BC Cancer Protocol Summary for Palliative Combination Chemotherapy for Metastatic Colorectal Cancer using Oxaliplatin, Fluorouracil, Leucovorin, and PANitumumab

Protocol Code:	*GIFFOXPAN*
Tumour Group:	*Gastrointestinal*
Contact Physician:	*GI Systemic Therapy*

ELIGIBILITY:
Patients must have:
- Metastatic colorectal adenocarcinoma not suitable for bevacizumab therapy,
- Wild type RAS (tested on primary or metastatic tumour),
- Wild type BRAF (tested on primary or metastatic tumour), and
  - No prior chemotherapy in the advanced setting, or
  - Received single agent capecitabine or fluorouracil treatment first-line as the result of frailty, but who are now well enough to receive combination chemotherapy, or
  - Progressed on single agent capecitabine or fluorouracil therapy first-line and treatment escalation/combination chemotherapy is desired

Patients should have:
- ECOG performance status 0 to 2
- Adequate marrow reserve, renal and liver function

Note: Patient treated with this regimen would not be eligible for subsequent-line EGFR inhibitor therapy (unless BRAF mutation newly identified). See funding algorithm for more details.

EXCLUSIONS:
Patients must not have:
- Mutant RAS or mutant BRAF tumours
- Interstitial pneumonitis or pulmonary fibrosis
- Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions)
- Avoid oxaliplatin in patients with congenital long QT syndrome.

CAUTIONS:
- Patients with: 1) previous pelvic radiotherapy; 2) recent MI; 3) uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure, or other serious medical illness.
- Patients with baseline greater than 3 loose BM per day (in patients without colostomy or ileostomy.)
- Patients with symptomatic peripheral neuropathy.

TESTS AND MONITORING:

- **Baseline:** CBC and differential, platelets, creatinine, LFTs (bilirubin, ALT, alkaline phosphatase), sodium, potassium, magnesium, calcium, *DPYD* test (not required if previously tested, or tolerated fluorouracil or capecitabine), appropriate imaging study. Optional: CEA, CA 19-9.
- **Prior to each cycle:** CBC and differential, platelets, creatinine, LFTs (bilirubin, ALT, alkaline phosphatase), sodium, potassium, magnesium, calcium
- For patients on warfarin, weekly INR during fluorouracil therapy until stable warfarin dose established, then INR prior to each cycle.
- If clinically indicated: CEA, CA 19-9
- Baseline and routine ECGs for patients at risk of developing QT prolongation (at the discretion of the ordering physician). See Precautions.
- Quantitative evaluation of disease response status every six to twelve weeks; discontinue therapy if any progression of disease.
- **Post-treatment:** monthly sodium, potassium, magnesium, calcium for 2 months after last treatment dose or as recommended by MRP.

PREMEDICATIONS:

- Antiemetic protocol for high-moderate emetogenic chemotherapy (see SCNAUSEA)
- **Counsel patients to avoid cold drinks and exposure to cold air, especially for 3-5 days following oxaliplatin administration.**
- **Cryotherapy (ice chips) should NOT be used as many exacerbate Oxaliplatin-induced pharyngo-laryngeal dysesthesias.**
- Consider preemptive therapy for PANitumumab-induced dermatologic toxicity (see below).

TREATMENT:

DRUG	DOSE	BC Cancer Administration Guidelines
PANitumumab	6 mg/kg	IV in NS 100 mL over 1 hour using a 0.2 micron in-line filter If tolerated, administer over 30 minutes in subsequent cycles. Flush lines pre and post infusion with NS.
oxaliplatin**	85 mg/m^2	IV in D5W 250 to 500 mLover 2 hours. Flush lines pre infusion with D5W (oxaliplatin is NOT compatible with NS).
leucovorin**	400 mg/m^2	IV in D5W 250 mL over 2 hours
fluorouracil	400 mg/m^2	IV push, after Leucovorin, THEN
fluorouracil	2400 mg/m^2	IV over 46 hours in D5W to a total volume of 230 mL by continuous infusion at 5 mL/h via Baxter LV5 INFUSOR ***

Repeat every 14 days until disease progression or unacceptable toxicity.

