Regimen Monograph

A - Regimen Name

ENCO+PNTM Regimen

Encorafenib-Panitumumab

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 panitumumab 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.)

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

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B - Drug Regimen

encorafenib	300 mg	PO	Daily, Days 1 to 28
PANitumumab	6 mg /kg	IV	Days 1, 15

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

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.

Other Supportive Care:

- As sun exposure may exacerbate skin reactions, patients should be advised to use sunscreen, wear a hat and limit sun exposure.
- The following has been shown to be of benefit when used from the day before treatment to 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 product monograph and Canadian recommendations for the management of skin rash during EGFR-targeted monoclonal antibody treatment for GI malignancies. (Melosky 2009)

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E - Dose Modifications

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

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)
0	300
-1	225
-2	150
-3	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 improves to Grade < 1, resume at same dose.
	Grade 2 not responding to ocular therapy	Hold encorafenib for up to 6 weeks. If improves 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 panitumumab 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

Panitumumab Dosage Modification for Toxicity

Toxicity	Action^,#	Dose Modification# (% previous dose)
≥ grade 3 skin (1st occurrence)	Hold until ≤ grade 2*	Restart at 100%
≥ grade 3 skin (2nd occurrence)	Hold until ≤ grade 2*	Restart at 80%
≥ grade 3 skin (3rd occurrence)	Hold until ≤ grade 2*	Restart at 60%
≥ grade 3 skin (4th occurrence)	Discontinue	n/a
Skin or soft tissue with severe or life-threatening inflammatory or infectious complications	Hold or discontinue, depending on severity	n/a
SJS/TEN	Discontinue	n/a
≥ grade 3 diarrhea or dehydration	Hold until ≤ grade 2	Consider dose reduction, if appropriate
ILD/pneumonitis	Hold and investigate	If confirmed, discontinue.
Keratitis or ulcerative keratitis	Hold or discontinue, depending on severity or persistence	n/a

*Hold for 1 to 2 doses until recovery. Discontinue if no recovery within 4 weeks.

^For treatment of skin reactions, may refer to the Canadian recommendations for the management of skin rash during EGFR-targeted monoclonal antibody treatment for GI malignancies (Melosky 2009).

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

Panitumumab - 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. • Manage the symptoms. **Restart:** • Restart the infusion at 50% of the rate at which the IR occurred.	• Re-challenge the infusion at 50% of the rate at which the IR occurred.
3 or 4	• Stop the infusion. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Hepatic Impairment

The safety and efficacy of **panitumumab** have not been studied in hepatic impairment.

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

The safety and efficacy of **panitumumab** have not been studied in renal impairment. Acute renal failure has been observed in patients experiencing severe diarrhea and dehydration (see dosage with toxicity table for management).

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. No information found on the safety and efficacy of encorafenib in combination with panitumumab in the elderly.

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F - Adverse Effects

Refer to encorafenib, PANitumumab drug monograph(s) for additional details of adverse effects.

The following adverse effects table is based on the ENCO+CETU regimen. It also includes severe or life-threatening adverse effects reported with panitumumab from other sources.

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 • 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 / infusion reactions • Nephrotoxicity • Eye disorders • Secondary malignancy • Soft tissue / skin necrosis • Hand-foot syndrome • Stevens-Johnson syndrome • Toxic epidermal necrolysis

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G - Interactions

Refer to encorafenib, PANitumumab 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.

