Regimen Monograph

A - Regimen Name

ENCO+CETU Regimen

Encorafenib - 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

For patients with previously treated BRAF V600E-mutated metastatic colorectal cancer (mCRC)*, who have good performance status, adequate organ function, and have not received prior EGFR or BRAF inhibitors.

*Patients with small bowel adenocarcinoma or appendiceal carcinoma may be considered for cetuximab funding if funding criteria are met. Refer to NDFP form for details.

Supplementary Public Funding

encorafenib
Exceptional Access Program (encorafenib - In combination with cetuximab or panitumumab in previously treated BRAF V600E-mutated metastatic colorectal cancer, according to clinical criteria) (EAP Website) (Refer to EAP for full details.)

cetuximab
New Drug Funding Program (Cetuximab - In Combination with Encorafenib for Previously Treated Metastatic Colorectal Cancer) (NDFP Website)

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B - Drug Regimen

Weekly Cetuximab Schedule:

encorafenib	300 mg	PO	Daily Continuous
cetuximab	400 mg /m²	IV	Day 1, Week 1 (loading dose)
Then			
cetuximab	250 mg /m²	IV	Day 1, Week 2 onwards

OR

Q2 Weeks Cetuximab Schedule:

encorafenib	300 mg	PO	Daily Continuous
cetuximab	500 mg /m²	IV	Day 1

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C - Cycle Frequency

Encorafenib: **CONTINUOUS TREATMENT**

Cetuximab 250 mg/m^2 : **REPEAT WEEKLY** or
Cetuximab 500 mg/m^2 : **REPEAT EVERY 2 WEEKS**

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal

- 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.

Cetuximab Premedications (prophylaxis for infusion reaction):

- H1-receptor antagonist (e.g. diphenhydramine 50 mg IV) 30-60 minutes prior to the dose.
- Corticosteroid IV 30-60 minutes prior to the dose.
- Consider discontinuing pre-medications after the 2nd infusion based on clinical judgment and the presence/severity of IR.

Other Supportive Care:

- Patients should use sun protection while receiving cetuximab and for 2 months after treatment completion.
- Consider pre-emptive therapy for EGFR inhibitor-related skin toxicity; the following was shown to be of benefit with panitumumab treatment, starting the day before treatment and continued until week 6. (Lacouture et al, 2010):
  - Skin moisturizer applied to the face, hands, feet, neck, back and chest in the morning
  - Sunscreen to exposed areas (SPF ≥ 15, UVA and UVB) before going outdoors
  - Hydrocortisone 1% cream to the face, hands, feet, neck, back and chest at bedtime
  - Doxycycline (or minocycline) PO
- Refer to the Canadian recommendations for the management of skin rash during EGFR-targeted monoclonal antibody treatment for GI malignancies. (Melosky et al, 2009)

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E - Dose Modifications

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

BRAF V600E mutation should be confirmed by a validated test prior to starting treatment.

Correct electrolyte imbalances prior to and during treatment.

A dermatologic evaluation should be performed prior to initiating treatment.

Refer to Interactions Section for dosing recommendations when co-administered with CYP3A4 inhibitors.

Dosage with toxicity

Dose Level	Encorafenib Dose (mg daily)	Cetuximab Dose (mg/m² q2 weeks)	Cetuximab Dose (mg/m² weekly)
0	300	500	250
-1	225	400	200
-2	150	300	150
-3	Discontinue	Discontinue	Discontinue

Encorafenib Dosage Modification for Toxicity

Toxicity / Severity		Action#
Non-cutaneous malignancy		Discontinue if RAS mutation-positive.
Any new or worsening visual disturbance		Refer to ophthalmologist.
Uveitis	Grade 1 not responding to ocular therapy	Hold encorafenib for up to 6 weeks. If improved to Grade < 1, resume at same dose.
	Grade 2 not responding to ocular therapy	Hold encorafenib for up to 6 weeks. If improved to Grade ≤ 1, resume at 1 dose level ↓.
	Grade 3	
	Grade 4	Discontinue.
QT Prolongation	QTcF > 500 ms AND ≤ 60 ms increase from baseline	Hold until QTcF ≤ 500 ms, then resume at 1 dose level ↓. If > 1 recurrence, discontinue.