****Oxaliplatin and leucovorin may be infused over the same two hour period by using a Y- site connector placed immediately before the injection site. Oxaliplatin and leucovorin should not be combined in the same infusion bag. Oxaliplatin is not compatible with normal saline. Do not piggyback or flush lines with normal saline immediately before or after oxaliplatin. *Leucovorin dose remains at 400 mg/m^2 IV over 2 hours when concurrent oxaliplatin is omitted.***

*** Alternative administration:

- For 3000 to 5500 mg dose **select INFUSOR per dose range below (doses outside** dose banding range are **prepared as ordered**)**:**

Dose Banding Range	Dose Band INFUSOR (mg)
Less than 3000 mg	Pharmacy to mix specific dose
3000 to 3400 mg	3200 mg
3401 to 3800 mg	3600 mg
3801 to 4200 mg	4000 mg
4201 to 4600 mg	4400 mg
4601 to 5000 mg	4800 mg
5001 to 5500 mg	5250 mg
Greater than 5500 mg	Pharmacy to mix specific dose

- Inpatients: 1200 mg/m^2/day in D5W 1000 mL continuous infusion daily over 23 h for two days

Patients with PICC lines should have a weekly assessment of the PICC site for evidence of infection or thrombosis.

DOSE MODIFICATIONS (A,B,C,D,E):

Fluorouracil Dosing Based on DPYD Activity Score (DPYD-AS)
Refer to "Fluorouracil and Capecitabine Dosing Based on DPYD Activity Score (DPYD-AS)" on www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual.

A. Dose Modifications for NEUROLOGIC Toxicity (oxaliplatin)
B. Dose Modifications for HEMATOLOGIC Toxicity (oxaliplatin and fluorouracil)
C. NON-HEMATOLOGIC, NON-NEUROLOGIC Toxicity (oxaliplatin, fluorouracil and PANitumumab)
D. DERMATOLOGIC Toxicity (PANitumumab)
E. HYPOMAGNESEMIA (PANitumumab)

Table 1 - Dose Reduction Levels for oxaliplatin, fluorouracil and PANitumumab (A,B,C)

Agent	Starting Dose	Dose Level -1	Dose Level -2*
oxaliplatin	85 mg/m^2	65 mg/m^2	50 mg/m^2
fluorouracil IV push	400 mg/m^2	320 mg/m^2	200 mg/m^2
fluorouracil Infusion	2400 mg/m^2	2000 mg/m^2	1600 mg/m^2
PANitumumab	6 mg/kg	4.8 mg/kg	3.6 mg/kg

If IV push fluorouracil is delayed/omitted, leucovorin may also be delayed/omitted or reduced to 20 mg/m^2 IV push.

*** For any additional dose reductions, use 20% less than previous level or consider discontinuing this regimen.**

Table 2 - Oxaliplatin Neurotoxicity Definitions

Grade 1	Paresthesias / dysesthesias of short duration that resolve; do not interfere with function
Grade 2	Paresthesias / dysesthesias interfering with function, but not activities of daily living (ADL)
Grade 3	Paresthesias / dysesthesias with pain or with functional impairment which interfere with ADL
Grade 4	Persistent paresthesias / dysesthesias that are disabling or life-threatening
Pharyngo-laryngeal dysesthesias (investigator discretion used for grading): Grade 0 = none; Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe	

Neuropathy may be partially or wholly reversible after discontinuation of therapy; patients with good recovery from Grade 3 (not Grade 4) neuropathy may be considered for re-challenge with Oxaliplatin, with starting dose one level below that which they were receiving when neuropathy developed

