BC Cancer Protocol Summary for Third Line Treatment of Metastatic Colorectal Cancer Using Cetuximab in Combination with Irinotecan

Protocol Code	*GIAVCETIR*
Tumour Group	*Gastrointestinal*
Contact Physician	*GI Systemic Therapy*

ELIGIBILITY

Patients must have:

- Metastatic colorectal adenocarcinoma,
- Previous treatment with fluorouracil or capecitabine, irinotecan and oxaliplatin,
- Wild type RAS (tested on primary or metastatic tumour), and
- Wild type BRAF (tested on primary or metastatic tumour)

Patients should have:

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

Note: patients may receive one of GIAVPANI or GIAVCETIR – not both

EXCLUSIONS

Patients must not have:

- Mutant RAS or mutant BRAF tumours
- Symptomatic brain metastases, interstitial pneumonitis or pulmonary fibrosis

CAUTIONS

- 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 & differential, platelets, sodium, potassium, magnesium, calcium, creatinine, bilirubin, ALT, Alkaline Phosphatase. Optional: CEA
- Prior to each cycle: CBC & differential, platelets, sodium, potassium, magnesium, calcium, LFTs (Bilirubin, ALT, Alkaline Phosphatase)
- If clinically indicated: CEA
- Post treatment: monthly sodium, potassium, magnesium, calcium for 2 months after last cetuximab treatment
- Quantitative evaluation of disease response status every six to twelve weeks; discontinue therapy if any progression of disease.

PREMEDICATIONS:

- Antiemetic protocol for high moderate 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.
- dexamethasone 8 to 12 mg PO and diphehydrAMINE 50 mg PO 30 to 60 minutes prior to cetuximab.
- Consider preemptive therapy for cetuximab-induced dermatologic toxicity (see below).

TREATMENT:

Cycle 1

Drug	Dose	BC Cancer Administration Guideline
cetuximab (first dose)	500 mg/m^2	IV over 2 hours using a 0.2 micron in-line filter. Observe for 1 hour post-infusion. Obtain vital signs pre-infusion, at 1 hour, and post-infusion*.
irinotecan	180 mg/m^2	IV in 500 mL D5W over 1 hour 30 min

Cycle 2 and higher

Drug	Dose	BC Cancer Administration Guideline
cetuximab (subsequent dose)	500 mg/m^2	IV over 1 hour using a 0.2 micron in-line filter. For second dose only: observe for 1 hour post-infusion. Obtain vital signs pre-infusion and 1 hour post-infusion*.
irinotecan	180 mg/m^2	IV in 500 mL D5W over 1 hour 30 min

*1 hour observation period following end of 1st and 2nd cetuximab infusions; If no infusion reactions occur for 2 consecutive doses, then may discontinue observation period and vital signs.

- cetuximab requires no dilution. It may contain a small amount of easily visible cetuximab particulates.
- normal saline may be used to flush line at the end of the infusion

Repeat every 2 weeks x 12 cycles. If there is continued evidence of response or stable disease by imaging or tumour markers, may apply for additional cycles via Compassionate Access Program.

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

DOSE MODIFICATIONS:

1. Hematological:

ANC (x10^9/L)		Platelets (x10^9/L)	cetuximab Dose	irinotecan Dose
greater than or equal to 1.5	and	greater than or equal to 75	500 mg/m^2	180 mg/m^2
1.0 to less than 1.5	or	50 to less than 75	Delay until ANC greater than or equal to 1.5 and platelets greater than or equal to75 then resume at same dose	
0.5 to less than 1.0	or	10 to less than 50	Delay until ANC greater than or equal to 1.5 and platelets greater than or equal to75 then resume cetuximab at same dose and irinotecan at 150 mg/m^2.	
less than 0.5*	Or	less than 10	Delay until ANC greater than or equal to 1.5 and platelets greater than or equal to75 then resume cetuximab at same dose and irinotecan at 120 mg/m^2.	

*If ANC remains less than 0.5 after 2 weeks, discontinue irinotecan. May continue cetuximab at oncologist's discretion, if evidence of non-progression.

Fever or other evidence of infection must be assessed promptly and treated aggressively.

2. Diarrhea:

Grade	Description	cetuximab Dose	irinotecan Dose
1 to 2	Increase of up to 6 stools, or nocturnal stools or moderate increase in loose watery colostomy output	500 mg/m^2	180 mg/m^2
3	Increase of 7 to 9 more stools/day or incontinence, malabsorption, severe increase in loose watery colostomy output, grossly bloody diarrhea,	Delay until grade 2 or less within 2 weeks then resume at cetuximab 400 mg/m^2 and irinotecan 150 mg/m^2	
4	Increase of 10 or more stools/day or dehydration requiring parenteral support	Delay until grade 2 or less within 2 weeks then resume at cetuximab 300 mg/m^2 and irinotecan 120 mg/m^2	

*if diarrhea remains greater than grade 2 for greater than 2 weeks, discontinue irinotecan.