		QTcF > 500 ms AND > 60 ms increase from baseline	Discontinue.
	Increase in AST or ALT	Grade 2, without improvement for 2 weeks	Hold until ≤ Grade 1 or baseline. Resume at same dose.
		Grade 3 or 4	See Other Adverse Reactions below.
	Hand-foot Syndrome	Grade 2, without improvement for 2 weeks	Hold until ≤ Grade 1. Resume at same dose for first occurrence. Resume at same dose or with 1 dose level ↓ if recurrent.
		Grade 3	Hold until ≤ Grade 1. Resume with 1 dose level ↓.
	Other Dermatologic Reactions*	Grade 2, without improvement for 2 weeks	Hold until ≤ Grade 1. Resume at same dose.
		Grade 3	Hold until ≤ Grade 1. Resume at same dose for first occurrence. Resume at 1 dose level ↓ if recurrent.
		Grade 4	Discontinue.
	Other Adverse Reactions (including hemorrhage)*	Grade 2, recurrent	Hold for up to 4 weeks. If improves to ≤ Grade 1 or baseline, resume at 1 dose level ↓. Discontinue if no improvement.
		Grade 3, 1st occurrence	
		Grade 3, recurrent	Consider discontinuing.
		Grade 4, 1st occurrence	Discontinue <u>OR</u> Hold for up to 4 weeks. If improves to ≤ Grade 1 or baseline, resume at 1 dose level ↓. Discontinue if no improvement.
		Grade 4, recurrent	Discontinue.

#In the event that either encorafenib or cetuximab is discontinued due to unacceptable toxicity, the other drug must also be discontinued.

*Excluding new primary cutaneous malignancies, other ocular events, ILD/pneumonitis, cardiac dysfunction, CPK elevation, rhabdomyolysis, and VTE

Cetuximab Dosage Modification for Non-skin Toxicity

Toxicity	Action	Next cycle*
Pneumonitis	Hold and investigate	Discontinue if confirmed.
Keratitis	Hold and refer to ophthalmologist	Consider discontinuation

*In the event that either encorafenib or cetuximab is discontinued due to unacceptable toxicity, the other drug must also be discontinued.

Cetuximab Dosage Modification for Toxicity

Grade 3 or 4 Rash	Action	Outcome	Cetuximab Dose*
1st occurrence	Delay infusion 1 to 2 weeks	Improvement	Resume at same dose
		No improvement	Discontinue
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement	Resume at 1 dose level ↓
		No improvement	Discontinue
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement	Resume at 1 dose level ↓
		No improvement	Discontinue
4th occurrence OR any occurrence of SJS/TENS	Discontinue		

*In the event that either encorafenib or cetuximab is discontinued due to unacceptable toxicity, the other drug must also be discontinued.

Cetuximab - Management of Infusion-related Reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • The infusion may be restarted at a slower rate (50% of the rate at which the IR occurred) once symptoms have resolved.	• Re-challenge with a reduced infusion rate of 50% at which the infusion reaction occurred.
3 or 4	• Stop treatment. • Aggressively manage symptoms. **Restart:** • Once symptoms resolve, the infusion can be restarted at a slower rate, unless a serious reaction occurred (i.e. vital signs compromised; anaphylaxis).	• Permanently discontinue (do not re-challenge).

Hepatic Impairment

Population pharmacokinetic model suggests hepatic impairment has no significant impact on **cetuximab** pharmacokinetics.

For increased AST/ALT during **encorafenib** treatment, refer to dose modifications table above.

Hepatic Impairment	Encorafenib Starting Dose
Mild (Child-Pugh Class A)	300 mg Daily
Moderate (Child-Pugh Class B)	No data available.
Severe (Child-Pugh Class C)	

Renal Impairment

Population pharmacokinetic model suggests renal impairment has no significant impact on **cetuximab** pharmacokinetics.

Encorafenib:

Creatinine Clearance (mL/min)	Encorafenib Starting Dose
≥ 30	No dose adjustment recommended
< 30	No data available.

Dosage in the Elderly

No dose adjustment required for patients ≥ 65 years. There are insufficient data around the use of encorafenib in combination with cetuximab for mCRC in patients ≥ 65 years or older to assess differences in efficacy or safety compared to younger patients.

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F - Adverse Effects

Refer to encorafenib, cetuximab 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
• Fatigue	• Nausea, vomiting • Diarrhea • Rash, pruritus, dry skin (may be severe) • Anorexia • Nail disorder • Musculoskeletal pain	• Headache • Infusion reactions (with cetuximab; may be severe) • Abnormal electrolyte(s) (↓ K, Mg, Na; may be severe) • Hemorrhage (may be severe) • Constipation • Melanocytic nevus • Hyperglycemia • Insomnia • Peripheral neuropathy • Dyspnea	• Arterial / venous thromboembolism • Arrhythmia • QT interval prolonged • Pneumonitis • Hepatotoxicity • Pancreatitis • GI obstruction / perforation • Hypersensitivity • Nephrotoxicity • Eye disorders • Secondary malignancy • Hand-foot syndrome • Stevens-Johnson syndrome • Toxic epidermal necrolysis

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G - Interactions

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

- Avoid if possible concomitant use of strong or moderate CYP3A4 inhibitors with encorafenib. Reduce encorafenib dose if used in combination; see dosage table below.
- Avoid concomitant use of strong or moderate CYP3A4 inducers with encorafenib.
- Avoid concomitant use with sensitive CYP3A4 substrates (e.g., hormonal contraceptives) where a minimal decrease in concentration may lead to therapeutic failure. If coadministration of a sensitive substrate cannot be avoided, adjust substrate dose based on its product monograph recommendations.
- Avoid concomitant use of QT/QTc prolonging agent with encorafenib due to additive risk of toxicity.
- Additive mucocutaneous toxicity may occur when cetuximab is given in combination with radiation.

