

# BCCA Protocol Summary Third Line Treatment of Metastatic Colorectal Cancer Using Cetuximab in Combination with Irinotecan

**Protocol Code**

*UGIAVCETIR*

**Tumour Group**

*Gastrointestinal*

**Contact Physician**

*GI Systemic Therapy*

## **ELIGIBILITY:**

Patients with:

- metastatic colorectal adenocarcinoma, previously treated with fluorouracil, irinotecan and oxaliplatin
- Wild type KRAS primary or metastatic tumours\*
- ECOG performance status less than or equal to 2
- Adequate marrow reserve (ANC greater than or equal to  $1.5 \times 10^9/L$ , platelets greater than  $100 \times 10^9/L$ )
- Adequate renal (Creatinine less than or equal to  $1.5 \times ULN$ ) and liver function (Bilirubin less than or equal to 26 micromol/L; AST/ Alkaline Phosphatase less than or equal to  $5 \times ULN$ )

A BCCA “Compassionate Access Program” request with appropriate clinical information for each patient must be approved prior to treatment. **Note:** Approvals will only be given for one of UGIAVPANI or UGIAVCETIR – not both.

\*[www.bccancer.bc.ca/HPI/labservices/PathologyRequestForms](http://www.bccancer.bc.ca/HPI/labservices/PathologyRequestForms)

## **EXCLUSIONS:**

Patients with:

- Mutant KRAS tumours
- Greater than 3 loose stools per day in patients without colostomy or ileostomy
- Symptomatic brain metastases, interstitial pneumonitis or pulmonary fibrosis

## **TESTS:**

- Baseline: CBC & differential, electrolytes, magnesium, calcium, creatinine, bilirubin, AST/Alkaline Phosphatase,
- Prior to each cycle: CBC & differential, electrolytes, magnesium, calcium
- For patients on warfarin, weekly INR until stable warfarin dose established, then INR at beginning of each cycle.
- Post treatment: monthly electrolytes, magnesium, calcium for 2 months after last cetuximab treatment

**PREMEDICATIONS:**

- Anti emetic protocol for high moderate emetogenic chemotherapy (see SCNAUSEA)
- Prochlorperazine should be avoided on the same day as irinotecan treatment due to the increased incidence of akathisia
- Dexamethasone 8 - 12 mg po and Diphenhydramine 50 mg po 30-60 minutes prior to Cetuximab

**TREATMENT:****Cycle 1**

Drug	Dose	BCCA Administration Guideline
Cetuximab (first dose)	500 mg/m <sup>2</sup>	IV over 2 hours using a 0.22 micron in-line filter. Observe for 1 hour post-infusion*
Irinotecan	180 mg/m <sup>2</sup>	IV in 500 ml D5W over 1 hour 30 min

**Cycle 2 and higher**

Drug	Dose	BCCA Administration Guideline
Cetuximab (subsequent dose)	500 mg/m <sup>2</sup>	IV over 1 hour using a 0.22 micron in-line filter. For second dose only: observe for 1 hour post-infusion.*
Irinotecan	180 mg/m <sup>2</sup>	IV in 500 ml D5W over 1 hour 30 min

\*1 hour observation period following end of 1<sup>st</sup> and 2<sup>nd</sup> cetuximab infusions; may discontinue observation period if no infusion reactions occur for 2 consecutive doses.

- 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 10 cycles. If there is continued evidence of response or stable disease by imaging or tumour markers, 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 <sup>9</sup> /L)		Platelets (x10 <sup>9</sup> /L)	Cetuximab Dose	Irinotecan Dose
greater than or equal to 1.5	and	greater than or equal to 75	500mg/m <sup>2</sup>	180mg/m <sup>2</sup>
1.0-1.4	or	50-74	Delay until ANC greater than or equal to 1.5 and platelets greater than or equal to 75 then resume at same dose	
less than 1.0	or	less than 50	Delay until ANC greater than or equal to 1.5 and platelets greater than or equal to 75 then resume cetuximab at same dose and irinotecan at 150 mg/m <sup>2</sup> .	
less than 0.5*	Or	less than 10	Delay until ANC greater than or equal to 1.5 and platelets greater than or equal to 75 then resume cetuximab at same dose and irinotecan at 120 mg/m <sup>2</sup> .	

\*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
1-2	Increase of up to 6 stools, or nocturnal stools or moderate increase in loose watery colostomy output	500mg/m <sup>2</sup>	180mg/m <sup>2</sup>
3	Increase of 7-9 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 <sup>2</sup> and irinotecan 150mg/m <sup>2</sup>	
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 <sup>2</sup> and irinotecan 120 mg/m <sup>2</sup>	

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

### 3. 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 1-3 (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 4-6. 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.)

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 1-2 weeks or longer as needed.

3	Severe, generalised erythroderma or macular, popular or vesicular eruption	<p>Withhold infusion for 2 to 4 weeks:</p> <ul style="list-style-type: none"> <li>▪ 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</li> <li>▪ If no improvement, discontinue cetuximab</li> </ul> <p>Continue treatment with clindamycin 2% and hydrocortisone 1% in a lotion to be applied topically BID as needed + Minocycline 100 mg PO BID for 1-2 weeks or longer as needed.</p>
4	Generalized exfoliative, ulcerative or blistering skin toxicity	Discontinue treatment.

There is evidence that prophylactic therapy with topical products and antibiotics can be beneficial, however this is not the standard of care at this time due to the unknown impact on treatment efficacy.

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 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).

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	1 <sup>st</sup> 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 0.25 mg – 0.5 mg IV or SC. This dose may be repeated at the physician's discretion. Prophylactic atropine may be required for subsequent treatments.

## 5. 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.

Grade	Serum Magnesium	Management
1	0.5 mmol/L to less than LLN	Continue Cetuximab. Consider daily oral magnesium replacement
2	0.4 to 0.49 mmol/L	Continue Cetuximab and initiate daily oral magnesium replacement and magnesium sulfate 4G IV every 2 weeks
3	0.3 to 0.39 mmol/L	if symptomatic - hold Cetuximab until improved to Grade 2. If asymptomatic – increase supplementation to magnesium sulfate 4G IV weekly
4	Less than 0.3 mmol/L	Hold Cetuximab until asymptomatic and improved to Grade 2 – increase supplementation to magnesium sulfate 4G IV 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:

- 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** 0.25 - 1 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
2. **Gilbert's Disease** increases the risk of irinotecan-induced toxicity (Ann Oncol 1997;8:1049-51). A screen for Gilbert's Disease using direct/indirect serum bilirubin is recommended. If present, reduce the starting dose to 130 mg/m<sup>2</sup>.
  3. **Hepatic Dysfunction:** Irinotecan has not been studied in patients with bilirubin greater than 35 micromol/L or AST greater than 3x the upper limit of normal if no liver metastases, or AST greater than 5x the upper limit of normal with liver metastases.
  4. **Pulmonary toxicity:** Interstitial Lung Disease has been observed with EGFR Inhibitors. Treatment should be withheld in the event of onset or worsening respiratory symptoms. If pneumonitis or lung infiltrates are confirmed, treatment should be discontinued.
  5. **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.

**Call Dr. Sanjay Rao or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.**

Date activated: August 1, 2009

Date revised: 1 February 2012 (cetuximab observation period revised)

#### **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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3. Roca J, et al: Cetuximab given every 2 weeks (q2w) plus Irinotecan, as Feasible Option, for Previously Treated Patients (pts) with Metastatic Colorectal Cancer (MCRC). J Clin Oncol 2008; 26: May 20 suppl; abstr 15122.
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.