Practice Guideline: Systemic Therapy Summary

Third-Line Treatment of Stage IV or Advanced, Unresectable Colorectal Carcinoma with Cetuximab (GAST – Cetuximab)
Gastro-Intestinal Disease Site Group

Effective: February 2009
Updated: May 2015
ACKNOWLEDGEMENT AND SPONSORSHIP DISCLAIMERS

In accordance with the CCMB policy no. 01.001, “Conflict of Interest”, the members of the Gastro-Intestinal (GI) Disease Site Group (DSG) have disclosed conflicts of interest. Members have disclosed the following conflicts of interest: Dr. Ralph PW Wong (Medical Oncologist) has participated in Amgen and Bristol-Myers Squibb advisory boards. As members have adhered to the CCMB policy no. 01.014, “Interaction with Industry Representatives”, the developers are satisfied this STS has been developed without bias.
Preface

This document has been prepared by the Winnipeg Regional Health Authority/CancerCare Manitoba (WRHA/CCMB) Oncology Pharmacotherapeutic (P&T) Subcommittee’s Systemic Therapy Summaries Working Group, as a means of disseminating drug information and formulary decisions made by the Subcommittee. The CCMB Provincial Pharmacy Program, Provincial Oncology Drug Program (PODP) and Clinical Practice Guidelines Initiative (CPGI) have contributed to the development of this summary.

Systemic Therapy Summaries (STS) are being developed for drugs/or indications where the P&T Subcommittee, based on scientific data, has accepted clinical benefit. The P&T Subcommittee Chair and the CPGI Lead/Advisory Panel Chair approve all STS documents.

The content of this STS was in large part adapted from the Formulary Addition Request submitted to the P&T Subcommittee by the CCMB Gastro-Intestinal (GI) Disease Site Group (DSG), February 2009. This document will be reviewed, and updated as necessary, once in every twelve-month period; unless emerging evidence from scientific research dictates otherwise.

Purpose

This document is intended as a guide to facilitate the safe and effective clinical use of cetuximab in the third-line treatment of stage IV or advanced, unresectable colorectal carcinoma.

For this purpose, it may be used by qualified and licensed healthcare practitioners involved with the care of oncology patients, which may include (but is not limited to): physicians, nurses, and pharmacists at CancerCare Manitoba, Community Cancer Programs Network (CCPN) sites and WRHA Community Oncology Program sites.

Disclaimer

Use of this document should not preclude use of the practitioner’s independent clinical judgment, nor should it replace consultation with the oncologist.

It is the responsibility of the practitioner to develop an individualized treatment plan for each patient under his/her care, and ideally this should take place within the context of a multidisciplinary team. The needs and preferences of the patient and the family should always be reflected in the plan of care.

This document is not a comprehensive drug monograph. Practitioners must refer to other sources for complete drug information.
Third-Line Treatment of Stage IV or Advanced, Unresectable Colorectal Carcinoma with Cetuximab

Protocol Code: GAST – Cetuximab

Developed by: Gastro-Intestinal (GI) Disease Site Group

Date of Presentation to P&T Subcommittee: February 17, 2009

Treatment Recommendation

The Gastro-Intestinal DSG recommends cetuximab monotherapy or dual therapy with irinotecan (see STS for Cetux-IRI) as a third-line treatment option in patients with stage IV or advanced, unresectable colorectal carcinomas who meet the inclusion criteria (see below).

Treatment Intent

- Non-curative
- Prolongation of overall survival (OS) and progression-free survival (PFS)

Rationale

Prior to epidermal growth factor receptor (EGFR) directed monoclonal antibody therapy for K-ras wild type, stage IV unresectable colorectal carcinoma, there was no standard approach for those that progressed, or that are intolerant to fluoropyrimidines, oxaliplatin- and irinotecan-based therapy. EGFR is over-expressed in the majority of colorectal cancers and has been associated with worse outcomes. Cetuximab is a recombinant, human/mouse chimeric monoclonal antibody that binds specifically to EGFR and significantly increases PFS and OS in patients who lack a mutation in the K-ras gene (approximately 60% of colorectal cancer patients).1

Clinical Benefit (Level Ib Evidence see Appendix I)

There have been a number of studies using monoclonal antibodies alone or in combination with chemotherapy.2 These studies have shown benefits in unselected populations. K-ras mutations are known to occur early in colon carcinogenesis; these lead to constitutive activation of K-ras, independent of EGFR. The frequency of K-ras mutations in colorectal carcinomas is estimated to be 40%. Single-arm studies support the hypothesis for K-ras as a biomarker for EGFR inhibitors. The original studies have been reanalyzed, taking into account the presence or absence of K-ras mutations.3

In the National Cancer Institute of Canada CTG CO.17 trial, patients were randomized between cetuximab versus best supportive care.4 No crossover was permitted on this study. Enrolment criteria were: performance status of 0-2 and disease progression following irinotecan- and oxaliplatin-based chemotherapy. In this trial, PFS in patients with wild-type K-ras tumours was 3.7 months versus 1.9 months in the control arm (HR, 0.40; p < 0.001). There
was a significant increase in OS of 9.5 versus 4.8 months (HR, 0.55; p < 0.001).

