

# BC Cancer Protocol Summary for Adjuvant Chemotherapy for Resected Pancreatic Adenocarcinoma Using Irinotecan, Oxaliplatin, Fluorouracil and Leucovorin

**Protocol Code:** GIPAJFIROX

**Tumour Group:** Gastrointestinal

**Contact Physician:** GI Systemic Therapy

## ELIGIBILITY:

- Resected pancreatic adenocarcinoma.
- Macroscopic complete resection (R0 or R1)
- ECOG 0-1

## EXCLUSIONS:

- Distant metastases
- Inflammatory bowel disease
- Uncontrolled hypertension, unstable angina, symptomatic congestive heart failure, myocardial infarction within the preceding 6 months, serious uncontrolled cardiac dysrhythmia
- Active infection
- Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions)
- Avoid in patients with congenital long QT syndrome

## CAUTIONS:

- [Adequate marrow reserve, renal and liver function](#)
- Patients with previous pelvic radiotherapy, 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
- [Patients with baseline hyperbilirubinemia \(greater than 26 micromol/L\)](#)

## TESTS AND MONITORING:

- Baseline CBC and differential, platelets, creatinine, LFTs (bilirubin, ALT, alkaline phosphatase), sodium, potassium, magnesium, calcium, random glucose, appropriate imaging study. Optional CA 19-9.
- **At the beginning of each cycle:** CBC and differential, platelets, creatinine, LFT's (bilirubin, ALT, alkaline phosphatase), sodium, potassium, magnesium, calcium, random glucose.
- If clinically indicated: CA 19-9
- For patients on warfarin, weekly INR during fluorouracil therapy until stable warfarin dose established, then INR at beginning of each cycle.
- Baseline and routine ECG for patients at risk of developing QT prolongation (at the discretion of the ordering physician). See Precautions.

**PREMEDICATIONS:**

- Antiemetic protocol for highly emetogenic chemotherapy (see SCNAUSEA)
- Atropine may be required for treatment or prophylaxis of diarrhea (see precautions)
- Prochlorperazine should be avoided on the same day as irinotecan treatment due to the increased incidence of akathisia.
- **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 may exacerbate Oxaliplatin-induced pharyngo-laryngeal dysesthesias.**

**TREATMENT:**

A cycle equals:

Drug	Dose	BC Cancer Administration Guidelines
oxaliplatin*	85 mg/m <sup>2</sup>	IV in 250 to 500 mL of D5W over 2 hours immediately followed by
leucovorin	400 mg/m <sup>2</sup>	IV in 250 mL D5W 1 hour 30 minutes
irinotecan	150 mg/m <sup>2</sup>	IV in 500 mL of D5W over 1 hour 30 minutes** Immediately followed by:
fluorouracil	2400 mg/m <sup>2</sup>	IV over 46 h in D5W to a total volume of 230 mL by continuous infusion at 5 mL/h via Baxter LV5 INFUSOR ***

Repeat every 14 days for a maximum of 12 cycles.

**\* Oxaliplatin is not compatible with normal saline. Do not piggyback or flush lines with normal saline.**

**\*\* Irinotecan and leucovorin may be infused at the same time by using a Y-connector placed immediately before the injection site. Irinotecan and leucovorin should not be combined in the same infusion bag. Leucovorin dose remains at 400 mg/m<sup>2</sup> IV over 1 hour and 30 minutes when concurrent irinotecan 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<sup>2</sup>/day in 1000 mL D5W by continuous infusion daily over 23 h for 2 days

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

All patients should be advised to obtain an adequate supply of loperamide (IMODIUM®) with directions for the management of diarrhea.

### DOSAGE MODIFICATIONS (A, B & C)

- A. Dose Modifications for NEUROLOGIC Toxicity
- B. Dose Modifications for HEMATOLOGIC Toxicity
- C. Dose Modifications for NON-HEMATOLOGIC, NON-NEUROLOGIC Toxicity

**Table 1 - Dose Reduction Levels for All Toxicity**

Agent	Starting Dose	Dose Level -1*
irinotecan	150 mg/m <sup>2</sup>	120 mg/m <sup>2</sup>
oxaliplatin	85 mg/m <sup>2</sup>	60 mg/m <sup>2</sup>
fluorouracil Infusion	2400 mg/m <sup>2</sup>	1800 mg/m <sup>2</sup>