A. Dose Modifications for Oxaliplatin NEUROLOGIC Toxicity

Toxicity Grade	**Duration of Toxicity**		**Persistent (present at start of next cycle)**
	1 – 7 days	**greater than 7 days**	
Grade 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	Maintain dose level	Maintain dose level	Decrease 1 dose level
Grade 3	1st time: ↓ 1 dose level 2nd time: ↓ 1 dose level	1st time: ↓ 1 dose level 2nd time: ↓ 1 dose level	Discontinue
Grade 4	Discontinue therapy	Discontinue therapy	Discontinue therapy
Pharyngolaryngeal **(see precautions)**	Increase duration of infusion to 6 hours	N/A	N/A

B. Dose Modifications for HEMATOLOGIC Toxicity (oxaliplatin and fluorouracil)

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	**ANC ($x10^9$/L)**	**oxaliplatin**	**fluorouracil**
▪ If ANC less than 1.2 on Day 1of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. ▪ If ANC is greater than or equal to 1.2 within 2 weeks, proceed with treatment at the dose level noted across from the **lowest ANC** result of the delayed week(s). ▪ If ANC remains less than 1.2 after 2 weeks, discontinue treatment.	1	greater than or equal to 1.2	Maintain dose level	Maintain dose level
	2	1.0 to less than 1.2	Maintain dose level	Maintain dose level
	3	0.5 to less than 1.0	↓ 1 dose level	Maintain dose level
	4	less than 0.5	↓ 1 dose level	omit IV push and ↓ 1 infusion dose level
	Grade	**Platelets ($x10^9$/L)**	**oxaliplatin**	**fluorouracil**
▪ If platelets less than 75 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. ▪ If platelets greater than or equal to 75 within 2 weeks, proceed with treatment at the dose level noted across from the **lowest platelets** result of the delayed week(s). ▪ If platelets remain less than 75 after 2 weeks, discontinue treatment.	1	greater than or equal to 75	Maintain dose level	Maintain dose level
	2	50 to less than 75	Maintain dose level	Maintain dose level
	3	10 to less than 50	↓ 1 dose level	Maintain dose level
	4	less than 10	↓ 2 dose levels	Maintain dose level

C. Dose Modifications for NON-HEMATOLOGIC, NON-NEUROLOGIC Toxicity (oxaliplatin, fluorouracil and PANitumumab)

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles
	Grade	**Diarrhea**	
▪ If diarrhea greater than or equal to Grade 2 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum 2 times. ▪ If diarrhea is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the **highest** Grade experienced. ▪ If diarrhea remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.	1	Increase of 2 to 3 stools/day, or mild increase in loose watery colostomy output	Maintain dose level
	2	Increase of 4 to 6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Maintain dose level
	3	Increase of 7 to 9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	↓ 1 dose level of IV push and infusional fluorouracil; ↓ 1 dose level of PANitumumab
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	↓ 1 dose level of oxaliplatin, IV push and infusional fluorouracil; ↓ 1 dose level of PANitumumab
	Grade	**Stomatitis**	
▪ If stomatitis greater than or equal to Grade 2 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum 2 times. ▪ If stomatitis is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the **highest** Grade experienced. ▪ If stomatitis remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.	1	Painless ulcers, erythema or mild soreness	Maintain dose level
	2	Painful erythema, edema, or ulcers but can eat	Maintain dose level
	3	Painful erythema, edema, ulcers, and cannot eat	↓ 1 dose level of IV push and infusional fluorouracil
	4	As above but mucosal necrosis and/or requires enteral support, dehydration	↓ 1 dose level of oxaliplatin, IV push and infusional fluorouracil

D. Dose Modifications for PANitumumab Dermatologic Toxicity

As a class, EGFR Inhibitors are characterized by cutaneous adverse effects, most commonly a papulopustular reaction involving the skin of the face and upper torso. This can leave the skin vulnerable to bacterial overgrowth and serious infection which may require aggressive interventions.
A well characterized clinical course has been identified. Within week 1 of treatment patients experience sensory disturbance with erythema and edema. During weeks 1 to 3 (median time of 14 days after start of therapy) the papulopustular eruption manifests, followed by crusting at week 4. Despite effective

treatment for rash, erythema and dry skin may persist in the areas previously affected during weeks 4 to 6. Most patients exhibit some degree of partial improvement during therapy and the rash generally resolves completely and without scarring following cessation of therapy (median time of 84 days after the last dose.)

