Regimen Monograph

A - Regimen Name

IRIN(Q2W)+CETU Regimen

Irinotecan (q2w)-Cetuximab

IRIN+CETU Regimen

Irinotecan-Cetuximab

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

Third-line treatment of EGFR-expressing metastatic colorectal, small bowel or appendiceal cancer, in patients with wild-type KRAS after failure of oxaliplatin and irinotecan-containing chemotherapy regimens.

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.

Supplementary Public Funding	**cetuximab** New Drug Funding Program (Cetuximab with Irinotecan - Metastatic Colorectal, Small Bowel, or Appendiceal Cancer) (NDFP Website)

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B - Drug Regimen

IRIN(Q2W)+CETU Schedule:

cetuximab[1]	500 mg /m²	IV *	Day 1; q14 days

* over 2 hours for the first dose, then over 1 to 2 hours for subsequent doses (if no infusion reactions observed in previous cycle)

[1] maximum infusion rate 10 mg/min

irinotecan	180 mg /m²	IV	Day 1; q14 days

IRIN+CETU Schedule:

Cetuximab (loading dose):

cetuximab[1]	400 mg /m²	IV	Cycle 1, day 1 ONLY

Cetuximab (Maintenance Dose):

cetuximab[1]	250 mg /m²	IV	Cycle 1, day 8 and then weekly thereafter

[1] maximum infusion rate 10 mg/min

and

Irinotecan every 3 weeks:

irinotecan	350 mg /m²	IV	Day 1 only

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C - Cycle Frequency

IRIN(Q2W)+CETU:*
Cetuximab and Irinotecan **REPEAT EVERY 14 DAYS**

IRIN+CETU:*
Cetuximab **REPEAT EVERY 7 DAYS**
AND
Irinotecan **REPEAT EVERY 21 DAYS**

*Continue until evidence of disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate (D1)
Minimal (D8, 15)

- Also refer to CCO Antiemetic Recommendations.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline

Other Supportive Care:

Irinotecan:

- Unless contraindicated, atropine 0.25-1mg IV/SC may be used for cholinergic adverse effects (early diarrhea)
- 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

Cetuximab:

- An H1 antagonist (e.g. 50 mg of diphenhydramine IV) is recommended with each dose

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and could be considered.

Dosage with toxicity

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 for irinotecan:

Regimen	Drug	Starting dose (mg/m^2)	Dose level -1 (mg/m^2)	Dose Level -2 (mg/m^2)	Dose Level -3 (mg/m^2)
Q2W	Irinotecan	180	140-150	110-120	
Q3W	Irinotecan	350	300	250	200

Irinotecan: Dose Modification for Toxicity

Toxicity grade[3]	At start of subsequent cycle[1,2]
1	No change
2	Diarrhea alone – no change
	Hematologic alone – no change
	Other [3]: ↓ 1 dose level
3	↓ 1 dose level
4 or febrile neutropenia	↓ 1 dose level
Pneumonitis	Hold; investigate and if confirmed, discontinue.

[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.

[3] Excludes alopecia, anorexia, and fatigue

Cetuximab: Dosage Modification for Dermatologic Toxicity and Related Disorders

Grade 3 or 4 Acneiform Rash	Action	Outcome	Cetuximab (weekly dosing)
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		

Cetuximab: Infusion Rate Modification for Infusion Reactions

Mild to moderate infusion reactions can be managed with slowing the infusion rate of cetuximab and with continued use of antihistamine medications (e.g. diphenhydramine) in subsequent doses.

Grade	Infusion rate
Grade 1 or 2	5 mg/min
Grade 3 or 4	Discontinue

Other Toxicities

Hold cetuximab and irinotecan for onset of symptoms suggesting pneumonitis. Investigate and discontinue permanently if confirmed.