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

**Table 2 - Oxaliplatin Neurotoxicity Definitions**

<b>Grade 1</b>	Paresthesias / dysesthesias of short duration that resolve; do not interfere with function
<b>Grade 2</b>	Paresthesias / dysesthesias interfering with function, but not activities of daily living (ADL)
<b>Grade 3</b>	Paresthesias / dysesthesias with pain or with functional impairment which interfere with ADL
<b>Grade 4</b>	Persistent paresthesias / dysesthesias that are disabling or life-threatening
<b>Pharyngo-laryngeal dysesthesias (investigator discretion used for grading):</b> 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	
<b>Grade 1</b>	Maintain dose level	Maintain dose level	Maintain dose level
<b>Grade 2</b>	Maintain dose level	Maintain dose level	Decrease 1 dose level
<b>Grade 3</b>	1 <sup>st</sup> time: ↓ 1 dose level 2 <sup>nd</sup> time: Discontinue	1 <sup>st</sup> time: ↓ 1 dose level 2 <sup>nd</sup> time: Discontinue	Discontinue
<b>Grade 4</b>	Discontinue therapy	Discontinue therapy	Discontinue therapy
Pharyngo-laryngeal (see precautions)	Increase duration of infusion to 6 hours	N/A	N/A

**May continue Irinotecan and 5-FU, even if oxaliplatin is discontinued due to neurotoxicity.**

**B. Dose Modifications for HEMATOLOGIC Toxicity based on day 1 CBC**

	CYCLE DELAY	DOSE REDUCTION		
		irinotecan	oxaliplatin	leucovorin / fluorouracil
ANC greater than or equal to $1.5 \times 10^9/L$ and platelets greater than or equal to $100 \times 10^9/L$	No cycle delay	No dose reduction		
ANC less than $1.5 \times 10^9/L$	<p>Delay the treatment until ANC greater than or equal to <math>1.5 \times 10^9/L</math> (until week 3 or week 4 if necessary) and resume cycle with G-CSF*</p> <p>If no recovery by week 4, consider discontinuing treatment, or add G-CSF*, or maintain only infusional fluorouracil**</p>	<p><b>1<sup>st</sup> episode:</b> dose reduction to <math>120 \text{ mg}/\text{m}^2</math></p> <p><b>2<sup>nd</sup> episode:</b> maintain dose at <math>120 \text{ mg}/\text{m}^2</math></p> <p><b>3<sup>rd</sup> episode:</b> discontinue treatment or maintain only infusional fluorouracil**</p>	<p><b>1<sup>st</sup> episode:</b> no dose reduction</p> <p><b>2<sup>nd</sup> episode:</b> dose reduction to <math>60 \text{ mg}/\text{m}^2</math></p> <p><b>3<sup>rd</sup> episode:</b> discontinue treatment or maintain only infusional fluorouracil**</p>	<p><b>1<sup>st</sup> episode:</b> no dose reduction</p>
		<b>NOTE: Dose reductions should be maintained for subsequent cycles.</b>		
At any time during the cycle: Febrile neutropenia or ANC less than $0.5 \times 10^9/L$ for more than 7 days, or infection with ANC less than $1.0 \times 10^9/L$		<p><b>1<sup>st</sup> episode:</b> dose reduction to <math>120 \text{ mg}/\text{m}^2</math> and add G-CSF</p> <p><b>2<sup>nd</sup> episode:</b> maintain dose at <math>120 \text{ mg}/\text{m}^2</math></p> <p><b>3<sup>rd</sup> episode:</b> consider discontinuing treatment or further dose reduction or maintain only infusional fluorouracil**</p>	<p><b>1<sup>st</sup> episode:</b> no dose reduction</p> <p><b>2<sup>nd</sup> episode:</b> dose reduction to <math>60 \text{ mg}/\text{m}^2</math></p> <p><b>3<sup>rd</sup> episode:</b> consider discontinuing treatment or further dose reduction or maintain only infusional fluorouracil**</p>	<p><b>1<sup>st</sup> episode:</b> no dose reduction</p>
		<b>NOTE: Dose reductions should be maintained for subsequent cycles.</b>		

