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

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

ELIGIBILITY:

Patients must have:

- Metastatic colorectal adenocarcinoma,
- Wild type RAS (tested on primary or metastatic tumour),
- Wild type BRAF (tested on primary or metastatic tumour), and
- One of the following indications for use:
  1. Patient not suitable for treatment with bevacizumab, and either:
     - 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,

  or

  2. Patient with left-sided* tumour with no prior treatment in the advanced setting, regardless of bevacizumab eligibility

* Left-sided = splenic flexure to rectum

Patients should have:

- ECOG performance status 0 to 2
- Adequate marrow reserve, renal and liver function

Notes:

- Consideration of first line oxaliplatin-based therapy (FOLFOX PANitumumab) should be given for those patients who have Gilbert's Syndrome or who may be compromised by potential irinotecan toxicities
- Patients treated with this regimen for left-sided colorectal cancer are eligible for subsequent-line bevacizumab
- Patients without left-sided cancer are not funded for subsequent-line bevacizumab
- Patients with left-sided colorectal cancer currently on first-line treatment with GIFOLFIRI or GICAPIRI without progression may receive GIFFIRPAN if all other eligibility criteria are met

EXCLUSIONS:

Patients must not have:

- Mutant RAS or mutant BRAF tumours
- Interstitial pneumonitis or pulmonary fibrosis

CAUTIONS:

- Patients with: 1) previous pelvic radiotherapy; 2) recent MI; 3) uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure, or 4) other serious medical illness
- Patients with baseline greater than 3 loose BM per day (in patients without colostomy or ileostomy)
- Patients with baseline hyperbilirubinemia (greater than 26 micromol/L) not explained by degree of liver metastases

TESTS:

- Baseline: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, albumin, sodium, potassium, *DPYD* test (not required if previously tested, or tolerated fluorouracil or capecitabine)
- Baseline if clinically indicated: CEA, CA 19-9, GGT, magnesium, calcium, ECG
- Prior to each cycle: CBC & Diff, creatinine, total bilirubin, ALT, magnesium
- If clinically indicated: CEA, CA 19-9, alkaline phosphatase, albumin, calcium, GGT, sodium, potassium, ECG
- For patients on warfarin, weekly INR during fluorouracil therapy until stable warfarin dose established, then INR prior to each cycle

PREMEDICATIONS:

- Antiemetic protocol for moderately 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.
- 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 line pre and post infusion with NS
irinotecan	180 mg/m^2	IV in 500 mL D5W over 1 hour 30 min*
leucovorin†	400 mg/m^2	IV in 250 mL D5W over 1 hour 30 min*
fluorouracil†	400 mg/m^2	IV push
fluorouracil	2400 mg/m^2	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 until disease progression or unacceptable toxicity.

* 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.

† fluorouracil IV push is optional in the advanced setting:

fluorouracil IV push	leucovorin administration options
fluorouracil IV push given	• leucovorin given as IV infusion OR • leucovorin given as 20 mg/m^2 IV push
fluorouracil IV push omitted	• leucovorin omitted OR • leucovorin given as IV infusion OR • leucovorin given as 20 mg/m^2 IV push

** 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 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.

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

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 HEMATOLOGIC Toxicity (irinotecan and fluorouracil)
B. NON-HEMATOLOGIC, NON-NEUROLOGIC Toxicity (irinotecan,fluorouracil,PANitumumab)
C. DERMATOLOGIC Toxicity (PANitumumab)
D. HYPOMAGNESEMIA (PANitumumab)

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

Agent	Dose Level 0 (Starting Dose)	Dose Level –1	Dose Level –2	Dose Level –3
PANitumumab	6 mg/kg	4.8 mg/kg	3.6 mg/kg	Discontinue Therapy
irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2	Discontinue Therapy
leucovorin	No dose modifications. ▪ If fluorouracil push is omitted, leucovorin may also be omitted or given as 20mg/m^2 IV push ▪ If irinotecan is omitted, leucovorin may be given as 20 mg/m^2 IV push			
fluorouracil push	400 mg/m^2	320 mg/m^2	240 mg/m^2	Discontinue Therapy
fluorouracil infusion	2400 mg/m^2	2000 mg/m^2	1600 mg/m^2	Discontinue Therapy