Hepatic Impairment

Transaminases	Bilirubin[1]	Irinotecan
	1-1.5 x ULN or Gilbert's	Consider ↓
> 3 x ULN*	2-4 x ULN	Omit
	≥ 4 x ULN	Omit

*or 5 x ULN with liver metastases

[1] Consider investigating for reversible causes such as biliary obstruction and re-evaluate after stent

Renal Impairment

The kidney is not a major route of excretion for irinotecan and cetuximab; no dose adjustment anticipated to be required.

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 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 • Diarrhea (may be severe) • Constipation	• Cough, dyspnea • Hypomagnesemia • Headache • Mucositis • Insomnia • Nail disorder • Myelosuppression +/- infection, bleeding (may be severe) • Fever	• Infusion-related reaction • Mood changes • Dizziness • Dry mouth • Musculoskeletal pain	• Hemorrhage • Keratitis, optic neuritis • Arterial / venous thromboembolism • Arrhythmia • GI obstruction / perforation • Pancreatitis • Pneumonitis • Renal failure • Tumour lysis syndrome

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G - Interactions

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

- Additive skin toxicity may occur when cetuximab is given in combination with radiation
- 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 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

Contraindications:

- Patients with known hypersensitivity to cetuximab, murine protein or any components of this product
- Treatment of colorectal cancer in patients with RAS mutations (exon 2, 3, 4) or RAS unknown status
- Patients with ECOG performance status of 3 or 4
- Patients with moderate to severe hepatic dysfunction
- Avoid in patients with hereditary fructose intolerance since the product contains sorbitol
- Avoid the use of live or live attenuated vaccines

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.
- The concurrent administration of irinotecan with irradiation is not recommended.

Pregnancy/Lactation:

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Breastfeeding is not recommended during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects: Unknown

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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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC, liver & renal function tests; baseline and at each cycle
- Electrolytes, including serum magnesium, potassium and calcium; baseline, at each cycle and as clinically indicated, and monthly for 2 months following completion of therapy
- Clinical toxicity assessment including infection, bleeding, hypersensitivity, diarrhea and other GI effects, pancreatitis, cholinergic symptoms, respiratory, skin and CNS toxicity, thromboembolism 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

IRIN(Q2W)+CETU	First cycle: 3.5 hours; Subsequent cycles: 2.5 hours
IRIN+CETU	First cycle: 3.5 hours; Subsequent cycles: 2.5 hours

Pharmacy Workload **(average time per visit)**

IRIN(Q2W)+CETU	42.012 minutes
IRIN+CETU	30.512 minutes

Nursing Workload **(average time per visit)**

IRIN(Q2W)+CETU	62.5 minutes
IRIN+CETU	62.5 minutes

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K - References

Cetuximab drug monograph, Ontario Health (Cancer Care Ontario).

Cunningham D et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. NEJM 2004; 351(4): 337-45.

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Mbrati H, De la Fourchardiere C, Desseigne F, et al. Irinotecan associated with cetuximab given every 2 weeks versus cetuximab weekly in metastatic colorectal cancer. Journal of Cancer Research and Therapeutics 2009; 5(4): 272-6.

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Roca JM, Alonso V, Pericay C, et al. Cetuximab given every 2 weeks plus irinotecan is an active and safe option for previously treated patients with metastatic colorectal cancer. Chemotherapy. 2010;56(2):142-6.

Sobrero A, et al. EPIC: Phase III trial of cetuximab plus irinotecan After fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. JCO 2008; 28(14): 2311-9.

Tabernero J, Ciardiello F, Rivera F, et al. Cetuximab administered once every second week to patients with metastatic colorectal cancer: a two-part pharmacokinetic/pharmacodynamics phase I dose-escalation study. Ann Oncol 2010;21:1537–45

Wilke H et al. Cetuximab plus irinotecan in heavily pretreated metastatic colorectal cancer progressing on irinotecan: MABEL Study. JCO 2008; 26(33): 5335-43.

PEBC Advice Documents or Guidelines

- The Role of Primary Tumour Location in the Selection of Biologics for the Treatment of Unresectable Metastatic Colorectal Cancer

August 2025 Updated Pregnancy/Lactation section

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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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