	CYCLE DELAY	DOSE REDUCTION		
		irinotecan	oxaliplatin	leucovorin / fluorouracil
Platelets less than 100 x 10 <sup>9</sup> /L	<p>Delay the treatment until recovery (platelets greater than or equal to 100x10<sup>9</sup>/L).</p> <p>If no recovery by week 4, <b>consider discontinuing treatment.</b></p>	<p><b>1<sup>st</sup> episode:</b> no dose reduction</p> <p><b>2<sup>nd</sup> episode:</b> dose reduction to 120 mg/m<sup>2</sup></p> <p><b>3<sup>rd</sup> episode:</b> <b>consider discontinuing treatment</b></p>	<p><b>1<sup>st</sup> episode:</b> dose reduction to 60 mg/m<sup>2</sup></p> <p><b>2<sup>nd</sup> episode:</b> maintain dose at 60 mg/m<sup>2</sup></p> <p><b>3<sup>rd</sup> episode:</b> <b>consider discontinuing treatment</b></p>	<p><b>1<sup>st</sup> episode:</b> no dose reduction</p> <p><b>2<sup>nd</sup> episode:</b> ↓ 1 dose level of infusional fluorouracil</p>
<b>NOTE: Dose reductions should be maintained for subsequent cycles.</b>				
Any time during the cycle: Platelets less than 50 x 10 <sup>9</sup> /L		<p><b>1<sup>st</sup> episode:</b> no dose reduction</p> <p><b>2<sup>nd</sup> episode:</b> dose reduction to 120 mg/m<sup>2</sup></p> <p><b>3<sup>rd</sup> episode:</b> <b>discontinue treatment</b></p>	<p><b>1<sup>st</sup> episode:</b> dose reduction to 60 mg/m<sup>2</sup></p> <p><b>2<sup>nd</sup> episode:</b> maintain dose at 60 mg/m<sup>2</sup></p> <p><b>3<sup>rd</sup> episode:</b> <b>discontinue treatment</b></p>	<p><b>1<sup>st</sup> episode:</b> no dose reduction</p> <p><b>2<sup>nd</sup> episode:</b> ↓ 1 dose level of infusional fluorouracil</p> <p><b>3<sup>rd</sup> episode:</b> continue infusional fluorouracil</p>
<b>NOTE: Dose reductions should be maintained for subsequent cycles.</b>				

\* may discuss with patient and evaluate on a case by case basis. Use of prophylactic G-CSF is advised when cycle delay is due to hematologic toxicity involving ANC and lasting at least 1 week.

\*\* infusional fluorouracil + leucovorin

### C. Dose Modifications for NON-HEMATOLOGIC, NON-NEUROLOGIC Toxicity

At the Beginning of a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles
	Grade	Diarrhea*	
<ul style="list-style-type: none"> <li>▪ If recurrent diarrhea (more than 48 hours) despite high doses of loperamide : No dose reduction for irinotecan, oxaliplatin and infusional fluorouracil after recovery except if grade 3-4 diarrhea, or diarrhea + fever and/or ANC less than <math>1.0 \times 10^9/L</math>.</li> <li>▪ If isolated grade 3-4 diarrhea or diarrhea + fever or diarrhea + ANC less than <math>1.0 \times 10^9/L</math>, then proceed with treatment at the Grade experienced, for both diarrhea and febrile neutropenia. For febrile neutropenia add G-CSF.</li> </ul>	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	<b>1<sup>st</sup> episode:</b> dose reduce irinotecan to $120 \text{ mg/m}^2$  <b>2<sup>nd</sup> episode:</b> in addition, dose reduce oxaliplatin to $60 \text{ mg/m}^2$ and infusional fluorouracil to $1800 \text{ mg/m}^2$  <b>3<sup>rd</sup> episode:</b> <b>stop irinotecan.</b>
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	<b>1<sup>st</sup> episode:</b> dose reduce irinotecan to $120 \text{ mg/m}^2$  <b>2<sup>nd</sup> episode:</b> in addition, dose reduce oxaliplatin to $60 \text{ mg/m}^2$ and infusional fluorouracil to $1800 \text{ mg/m}^2$  <b>3<sup>rd</sup> episode:</b> <b>stop irinotecan.</b>

\* Please refer to "Precautions: Diarrhea" for additional information on management of diarrhea.

	Grade	Stomatitis	
<ul style="list-style-type: none"> <li>▪ If stomatitis is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the <b>highest</b> Grade experienced.</li> <li>▪ If stomatitis greater than or equal to Grade 2 on Day 1 of cycle, hold treatment. Perform weekly checks, maximum 2 times.</li> <li>▪ If stomatitis remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.</li> </ul>	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	Dose reduce infusional fluorouracil to $1800 \text{ mg/m}^2$
	4	As above but mucosal necrosis and/or requires enteral support, dehydration	Dose reduce all drugs: oxaliplatin to $60 \text{ mg/m}^2$ , irinotecan to $120 \text{ mg/m}^2$ and infusional fluorouracil to $1800 \text{ mg/m}^2$

## Hand-Foot Syndrome

If grade 3-4 toxicity occurs, infusional fluorouracil should be reduced to 1800 mg/m<sup>2</sup> for the remaining courses.