Consideration should be given to preemptive or reactive treatment of EGFR Inhibitor skin toxicity. **Preemptive therapy** includes doxycycline (or minocycline) 100 mg po bid and clindamycin 2%/hydrocortisone 1% skin lotion at cycle 1 for the first six weeks. Preemptive therapy was compared to reactive management and resulted in decreased grade ≥ 2 skin toxicity and decreased impairment in quality of life.

Reactive management is summarized below.

Grade	Toxicity (adapted from CTCAE and Melosky et al.)	PANitumumab dose
1	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness OR Macular or papular eruption or erythema with no associated symptoms	Maintain dose level Consider clindamycin 2% and hydrocortisone 1% in a lotion to be applied topically BID as needed.
2	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms OR Macular or papular eruption or erythema with pruritus or other symptoms that are tolerable or interfere with daily life	Maintain dose level Consider clindamycin 2% and hydrocortisone 1% in a lotion to be applied topically BID as needed and minocycline 100 mg PO BID for 1 to 2 weeks or longer as needed.
3	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated OR Severe, generalised erythroderma or macular, papular or vesicular eruption	Withhold infusion for 2 to 4 weeks: ▪ When improvement to Grade 2 or less, resume at: 1st occurrence: Resume at 100% of previous dose 2nd occurrence: Resume at 80% of previous dose 3rd occurrence: Resume at 60 % of previous dose Continue treatment with clindamycin 2% and hydrocortisone 1% in a lotion to be applied topically BID as needed and minocycline 100 mg PO BID for 1 to 2 weeks or longer as needed.
4	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated OR Generalized exfoliative, ulcerative or blistering skin toxicity	Discontinue treatment.

The prevention or management of EGFR inhibitor related skin toxicities not only improves or maintains patient quality of life, it prevents dose reduction or discontinuation of potentially effective therapy.

It is recommended that patients wear sunscreen and a hat and limit sun exposure as sunlight can exacerbate any skin reactions.

Activities and skin care products that dry the skin should be avoided such as long, hot showers, alcohol-based or perfumed skin care products. Greasy ointments should be avoided. Frequent moisturizing with alcohol-free emollient creams is recommended.

This rash is distinct from acne vulgaris and therefore, other topical acne treatments should not be applied.

Other less frequent manifestations are: dry skin, pruritus, fissures, palmar-plantar rash, hyperkeratosis, telangiectasia, hyperpigmentation, and blisters.

E. Dose Modifications and Management for PANitumumab Hypomagnesemia

Serious cases may be asymptomatic and have been reported greater than 6 weeks after initiation of treatment. Symptoms include severe weakness and fatigue. Concern is cardiac arrhythmias which may be associated with hypokalemia. Magnesium levels should be monitored closely and regular infusions of Magnesium Sulfate as well as oral supplementation may be required. Monitoring of potassium and calcium may also be required.

IV	Serum Magnesium	Management
1	0.5 mmol/L to less than LLN	Continue PANitumumab. Consider daily oral magnesium replacement
2	0.4 to less than 0.5 mmol/L	Continue PANitumumab and initiate daily oral magnesium replacement and magnesium sulfate 5 G IV in 100 mL NS over 3 hours every 2 weeks
3	0.3 to less than 0.4 mmol/L	if symptomatic - hold PANitumumab until improved to Grade 2. If asymptomatic – increase supplementation to magnesium sulfate 5 G IV in 100 mL NS over 3 hours weekly
4	Less than 0.3 mmol/L	Hold PANitumumab until asymptomatic and improved to Grade 2 – increase supplementation to magnesium sulfate 5 G IV in 100 mL NS over 3 hours twice weekly.

