Regimen Monograph

A - Regimen Name

MFOLFOX6+PNTM Regimen

Folinic Acid (Leucovorin)-Fluorouracil-Oxaliplatin-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 the treatment of patients with wild-type* RAS metastatic colorectal (mCRC), small bowel or appendiceal cancer in the first-line setting who have a contraindication or intolerance to bevacizumab, who did not have disease progression on bevacizumab, and who would otherwise be treated with combination chemotherapy alone. Patients should have good performance status. (Refer to NDFP panitumumab eligibility form below for detailed funding criteria.)
*RAS testing must be complete prior to dosing. Panitumumab is not indicated for patients with RAS mutant mCRC or for whom RAS mutation status is unknown.

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B - Drug Regimen

PANitumumab	6 mg /kg	IV	Day 1
oxaliplatin	85 mg /m²	IV over 2 hours	Day 1
leucovorin	400 mg /m²	IV over 2 hrs (concurrently with oxaliplatin)	Day 1
fluorouracil	400 mg /m²	IV bolus, after leucovorin	Day 1
THEN			
fluorouracil	2400 mg /m²	IV continuous infusion over 46 hours only	Start on Day 1

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C - Cycle Frequency

REPEAT EVERY 14 DAYS

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Other Supportive Care:

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

Panitumumab:

The following has been shown to be of benefit (in a randomized phase 2 study for prevention of rash) when used from day -1 to week 6:

- Skin moisturizer applied to the face, hands, feet, neck, back and chest in the morning
- Sunscreen to exposed areas (SPF 30, UVA and UVB) in the morning
- Hydrocortisone cream (1%) to the face, hands, feet, neck, back and chest at bedtime
- Doxycycline (or minocycline) PO

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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 acute grade 2-4 toxicity develops, treatment should be stopped immediately and permanent discontinuation considered based on clinical assessment of the toxicities.

Dosage with toxicity

Dose modifications for FOLFOX

Toxicity Grade	Oxaliplatin^	Fluorouracil^
Persistent(1) Grade 2 neurotoxicity	↓ from 85 → 65 mg/m^2	No change
Transient(1) Grade 3 neurotoxicity	↓ from 85 → 65 mg/m^2	No change
Persistent(1) ≥ Grade 3 neurotoxicity or any Grade 4 neurotoxicity	Discontinue	No change
≥ Grade 3 GI toxicity (after prophylaxis) OR Grade 3 or 4 Platelets OR Grade 3 or 4 Neutropenia (including febrile neutropenia)*	↓ from 85 → 65 mg/m^2 *	Reduce by 20% *
Sepsis / septic shock	Discontinue	Discontinue
Other ≥ grade 3 related organ toxicity(2)	↓ from 85 → 65 mg/m^2	Reduce by 20%
Pharyngolaryngeal dysesthesia	Hold; then increase duration of infusion to 6 hours(3)	No change
Pneumonitis	Hold, investigate; discontinue permanently if confirmed.	
RPLS or Hemolytic uremic syndrome or any signs of microangiopathic hemolytic anemia	Discontinue permanently	

^Do not re-treat until the ANC ≥ 1.5 x 10^9/L and the platelets ≥ 75-100 x 10^9/L, GI and neurotoxicities have resolved and

other non-hematologic toxicities ≤ grade 1.

[1] Transient = >7 days - <1 cycle; persistent = ≥ 1 cycle

[2] For skin toxicity, reduce 5FU dose only

[3] If oxygen saturation is normal, an anxiolytic agent may be given.

* Discontinue if sepsis / septic shock

Dose modifications for panitumumab

Toxicity	Action	Panitumumab dose (% 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.
Mild to moderate hypersensitivity	↓ Infusion rate by 50%	n/a
Severe hypersensitivity	Hold and consider discontinuing permanently	n/a
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.		

Hepatic Impairment

No dosage adjustment is requried for leucovorin. Omit leucovorin if 5-fluorouracil is omitted.

Bilirubin		AST/ALT	oxaliplatin	5-fluorouracil	panitumumab
1-2 x ULN			no change	Caution	no data
>2 and ≤ 4 x ULN	And/or	2-4 x ULN	no change	Caution	no data
>4 x ULN	And/or	4 x ULN	no data	OMIT if Bilirubin > 4 x ULN	no data
ANY	And	> 4 X ULN	no data	OMIT if Bilirubin > 4 x ULN	no data

Renal Impairment

Acute renal failure has been observed in patients experiencing severe diarrhea and dehydration (see dosage with toxicity table for management). No dosage adjustment is required for leucovorin.

Creatinine Clearance (mL/min)	oxaliplatin	5-fluorouracil	panitumumab
50-80	no change	no change	no change
30-<50	Caution	no change	no data
<30	discontinue	caution, consider dose ↓	no data

Dosage in the Elderly

No overall differences in safety or efficacy were observed in patients aged 65 and older compared to younger patients. No dose modifications are required, however patients ≥ 65 years have more eye, skin, GI toxicities and fatigue, compared to younger patients when receiving panitumumab in combination with FOLFOX.