### PRECAUTIONS:

- 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 minutes30 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 SCOXR: BC Cancer Inpatient Protocol Summary for Oxaliplatin Desensitization for more information.
- 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	1. Present
O <sub>2</sub> 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
<b>Treatment</b>	Anxiolytics; observation in a controlled clinical setting until symptoms abate or at physician's discretion	Oxygen, steroids, epinephrine, bronchodilators; Fluids and vasopressors if appropriate

3. **Pulmonary toxicity:** Severe pulmonary toxicity consisting of dyspnea, fever and reticulonodular pattern on chest x-ray has been reported rarely with oxaliplatin. Supportive care is required. 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**.
4. **Diarrhea:** may be life threatening and requires prompt, aggressive treatment.
  - **Early diarrhea** or abdominal cramps occurring within the first 24 hours is treated with **atropine** 0.3 to 1.2 mg IV or SC. Prophylactic atropine may be required for subsequent treatments.
  - **Late diarrhea** has an onset of 5 to 11 days post-treatment, a duration of 3 to 7 days and must be treated promptly with **loperamide** (eg, IMODIUM®). The loperamide dose is higher than recommended by the manufacturer. Instruct patient to have loperamide on hand and start treatment at the first poorly formed or loose stool, or earliest onset of more frequent stool than usual:
    - **4 mg stat**
    - **then 2 mg every 2 hours until diarrhea-free for 12 hours without exceeding an overall treatment duration of 48 h**
    - may take 4 mg every 4 hours at night
  - The use of drinks such as GATORADE® or POWERADE® to replace fluid & body salts is recommended.
  - Consideration should be given to the use of an oral fluoroquinolone (e.g., ciprofloxacin) in patients with persistent diarrhea (more than 48 hours) despite adequate loperamide or if fever develops in the setting of diarrhea, even without neutropenia.
  - In case of persistent (longer than 48 hours) and/or severe diarrhea, consider hospitalization and parenteral rehydration. Loperamide would be replaced by another antidiarrheal treatment left to the physician's choice. Eliminate the possibility of pseudomembranous colitis if diarrhea persists.
  - Patients with vomiting or fever or with a performance status > 2 concomitant to diarrhea should be rapidly hospitalized to receive parenteral support. Loperamide and fluoroquinolone must be prescribed to the patient in advance upon exiting the hospital so that he/she has both medications with him/her if diarrhea reoccurs.
5. **Other cholinergic symptoms:** may occur during or shortly after infusion of irinotecan including rhinorrhea, increased salivation, lacrimation, diaphoresis and flushing. These should be treated with atropine 0.3 mg to 0.6 mg IV or SC. This dose may be repeated at the physician's discretion. Blood pressure and heart rate should be monitored. Prophylactic atropine may be required for subsequent treatments.
6. **QT prolongation and torsades de pointes** are 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.
7. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively. **GCSF support should be initiated for further cycles after an episode of febrile neutropenia.**
8. **Gilbert's syndrome:** Increases the risk of irinotecan-induced toxicity. A screen for Gilbert's Syndrome using direct/indirect serum bilirubin is recommended.



9. **Hepatic dysfunction:** Irinotecan has not been studied in patients with bilirubin greater than 35 micromol/L or ALT greater than 3x the upper limit of normal if no liver metastases, or ALT greater than 5x the upper limit of normal with liver metastases. The risk of severe neutropenia may be increased in patients with a serum bilirubin of 17 to 35 micromol/L.
10. **Prior pelvic radiotherapy** or radiotherapy to greater than 15% of the bone marrow bearing area may increase the degree of myelosuppression associated with this regimen, and caution is recommended in these cases. Close monitoring of the CBC is essential.
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. **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.
13. **Extravasation:** Oxaliplatin causes irritation if extravasated. Refer to BC Cancer [Extravasation Guidelines](#).
14. **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.
15. 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.
16. **Potential Drug Interactions:** Anticonvulsants and other drugs which induce Cytochrome P450 3A4 isoenzyme activity e.g. carbamazepine, phenytoin and St John's Wort may decrease the therapeutic and toxic effects of irinotecan. Prochlorperazine may increase the incidence of akathisia and should be avoided on the day of irinotecan treatment.
17. **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.
18. **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:**

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6. Mathijssen RHJ, Verweij J, de Bruijn P, et al. Effects of St. John's Wort on irinotecan metabolism. *J Natl Cancer Inst* 2002;94(16):1247-9.