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, PANitumumab 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: Panitumumab

- DO NOT administer as an IV push or bolus; MUST be administered using an IV infusion pump.
- Diluted with 0.9% sodium chloride only. Do not mix with other drugs or IV solutions.
- Dilute in a total volume of 100mL in sodium chloride 0.9% (Final concentration must be ≤ 10mg/mL). Infuse IV over 60 minutes. May give via peripheral line or in-dwelling catheter. If the first infusion is tolerated, subsequent infusions may be given over 30 to 60 minutes.
- Doses higher than 1000mg should be diluted in 150mL 0.9% sodium chloride injection, and infused IV over 90 minutes.
- Compatible with 0.9% sodium chloride in PVC bags or polyolefin bags
- Administer using a low-protein binding 0.2 micron or 0.22 micron in-line filter.
- Solution may contain a small amount of visible, amorphous, panitumumab particulates that will be removed by the low protein binding in-line filter during infusion.
- Do not shake. Mix diluted solution by gentle inversion.
- Flush line before and after administration with 0.9% sodium chloride.
- Missed Dose: Panitumumab should be given within 3 days of scheduled dose. If a dose is missed, it should be administered as soon as possible and the next dose should be given on a new schedule relative to last administered dose.
- Keep unopened vials refrigerated (2 to 8°C) in the original carton. Protect from direct sunlight and do not freeze.

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

Contraindications

- Patients who have a hypersensitivity to these drugs or any of their components
- Panitumumab is NOT indicated for patients with RAS mutant mCRC or for whom RAS mutation status is unknown.

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.
- In a phase III panitumumab trial, patients with ECOG 2 had increased toxicity and shortened survival compared to those with ECOG 0-1. Assess risk vs. benefit prior to treatment in patients with ECOG 2.
- Consider risks and benefits before starting panitumumab treatment in patients with a history of pulmonary fibrosis or ILD.
- Exercise caution with encorafenib in patients with diabetes, or risk factors for QT prolongation, including known long QT syndromes, bradyarrhythmias, heart failure, and taking other QT prolonging agents.
- Patients were excluded from encorafenib 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 in these patients.
- Use with caution in patients with a history of keratitis, ulcerative keratitis, or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration.
- Use caution when driving or operating a vehicle or potentially dangerous machinery as vision problems have been reported.
- The panitumumab formulation contains 0.15 mmol sodium (= 3.45 mg sodium) per mL of concentrate. This sodium content should be taken into consideration in patients on sodium restriction.

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: Probable

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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 calcium, magnesium and potassium); Baseline, before each panitumumab dose, and monthly for 8 weeks after completion of therapy
- Renal function tests; Baseline, before each panitumumab 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
- Clinical pulmonary exam; Baseline and clinically as indicated
- ECG (especially in patients at risk for QT prolongation); Baseline and as clinically indicated
- Clinical toxicity assessment for bleeding, thromboembolism, infusion reactions, hypersensitivity, fatigue, hyperglycemia, dehydration, new primary non-cutaneous malignancies, rash, 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)

Panitumumab:

Approximate Patient Visit	1 hour
Pharmacy Workload (average time per visit)	17.887 minutes
Nursing Workload (average time per visit)	40.75 minutes

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K - References

CADTH Reimbursement Recommendation: Encorafenib (for the treatment of patients with metastatic colorectal cancer with a BRAF V600E mutation after prior therapy). Canadian Journal of Health Technologies. July 2021.

Encorafenib drug monograph. Ontario Health (Cancer Care Ontario).

Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, binimetinib, and cetuximab in BRAF V600E-mutated colorectal cancer. N Engl J Med 2019; 38:1632-43.

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.

Melosky B, Burkes R, Rayson D, et al. Management of skin rash during EGFR-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations. Current Oncology 2009; 16(10): 14-24

Panitumumab drug monograph. Ontario Health (Cancer Care Ontario).

Rausch C, Schwicht C, Doedens D, et al. Panitumumab can safely and effectively be substituted for cetuximab in the treatment of BRAF V600Emut metastatic colorectal cancer (mCRC) - A case series. Eur J Cancer 2022 Oct;174:37-39.

Tabernero J, Grothey A, Van Cutsem E, et al. Encorafenib plus cetuximab as a new standard of care for previously treated *BRAF* V600E-mutant metastatic colorectal cancer: updated survival results and subgroup analyses from the BEACON study. J Clin Oncol 2021 Feb 1;39(4):273-84.

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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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