**Patient Population and Selection Criteria**

**Inclusion criteria**

- Stage IV colorectal cancer; **AND**
- Radiologically confirmed disease progression after first- and second-line therapy for stage IV disease (including therapy with fluoropyrimidines, oxaliplatin and irinotecan) or intolerance to these therapies; **AND**
- Wild-type (non-mutated) form of the *KRAS* gene; **AND**
- An Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 2 (see Appendix II)

**CCMB Formulary Status**

1. **Formulary definition**
   - Restricted*

   *Approved and funded by CCMB, provided that criteria for use are met and request is adjudicated by the DSG Chair or Designate

2. **Adjudication process**
   - Complete “Restricted Drug Form – GI DSG – COLORECTAL” (J:\Pharmacy\FORMS)
   - Approval required by: GI DSG Chair or Designate
   - After 2 months of therapy, repeat imaging is required to document disease stability or response; if patients respond or are stable, 2 more months will be granted approval by the GI DSG Chair or Designate
Implementation and Safety Considerations

- Notify physician before administering full doses of chemotherapy if platelets less than 100 x 10^9/L or absolute neutrophil count (ANC) less than 1.5 x 10^9/L.
- Establish IV of NaCl 0.9% 500 mL for medication administration and any hypersensitivity reaction.
- Flush line with NaCl 0.9% after infusion – DO NOT mix with dextrose 5% in water (D5W).

PLEASE NOTE: This regimen consists of a loading dose and 7 maintenance doses given every day for 1 week.

### Treatment Regimen – GAST – Cetuximab

1 cycle = 7 days (planned treatment until disease progression)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>CCMB Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>400 mg/m², loading dose</td>
<td>Do not give IV push</td>
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<tr>
<td></td>
<td></td>
<td>IV undiluted over 2 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Do not exceed 10 mg/min (5 mL/min) infusion rate</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>250 mg/m², doses 2-8</td>
<td>IV undiluted over 1 hour</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Do not exceed 10 mg/min (5 mL/min) infusion rate</td>
</tr>
</tbody>
</table>

### Pre-Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>CCMB Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>50 mg</td>
<td>IV over 15 minutes, 30-60 minutes prior to cetuximab administration</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>8 mg</td>
<td>IV over 15 minutes, 30-60 minutes prior to cetuximab administration</td>
</tr>
</tbody>
</table>
Supportive Care

It is recommended that the day before treatment with cetuximab, patients start a pre-emptive skin treatment, which includes:

1. Applying moisturizer to face, hands, feet, neck, back, and chest daily in the morning
2. Applying a broad-spectrum sunscreen before going outdoors (minimum SPF 15, PABA free, zinc oxide or titanium dioxide preferred)
3. Applying hydrocortisone 1% cream to face, hands, feet, neck, back, and chest at bedtime (outpatient prescription)
4. Doxycycline 100 mg orally twice daily (outpatient prescription)
Clinical Monitoring and Follow-Up Recommendations\textsuperscript{6,7}

Hematology, chemistry and required tests

- At baseline:
  - Complete blood count (CBC) with differential, sodium, potassium, chloride, magnesium, calcium, albumin, urea, serum creatinine, bilirubin, aspartate aminotransferase (AST), alkaline phosphatase, lactate dehydrogenase (LDH), glucose, carcinoembryonic antigen (CEA)

- Before each dose:
  - CBC with differential, sodium, potassium, chloride, magnesium, calcium, albumin, LDH, glucose, CEA (if tumour marker elevated at baseline)

- Post-treatment:
  - Sodium, potassium, chloride, magnesium, calcium, albumin (once per month, for two months following treatment completion)

Clinical toxicity assessment

- At baseline:
  - Clinical pulmonary exam

- Before each dose:
  - Vital signs (blood pressure, heart rate, respiratory rate and temperature), and assess for dermatologic, pulmonary and ophthalmic toxicities, diarrhea and dehydration

- During infusion and post-dose:
  - Vital signs must be repeated halfway through infusion, and one hour post-infusion (most severe reactions occur with the first dose, but monitoring is required for every dose)