Oral preparations of magnesium may be poorly tolerated resulting in poor compliance due to potential for diarrhea. Diarrhea is dose dependent. Combination product with calcium may reduce incidence of diarrhea.

Magnesium Preparation	Elemental Magnesium content	Dosage
Magnesium complex	Each 250 mg tablet contains 250 mg	1 tablet twice daily
Magnesium glucoheptonate	Each 15 mL of 100 mg/mL solution contains 76.8 mg	15 to 30 mL up to 4 times daily
Magnesium oxide	Each 420 mg tablet contains 252 mg	1 tablet twice daily
Calcium/Magnesium	Each 333/167 tablet contains 167 mg	1 tablet 3 times daily

PRECAUTIONS:

1. **Platinum hypersensitivity** can cause dyspnea, bronchospasm, itching and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, epinephrine and bronchodilators. Vasopressors may be required. (see below)
   For Grade 1 or 2 acute hypersensitivity reactions no dose modification of oxaliplatin is required and the patient can continue treatment with standard hypersensitivity premedication:
   45 minutes prior to oxaliplatin:
   - dexamethasone 20 mg IV in 50 mL NS over 15 minutes

   30 minutes prior to oxaliplatin:
   - diphenhydrAMINE 50 mg IV in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)

   Reducing infusion rates (e.g., from the usual 2 hours to 4-6 hours) should also be considered since some patients may develop more severe reactions when rechallenged, despite premedications.

   The practice of rechallenging after severe life-threatening reactions is usually discouraged, although desensitization protocols have been successful in some patients. The benefit of continued treatment must be weighed against the risk of severe reactions recurring. The product monograph for oxaliplatin lists rechallenging patients with a history of severe HSR as a contraindication. Various desensitization protocols using different dilutions and premedications have been reported. Refer to USCOXRX: BC Cancer Inpatient Protocol Summary for Oxaliplatin Desensitization for more information.
2. **PANitumumab Hypersensitivity Reactions (HSR):** severe infusion reactions, including anaphylactic reactions, bronchospasm and hypotension have occurred with the administration of PANitumumab in approximately 1% of patients, very rarely with a fatal outcome. Late onset HSR have also occurred and it is recommended that patients be warned of this possibility.
3. **Pharyngo-laryngeal dysesthesia** is an unusual dysesthesia characterized by an uncomfortable persistent sensation in the area of the laryngopharynx without any objective evidence of respiratory distress (i.e. absence of hypoxia, laryngospasm or bronchospasm). This may be exacerbated by exposure to cold air or foods/fluids. If this occurs during infusion, stop infusion immediately and observe patient. Rapid resolution is typical, within minutes to a few hours. Check oxygen saturation; if normal, an anxiolytic agent may be given. The infusion can then be restarted at a slower rate at the physician's discretion. In subsequent cycles, the duration of infusion should be prolonged (see Dose Modifications above in the Neurological Toxicity table).

Clinical Symptoms	**Pharyngo-laryngeal Dysesthesia**	**Platinum Hypersensitivity**
Dyspnea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
O_2 saturation	Normal	Decreased
Difficulty swallowing	Present (loss of sensation)	Absent
Pruritus	Absent	Present
Cold induced symptoms	Yes	No
Blood Pressure	Normal or Increased	Normal or Decreased
Treatment	Anxiolytics; observation in a controlled clinical setting until symptoms abate or at physician's discretion	Oxygen, steroids, epinephrine, bronchodilators; Fluids and vasopressors if appropriate