A. Dose Modifications for HEMATOLOGIC Toxicity (irinotecan and fluorouracil)

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	ANC (x10^9/L)	irinotecan	fluorouracil
▪ If ANC less than 1.5 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. ▪ If ANC is greater than or equal to 1.5 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 1.5 after 2 weeks, discontinue treatment.	1	Greater than or equal to 1.5	Maintain dose level	Maintain dose level
	2	1.0 to less than 1.5	Maintain dose level	Maintain dose level
	3	0.5 to less than 1.0	↓ 1 dose level	↓ 1 dose level
	4	Less than 0.5	↓ 2 dose levels	↓ 2 dose levels
	Grade 4 neutropenia & greater than or equal to Grade 2 fever		↓ 2 dose levels	↓ 2 dose levels

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	**Platelets ($x10^9$/L)**	**irinotecan**	**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	↓ 1 dose level
	4	Less than 10	↓ 2 dose levels	↓ 2 dose levels

B. Dose Modifications for NON-HEMATOLOGIC Toxicity (irinotecan, fluorouracil, and PANitumumab)

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles (See Precautions #1)		
	Grade	Diarrhea	irinotecan	fluorouracil	PANitumumab
▪ If diarrhea greater than or equal to Grade 2 on Day 1 of any 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	Maintain dose level	Maintain dose level
	2	Increase of 4 to 6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Maintain dose level	Maintain dose level	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	↓ 1 dose level	↓ 1 dose level
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	↓ 2 dose levels	↓ 2 dose levels	↓ 2 dose levels

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	**Stomatitis**	**irinotecan**	**fluorouracil**
▪ If stomatitis greater than or equal to Grade 2 on Day 1 of any 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	Maintain dose level
	2	Painful erythema, edema, or ulcers but can eat	Maintain dose level	Maintain dose level
	3	Painful erythema, edema, ulcers, and cannot eat	Maintain dose level	↓ 1 dose level
	4	As above but mucosal necrosis and/or requires enteral support, dehydration	Maintain dose level	↓ 2 dose levels

C. 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, and 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, paronychia and blisters.

D. Dose Modifications and Management of 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 15mL of 100 mg/mL solution contains 76.8 mg	15 – 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. **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 mg subcutaneously. Dose may be repeated every 30 minutes as needed to a maximum of 1.2 mg. 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**
     - 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 despite adequate loperamide or if a fever develops in the setting of diarrhea, even without neutropenia. If diarrhea persists for longer than 48 hours then hospitalization for parenteral hydration should be considered.
   - Acute renal failure has been observed in patients with severe diarrhea and dehydration receiving PANitumumab. PANitumumab and chemotherapy should be withheld until resolution.
   - 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.
2. **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 subcutaneously. Dose may be repeated every 30 minutes as needed to a maximum of 1.2 mg. Prophylactic atropine may be required for subsequent treatments.
3. **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.

4. **Pulmonary Toxicity: Interstitial lung disease** has been reported 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. Severe pulmonary toxicity consisting of dyspnea, fever and reticulonodular pattern on chest x-ray has been reported rarely with irinotecan. Supportive care is required and respiratory consultation should be considered.
5. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
6. **Gilbert's syndrome:** Increases the risk of irinotecan-induced toxicity. A screen for Gilbert's Syndrome using direct/indirect serum bilirubin is recommended.
7. **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.
8. **Prior pelvic radiotherapy** or radiotherapy to greater than 15% of the bone marrow bearing area may increase the degree of myelosuppression associated with FOLFIRI, and caution is recommended in these cases. Close monitoring of the CBC is essential.
9. **Stomatitis**: Sucking ice chips may be considered for patients experiencing stomatitis. Remove dentures and place ice chips in mouth five minutes before chemotherapy. Continuously swish in mouth for 30 minutes, replenishing as ice melts. This may cause numbness or headaches, which subside quickly.
10. **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.
11. **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.
12. **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.
13. **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.
14. **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.

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