at each visit and monthly for 2 months following completion of therapy
- Clinical toxicity assessment for infection, bleeding, skin, nail, cardiac, thromboembolism, GI, respiratory effects, hypersensitivity and fatigue; at each visit
- 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 at each visit

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J - Administrative Information

Approximate Patient Visit	6 hours
Pharmacy Workload (average time per visit)	51.753 minutes
Nursing Workload (average time per visit)	86.5 minutes

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K - References

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.

Cheng AL, Cornelio G, Shen L, et al. Efficacy, Tolerability, and Biomarker Analyses of Once-Every-2-Weeks Cetuximab Plus First-Line FOLFOX or FOLFIRI in Patients With KRAS or All RAS Wild-Type Metastatic Colorectal Cancer: The Phase 2 APEC Study. Clin Colorectal Cancer 2017;16(2):e73-e88.

Cetuximab drug monograph, Cancer Care Ontario.

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.

FOLFIRI regimen monograph, Cancer Care Ontario.

Van Cutsem E, Kohne C-H, Hitre E et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009;360:1408-17.

Van Cutsem E et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor K-ras and BRAF mutation status. J Clin Oncol 2011;29(15):2011-2019.

PEBC Advice Documents or Guidelines

- 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 and Special Precautions sections and fluorouracil antidote information in the Other Notes section.

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L - Other Notes

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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last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

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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