4. **QT prolongation and torsades de pointes** has been reported with oxaliplatin: Use caution in patients with history of QT prolongation or cardiac disease and those receiving concurrent therapy with other QT prolonging medications. Correct electrolyte disturbances prior to treatment and monitor periodically. Baseline and periodic ECG monitoring is suggested in patients with cardiac disease, arrhythmias, concurrent drugs known to cause QT prolongation, and electrolyte abnormalities. In case of QT prolongation, oxaliplatin treatment should be discontinued. QT effect of oxaliplatin with single dose ondansetron 8 mg prechemo has not been formally studied. However, single dose ondansetron 8 mg po would be considered a lower risk for QT prolongation than multiple or higher doses of ondansetron, as long as patient does not have other contributing factors as listed above.
5. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
6. Oxaliplatin therapy should be interrupted if symptoms indicative of **pulmonary fibrosis** develop – nonproductive cough, dyspnea, crackles, rales, hypoxia, tachypnea or radiological pulmonary infiltrates. If pulmonary fibrosis is confirmed oxaliplatin should be discontinued.
7. **Interstitial Lung Disease**: has been observed with EGFR inhibitors. Interstitial lung disease and interstitial pneumonitis are rare (<1% for PANitumumab). Worsening of preexisting lung conditions is also reported with PANitumumab. Investigation of acute symptoms is warranted and PANitumumab should be withheld in the event of onset or worsening of respiratory symptoms. If pneumonitis or lung infiltrates are confirmed, treatment should be discontinued.
8. **Extravasation**: Oxaliplatin causes irritation if extravasated. Refer to BC Cancer Extravasation Guidelines.
9. **Venous Occlusive Disease** is a rare but serious complication that has been reported in patients (0.02%) receiving oxaliplatin in combination with fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Patients should be instructed to report any jaundice, ascites or hematemesis immediately.
10. Oxaliplatin therapy should be interrupted if **Hemolytic Uremic Syndrome (HUS)** is suspected: hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.
11. **Myocardial** ischemia and angina occurs rarely in patients receiving fluorouracil or capecitabine. Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment. If there is development of cardiac symptoms patients should have urgent cardiac assessment. Generally re-challenge with either fluorouracil or capecitabine is not recommended as symptoms potentially have a high likelihood of recurrence which can be severe or even fatal. Seeking opinion from cardiologists and oncologists with expert knowledge about fluorouracil / capecitabine toxicity is strongly advised under these circumstances. The toxicity should also be noted in the patient's allergy profile.
12. **Diarrhea:** Patients should report mild diarrhea that persists over 24 hours or moderate diarrhea (4 stools or more per day above normal, or a moderate increase in ostomy output). Mild diarrhea can be treated with loperamide (eg. IMODIUM®) following the manufacturer's directions or per the BC Cancer Guidelines for Management of Chemotherapy-Induced Diarrhea. In addition to the risk of diarrhea induced dehydration, patients on warfarin are at risk for an elevation in INR and an increased risk of bleeding. Acute renal failure has been observed in patients with severe diarrhea and dehydration receiving PANitumumab. PANitumumab and chemotherapy should be withheld until resolution.
13. **Dihydropyrimidine dehydrogenase (DPD) deficiency** may result in severe and unexpected toxicity – stomatitis, diarrhea, neutropenia, neurotoxicity – secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population.
14. **Possible drug interaction with fluorouracil and warfarin** has been reported and may occur at any time. For patients on warfarin, weekly INR during fluorouracil therapy is recommended until a stable warfarin dose is established. Thereafter, INR prior to each cycle. Consultation to cardiology/internal medicine should be considered if difficulty in establishing a stable warfarin dose is encountered. Upon discontinuation of fluorouracil, repeat INR weekly for one month.

15. **Possible drug interaction with fluorouracil and phenytoin and fosphenytoin** has been reported and may occur at any time. Close monitoring is recommended. Fluorouracil may increase the serum concentration of these two agents.

Call the GI Systemic Therapy physician at your regional cancer centre or the GI Systemic Therapy Chair Dr. Theresa Chan at (604) 930-2098 with any problems or questions regarding this treatment program.

References:

1. Schwartzberg L., 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;32:2240-2247.
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5. Lacouture M., Mitchell E., 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(8):1351-1357.