Assessment of treatment response

- After two months of therapy (i.e., 8 doses), repeat imaging will be obtained in order to document disease stability or response. If patients respond or are stable, two more months will be granted upon approval by the GI DSG Chair or Designate
## Common or Clinically Important Adverse Events*
*(Refer to individual drug monographs for full details of adverse events)*

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood/bone marrow</td>
<td>Anemia is reported in 9% of patients (3% severe)</td>
</tr>
</tbody>
</table>
| Dermatologic toxicities         | Acneiform rash occurred in 76-88% of patients receiving cetuximab in clinical trials. Reactions are usually mild-moderate, but severe acneiform rash occurred in 1-17% of patients.  
Skin rash, characterized by multiple pustular, macular or papular-appearing lesions, most commonly occurs on the face, upper back and chest, but can extend to the extremities.  
Rash commonly peaks in severity in the first 1-2 weeks of therapy and stabilizes in the following weeks. If the rash resolves or diminishes during the second month, erythema and dry skin remain in the areas previously dominated by papulopustular eruption.  
Rash resolves completely without scarring after completion of treatment (median time 84 days).  
The rash develops in the following phases: week 0-1 sensory disturbance with erythema and edema; weeks 1-3 papulopustular eruption; weeks 3-5 crusting; weeks 5-8 erythematotelangiectasias  
Dermatologic toxicities are commonly managed with topical clindamycin, steroid lotion and or minocycline or doxycycline. See dose modifications for treatment of rash. |
| Nail and hair changes           | Nail/periungual alterations (usually paronychia) and regulatory abnormalities of hair growth (alopecia of scalp, trichomegaly of eyelashes and hypertrichosis of face) have been observed. Trichomegaly of eyelashes can be painful and may require consultation with an ophthalmologist. |
| Electrolyte abnormalities       | Hypomagnesemia occurred in 55% of patients, and was severe in 6-17% of patients in clinical trials. Electrolyte replacement (including IV) was necessary in some patients. Hypomagnesemia can manifest as severe fatigue, irritability, paresthesias, cramps and hypocalcemia. Hypomagnesemia and accompanying hypocalcemia and hypokalemia may occur days to months after the start of treatment, and patients should be monitored regularly during treatment and after the completion of therapy. |
| Gastrointestinal toxicities     | Emetogenic potential = low (10-30%)  
Anti-emetics are not usually required  
In clinical studies of patients receiving cetuximab monotherapy, nausea was seen in 29% of patients (2% severe), constipation 26-46%, abdominal pain 26% (9% severe), diarrhea 25-39% (severe 2%) and stomatitis 10-25% |
| **Infusion-related reactions**<sup>8</sup> | Grade 1 and 2 reactions occurred in 15-21% of patients across all studies. In clinical studies, severe infusion reactions (Grade 3 and 4 reactions) were observed in 2-5% of patients, one fatal. Most severe reactions (90%) were associated with the first infusion of cetuximab despite the use of prophylactic antihistamines; however caution must be exercised with every dose |
| **Pulmonary toxicities**<sup>8</sup> | Dyspnea was reported in 17-48% of patients (7-16% severe). Interstitial lung disease (ILD) has been reported in four patients (less than 0.5%), including one fatality (See Precautions) |
| **Other**<sup>8</sup> | Asthenia/malaise was reported in 48% of patients (10% severe). Headache was seen in up to 38% of patients (3% severe) |

*CTCAE v. 4.0 See Appendix III*
## Precautions

<table>
<thead>
<tr>
<th>Infusion-related reactions</th>
<th>Infusion reactions included pyrexia, chills, rigors, dyspnea, bronchospasm, angioedema, urticaria, hypertension and hypotension. Vital signs (blood pressure, heart rate, respiratory rate and temperature) should be monitored prior to, halfway through and one hour after the completion of cetuximab infusion. Prophylactic diphenhydramine 50 mg IV and dexamethasone 8 mg IV should be administered 30 to 60 minutes prior to each cetuximab infusion. <strong>Management of infusion reactions:</strong> For mild or moderate (Grade 1 or 2) infusion reactions: reduce cetuximab infusion rate by 50%. Subsequent infusions should be administered at the lower rate. For severe (Grade 3 or 4) infusion reactions: discontinue cetuximab permanently. Reactions should be managed according to the CCMB standing order “Hypersensitivity Reaction Treatment for Cetuximab and Panitumumab”.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary toxicity</strong></td>
<td>In the event of acute onset or worsening pulmonary symptoms, cetuximab therapy should be held until symptoms are investigated. If ILD is confirmed, cetuximab should be discontinued permanently.</td>
</tr>
<tr>
<td><strong>Dermatologic toxicities</strong></td>
<td>Patients should be counseled to avoid: Exposure to sunlight, which is known to exacerbate skin reactions and hyperpigmentation Activities that dry the skin, such as long hot showers or baths Alcohol-based or perfumed skin and hair products Over-the-counter acne medication Application of greasy ointments And to: Moisturize skin frequently with alcohol-free emollient creams Use oatmeal baths for symptom relief</td>
</tr>
</tbody>
</table>
## Dose Modifications†