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F - Adverse Effects

Refer to oxaliplatin, leucovorin, fluorouracil, PANitumumab 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) • Neuropathy (may be severe) • Myelosuppression +/- infection, bleeding (may be severe) • Nausea, vomiting • Increased LFTs • Diarrhea (may be severe)	• Fatigue • Mucositis • Abnormal electrolytes (hypomagnesemia) • Paronychia • Anorexia, weight loss • Abdominal pain	• Constipation • Skin fissures • Cough, dyspnea • Edema • Musculoskeletal pain • Hand-foot syndrome • Abnormal eyelash growth • Pharyngolaryngeal dysesthesia	• GI obstruction • Hemorrhage • Hypersensitivity • Renal failure • Arterial / venous thromboembolism • Cardiotoxicity • Arrhythmia • Pancreatitis • Pneumonitis • Rhabdomyolysis • Hemolysis • Hemolytic uremic syndrome, ITP • Leukoencephalopathy • Guillain-Barre syndrome • Eye disorders • Radiation recall • Soft tissue necrosis • Veno-occlusive disease

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G - Interactions

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

- Monitor INR with warfarin and drug levels with phenytoin and adjust doses as needed.
- Monitor renal function closely with nephrotoxic drugs.

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H - Drug Administration and Special Precautions

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

Administration

Oxaliplatin:

- Oxaliplatin should always be administered before fluorouracil.
- May be mixed in 250-500 mL bag (D5W only - not NS, chloride containing or alkaline solutions, and should not be mixed with fluorouracil) and given by slow infusion. Concentration must be between 0.2 to 0.7 mg/mL
- Infuse IV over 2 hours. Increasing infusion time to 6 hours may decrease acute toxicity such as pharyngolaryngeal dysesthesia.
- Infusion may be given at the same time as Leucovorin in separate bags using a Y-site (not in the same bag) providing trometamol is not used as an excipient. May not be administered with fluorouracil.
- Do not use with injection equipment containing aluminum, as this can degrade platinum compounds.
- Unopened vials should be stored at 15-30°C; protect from light.

Leucovorin:

- 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.
- Continuous infusion using CADD pump or similar device.
- Leucovorin should not be mixed in the same infusion as 5-fluorouracil as a precipitate may form.
- Keep refrigerated; protect from light.

5-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

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 less than 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.
- Keep vials refrigerated in the original carton. Protect from direct sunlight and do not freeze.
- The manufacturer recommends diluted solutions to be used within 6 hours of preparation if stored at room temperature, or within 24 hours of dilution if stored at 2° to 8°C.

Contraindications:

- Oxaliplatin is contraindicated in patients with hypersensitivity to the drug or to other platinum agents (e.g. cisplatin, carboplatin) and in patients with severe renal impairment (Clcr < 30 mL/min). Patients should be warned about cold avoidance prior to treatment and ice for mucositis prophylaxis should not be used.
- Patients with hypersensitivity to leucovorin, fluorouracil, panitumumab or excipients in these products.
- Patients with ECOG performance status of 3 or 4.
- Patients with moderate to severe hepatic impairment.
- Patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity. Refer to the DPD Deficiency Guidance for Clinicians for more information.
- Do not use panitumumab in combination with bevacizumab.

Warnings / precautions:

- 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.
- Use with caution in patients with serious infections, poor nutritional state, those 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.
- Use with caution in patients with a history of pulmonary fibrosis or ILD.
- 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.
- If patients experience treatment-related effects on vision and/or ability to concentrate and react, they should not drive or operate machinery until the effect subsides.
- 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 **contraindicated** 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 **contraindicated** during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).

- Effects on fertility: Yes

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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; Baseline and before each dose
- Liver and renal function tests; baseline and before each dose
- Electrolytes (including calcium, magnesium and potassium); baseline and at each visit, until 8 weeks after completion of therapy
- Clinical pulmonary exam; Baseline and clinically as indicated
- Clinical assessment and grading of GI, skin, neurologic and respiratory effects, infusion reactions, infection, bleeding, cardiac and ophthalmic effects; at each visit

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

Suggested Clinical Monitoring

Pulmonary function tests; Baseline

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J - Administrative Information

Approximate Patient Visit	3.5 to 4 hours
Pharmacy Workload (average time per visit)	47.493 minutes
Nursing Workload (average time per visit)	79.167 minutes

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K - References

Panitumumab, oxaliplatin, fluorouracil, leucovorin drug monographs, Cancer Care Ontario.

Schwartzberg LS, Rivera F, Karthaus M, et al. PEAK: a randomized, multicenter phase II study of

panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol 2014;32(21):2240-7.

PEBC Advice Documents or Guidelines

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

November 2023 Modified Pregnancy/lactation 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.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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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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