Encorafenib Dose with CYP3A4 Inhibitors

Planned Dose (mg)	Encorafenib Dose* (mg daily)	
	with Strong CYP3A4 inhibitor	with Moderate CYP3A4 inhibitor
300	75	150
225	75	75
150	75^	75

*Resume previous dose after the inhibitor has been discontinued for 3 to 5 elimination half-lives.

^Monitor patients for adverse reactions and use clinical judgment; encorafenib exposure at 75mg daily (with a strong CYP3A4 inhibitor) is expected to be similar to the exposure at the 225mg daily dose (in the absence of a CYP3A4 inhibitor).

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H - Drug Administration and Special Precautions

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

Administration: Encorafenib

- Administer encorafenib with or without food.
- Capsules should be swallowed whole with water. Do not crush, dissolve, or open capsules.
- Grapefruit, starfruit, Seville oranges, their juices or products should be avoided during encorafenib treatment.
- If a dose is missed, patient may take within 12 hours of the missed dose. If more than 12 hours has elapsed from the missed dose, the dose should be skipped and taken at the next scheduled time. Extra capsules should not be taken to make up for a missed dose.
- Do not take an additional dose if vomiting occurs after taking encorafenib.
- Store at 15 - 30°C in the original bottle. Protect from moisture and do not remove the desiccant.

Administration: Cetuximab

- Do not shake or further dilute the solution.
- DO NOT administer as an IV push or bolus.
- Transfer undiluted solution into a compatible empty infusion container.
- Cetuximab is compatible with:
  - glass,
  - polyolefin, polyethylene, ethylene vinyl acetate (EVA), DEHP plasticized PVC, or PVC bags,
  - polyethylene, EVA, PVC, polybutadiene or polymethane infusion sets, and
  - polyethersulfone, polyamide or polysulfone in-line filters.
- 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 as tolerated. (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.
- Store unopened vials at 2-8°C.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Contraindications

- Patients who have a hypersensitivity to this drug or any of its components

Warnings/Precautions

- Patients must have a validated test to confirm BRAF V600/E mutation before treatment; paradoxical activation of MAP-kinase signaling may occur when BRAF wild-type cells are exposed to BRAF inhibitors, such as encorafenib.
- Cetuximab is not indicated for the treatment of colorectal cancer in patients with RAS mutations or unknown RAS status.
- Exercise caution with encorafenib in patients with diabetes or with risk factors for QT prolongation, including known long QT syndromes, bradyarrhythmias, heart failure, and taking other QT prolonging agents.
- Patients were excluded from clinical trials if they have a history of Gilbert's syndrome, abnormal LVEF, prolonged QTc (>480 ms), uncontrolled hypertension, and history or current evidence of retinal vein occlusion. Consider benefits vs risks of using encorafenib and cetuximab in these patients.
- Use caution when driving or operating a vehicle or potentially dangerous machinery as vision problems have been reported.
- Use caution in 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 cetuximab hypersensitivity.

Pregnancy and Lactation

- This regimen is not recommended for use in pregnancy. Adequate non-hormonal 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 treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects:
    - Encorafenib: Probable
    - Cetuximab: 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

- Electrolytes, including serum magnesium, potassium and calcium; Baseline, before each cetuximab dose, and monthly for 2 months following completion of therapy
- Renal function tests; Baseline, before each cetuximab dose, and as clinically indicated
- Liver function tests; Baseline, monthly, and as clinically indicated
- CBC; Baseline, and as clinically indicated
- Skin examination for any new cutaneous malignancies; Baseline, every 2 months during treatment, and continue for up to 6 months after the last dose
- ECG (especially in patients at risk for QT prolongation); Baseline and as clinically indicated
- Clinical toxicity assessment for infusion reactions, hypersensitivity, bleeding, thromboembolism, fatigue, hyperglycemia, new primary non-cutaneous malignancies, rash, nail, respiratory, ocular, and GI effects; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Outpatient prescription for home administration (encorafenib)

Cetuximab:

Approximate Patient Visit	First cycle; 2.5 hours; Subsequent cycles: 1.5 hours
Pharmacy Workload (average time per visit)	24.85 minutes
Nursing Workload (average time per visit)	55.595 minutes

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K - References

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

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Lacouture, ME, Mitchell EP, Piperdi B et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. J Clin Oncol 2010; 28: 1351-7.

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Somerset, Wiltshire, Avon and Gloucestershire Cancer Alliance. Cetuximab and Encorafenib. February 15, 2021.

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The Clatterbridge Cancer Centre NHS Foundation Trust. Encorafenib and Cetuximab Metastatic Colorectal Cancer. October 9, 2020.

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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.

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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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