(†adapted from Figure 5 of Melosky trial, journal reference page 24)\(^5\)

<table>
<thead>
<tr>
<th>Dermatologic toxicities</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild (Grade 1)</strong></td>
<td></td>
</tr>
<tr>
<td>Mild papular or pustular eruptions with little or no symptoms</td>
<td>Topical clindamycin 2% + hydrocortisone 1% in lotion base twice daily to affected area until resolution of rash</td>
</tr>
<tr>
<td><strong>Moderate (Grade 2)</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Moderate papular or pustular eruption or erythema; moderately symptomatic | Topical clindamycin 2% + hydrocortisone 1% in lotion base twice daily until improvement of rash by one grade  
PLUS  
Minocycline 100 mg orally twice daily OR doxycycline 100 mg orally once or twice daily for 4 weeks minimum, and for the duration of treatment as long as rash is symptomatic  
Scalp lesions: Topical clindamycin 2% + triamcinolone acetonide  
0.1% in equal parts of propylene glycol and water, until resolution |
| **Severe (Grade 3)** |  |
| Severe, extensive, painful, intolerable rash | Hold cetuximab for one to two weeks, and continue treatment with:  
Topical clindamycin 2% + hydrocortisone 1% in lotion base twice daily until improvement of rash to Grade 1 or 2  
PLUS  
Minocycline 100 mg orally twice daily or doxycycline 100 mg orally once or twice daily for 4 weeks minimum, and for the duration of treatment as long as rash is symptomatic  
Scalp lesions: Clindamycin powder 2% in amcinomide lotion twice daily  
If improvement: restart cetuximab (see below for dose)  
If no improvement: discontinue cetuximab permanently |
Restarting Cetuximab

After improvement of rash after held dose for 1 to 2 weeks, restart cetuximab as follows:

1\textsuperscript{st} occurrence: continue at 250 mg/m\textsuperscript{2}

2\textsuperscript{nd} occurrence: reduce to 200 mg/m\textsuperscript{2}

3\textsuperscript{rd} occurrence: reduce to 150 mg/m\textsuperscript{2}

4\textsuperscript{th} occurrence: discontinue permanently
References


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Approved By

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We gratefully acknowledge the support of CancerCare Manitoba, the CancerCare Manitoba Foundation and the Provincial Oncology Clinical Practice Guidelines Initiative.
## Appendix I

### Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Evidence obtained from meta-analysis of randomised controlled trials</td>
</tr>
<tr>
<td>Ib</td>
<td>Evidence obtained from at least one randomised controlled trial</td>
</tr>
<tr>
<td>IIA</td>
<td>Evidence obtained from at least one well-designed controlled study without randomisation</td>
</tr>
<tr>
<td>IIB</td>
<td>Evidence obtained from at least one other type of well-designed, quasi-experimental study</td>
</tr>
<tr>
<td>III</td>
<td>Evidence obtained from well-designed, non-experimental descriptive studies, such as comparative studies, correlation studies and case studies</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>

### Appendix II

#### ECOG Performance Status Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100)</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physical strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework or office work (Karnofsky 70-80)</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about greater than or equal to 50% of waking hours (Karnofsky 50-60)</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair greater than or equal to 50% of waking hours (Karnofsky 30-40)</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled, cannot carry on any self-care, totally confined to bed or chair (Karnofsky 10-20)</td>
</tr>
</tbody>
</table>

### Appendix III

**Common Terminology Criteria for Adverse Events (CTCAE) version 4.0**  
**Publish Date:** 18 May 2009

<table>
<thead>
<tr>
<th>Grades</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening consequences; urgent intervention indicated.</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death related to AE.</td>
</tr>
</tbody>
</table>

A semi-colon indicates ‘or’ within the description of the grade.  
A single dash (-) indicates a grade is not available.  
Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for grade selection.

**Grade 5:** Grade 5 (Death) is not appropriate for some AEs and therefore is not an option

**Activities of Daily Living (ADL):**  
* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.  
** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