3. Dose Modification for cetuximab DermatologicToxicity:

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. 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	Cetuximab dose
1	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	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 + minocycline 100 mg PO BID for 1 to 2 weeks or longer as needed.

Grade	Toxicity	Cetuximab dose
3	Severe, generalised erythroderma or macular, papular or vesicular eruption	Withhold infusion for 2 to 4 weeks: ▪ When improvement to Grade 2 or less, continue at 50% of original dose; If toxicities do not worsen, escalate by 25% increments of original dose until recommended starting dose is reached ▪ If no improvement, discontinue cetuximab Continue treatment with clindamycin 2% and hydrocortisone 1% in a lotion to be applied topically BID as needed + minocycline 100 mg PO BID for 1 to 2 weeks or longer as needed.
4	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 during treatment and for 2 months following the last dose of cetuximab.

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, paronychia and blisters.

4. Hypersensitivity Reactions:

Vital Signs (Temp, HR, RR, BP should be monitored prior to cetuximab infusion, halfway through infusion and 60 minutes post-infusion).

Observe for 1 hour following end of 1st and 2nd infusion. May discontinue observation period and vital signs if no infusion reaction for 2 consecutive doses.

90% of severe reactions were associated with the first infusion of cetuximab despite the use of prophylactic antihistamines; however, caution must be exercised with every infusion.

Grade	Description (NCIC-CTC)	Management	Cetuximab Dose
1	Transient rash, drug fever less than 38° C	Decrease infusion rate by 50%.	Maintain 50% reduction in infusion rate for all subsequent treatments.
2	Urticaria, drug fever greater than 38°C and/or asymptomatic bronchospasm	Stop cetuximab infusion. Administer bronchodilators. Resume infusion at 50% once reaction has resolved or decreased to Grade 1	1st occurrence – maintain 50% reduction in rate. At second occurrence of greater than or equal to grade 2 despite slower rate, discontinue.
3	Symptomatic bronchospasm requiring parenteral medication with or without urticaria; allergy-related edema/angioedema	Stop cetuximab and disconnect infusion tubing. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, iv fluids, vasopressors and oxygen as indicated.	Discontinue cetuximab
4	Anaphylaxis		

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. Prophylactic atropine may be required for subsequent treatments.

5. Dose Modifications and Management of cetuximab Hypomagnesemia

Serious cases may be symptomless 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 cetuximab. Consider daily oral magnesium replacement
2	0.4 to less than 0.5 mmol/L	Continue cetuximab 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 cetuximab 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 cetuximab 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 to 1.2 mg IV or SC. Prophylactic atropine may be required for subsequent treatments.
   - **Late diarrhea** has a median onset of 5 days post-treatment with this regimen and must be treated with **loperamide** (e.g., 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. Cetuximab 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 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.
3. **Hypersensitivity:** Cetuximab infusion associated symptoms, usually occur with the first dose (90%) but may be associated with subsequent doses. Grade 1 or 2 infusion reactions occur in up to 19% of patients receiving cetuximab alone. These may consist of chills, fever and dyspnoea. Grade 3 or 4 reactions usually occur within minutes of the first infusion and are characterized by bronchospasm, urticaria and hypotension. Mild infusion reactions are managed by slowing the infusion and antihistamine therapy. Severe infusion reactions occur in 3% of patients and are rarely (fewer than 1 in 1000) fatal. They are managed by immediate and permanent discontinuation of the infusion and appropriate emergency medical therapy with adrenaline, corticosteroids, IV antihistamines, bronchodilators and oxygen. Refer to BC Cancer Hypersensitivity Guidelines.
4. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.

5. **Gilbert's Disease** increases the risk of irinotecan-induced toxicity. A screen for Gilbert's Disease using direct/indirect serum bilirubin is recommended.
6. **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.
7. **Pulmonary toxicity**: **Interstitial lung disease** has been observed with EGFR inhibitors. Interstitial lung disease and interstitial pneumonitis are rare (<0.5% for cetuximab). Worsening of preexisting lung conditions is also reported with cetuximab. Investigation of acute symptoms is warranted and cetuximab 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.
8. **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.
9. **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.

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. Cunningham D, et al: Cetuximab Monotherapy and Cetuximab plus Irinotecan in Irinotecan-Refractory Metastatic Colorectal Cancer. NEJM 2004; 351:337 – 345.
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4. Pfeiffer P, Nielsen D, Bjerregaard J, et al. Biweekly cetuximab and irinotecan as third-line therapy in patients with advanced colorectal cancer after failure to irinotecan, oxaliplatin and 5-fluorouracil. Ann Oncol 2008;19(6):1141-5.
5. Martin-Martorell P, Rosello S, Rodriguez-Braun E, et al. Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. Br J Cancer 2008;99:455-8.