pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Cetuximab (Erbitux) **Submitted Funding Request:** For the treatment of EGFR-expressing K-RAS wild type metastatic colorectal carcinoma (mCRC) in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) for first line treatment	
Submitted By: Bristol-Myers Squibb Canada Withdrawn By Bristol-Myers Squibb Canada, November 25, 2013 **Submission Continued By:** The pCODR Provincial Advisory Group	**Manufactured By:** Bristol-Myers Squibb Canada
NOC Date: December 20, 2012	**Submission Date:** June 10, 2013
Initial Recommendation: October 31, 2013	**Final Recommendation:** January 10, 2014

pERC RECOMMENDATION	The pCODR Expert Review Committee (pERC) does not recommend funding cetuximab (Erbitux) for the first-line treatment of patients with K-RAS wild type unresectable metastatic colorectal carcinoma (mCRC). The Committee made this recommendation because it it was concerned that there was considerable uncertainty in the net clinical benefit of cetuximab plus FOLFIRI compared with bevacizumab plus FOLFIRI and because it is not cost-effective compared with bevacizumab plus FOLFIRI or bevacizumab plus FOLFOX. pERC acknowledged that there is a need for cetuximab in patients intolerant to, or with a contraindication to bevacizumab who would otherwise be treated with FOLFIRI; however, the cost-effectiveness of cetuximab plus FOLFIRI compared with FOLFIRI alone in patients intolerant to, or with a contraindication to bevacizumab is unknown.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Possibility of Resubmission to Support Funding** There is one ongoing study, CALGB-C80405, comparing cetuximab plus FOLFIRI with bevacizumab plus FOLFIRI. This study is expected to provide more robust information on the comparative effectiveness of cetuximab versus bevacizumab that could inform a resubmission for cetuximab in the first-line treatment of patients with K-RAS wild type unresectable mCRC. Also, information on the cost-effectiveness of cetuximab plus FOLFIRI compared with FOLFIRI alone in patients intolerant to or with a contraindication to bevacizumab could inform a resubmission for cetuximab.

SUMMARY OF pERC DELIBERATIONS

pERC deliberated on the results of two randomized controlled trials included in the pCODR systematic review. The CRYSTAL study (Van Cutsem 2009) compared cetuximab plus FOLFIRI (irinotecan, leucovorin, fluorouracil) with FOLFIRI alone and the FIRE-3 study (Heinemann 2013) compared cetuximab plus FOLFIRI with bevacizumab plus FOLFIRI. pERC noted that the current standard of care and most relevant comparator in the first-line treatment of metastatic colorectal cancer is bevacizumab plus FOLFIRI or plus FOLFOX (oxaliplatin, leucovorin, fluorouracil). However, pERC noted that in the FIRE-3 study, data on the K-RAS wild type population were only available in an abstract and that discordant results were observed between the overall survival and progression-free survival outcomes. pERC noted that an ongoing study, CALGB-C80405, is expected to provide more robust information in the future on the effectiveness of cetuximab plus FOLFIRI compared with bevacizumab plus FOLFIRI. Therefore, pERC agreed with the pCODR Clinical Guidance Panel that the potential net clinical benefit of cetuximab compared with bevacizumab is uncertain.

pERC's Deliberative Framework for drug funding recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC also discussed the results of the CRYSTAL study, even though FOLFIRI alone is not currently considered the most appropriate comparator in the first-line treatment of mCRC. pERC noted that statistically significant improvements in overall survival and progression-free survival were observed favouring cetuximab plus FOLFIRI. pERC also discussed the potential for cetuximab to convert initially unresectable patients to resectable with cetuximab treatment. However, pERC noted that this was a post-hoc analysis and neither study was designed or powered to evaluate conversion to resectability. Both studies included any patients who were unresectable, not just those who were potentially resectable, and criteria for potential resectability would need to be defined. pERC noted that in order to obtain relevant information on the rate of conversion to resectability, a study would need to be designed evaluating resectability as a primary or key secondary outcome in patients with mCRC who are potentially resectable. Therefore, pERC was unable to conclude that cetuximab provides a clinical benefit by converting more patients to resectability. pERC reviewed adverse events from the CRYSTAL study and noted that the information aligned with the expected toxicity profile of cetuximab, which is well-known as cetuximab is already used in mCRC patients as a third-line therapy. Considering all of these factors, pERC was unable to conclude that there is a net clinical benefit of cetuximab as a first-line therapy for all patients with K-RAS wild type mCRC but acknowledged that there is a clinical need for cetuximab as a first-line therapy in patients who are intolerant to or have a contraindication to bevacizumab. pERC noted that patients would still have access to cetuximab later in the management of mCRC as a third-line treatment but the Committee was not confident that there was sufficient evidence to change this treatment strategy (i.e. third-line use) and to provide access to cetuximab in the first-line treatment of patients with K-RAS wild-type mCRC.

pERC reviewed input from one patient advocacy group and concluded that treatment with cetuximab plus FOLFIRI would align with patient values. pERC noted that patients valued having more effective treatment options and considered that cetuximab could be another first-line treatment option that would provide a greater clinical benefit than treatment with FOLFIRI alone. Patient input also noted that patients experience adverse events such as peripheral neuropathy and gastrointestinal events from other treatments and patients would value having more tolerable treatment options. Therefore, pERC acknowledged that there is a need for cetuximab in patients who are intolerant to or have a contraindication to bevacizumab. Upon reconsideration of the pERC initial recommendation, pERC considered the feedback from the Patient Advocacy Group regarding the need for a treatment option for patients intolerant to bevacizumab. pERC recognized this but unfortunately noted that they still did not have information to inform the cost-effectiveness of cetuximab plus FOLFIRI compared with FOLFIRI alone in patients intolerant to or with a contraindication to bevacizumab. pERC further emphasized the discrepancies in the data available from the FIRE-3 study, comparing cetuximab with bevacizumab, and reiterated that the ongoing study CALGB-C80405 is likely to provide more robust information on the comparative effectiveness of cetuximab versus bevacizumab in the future. With respect to the use of

cetuximab plus FOLFIRI to convert unresectable liver metastatses to resectable, pERC confirmed that neither the FIRE-3 study nor the CRYSTAL study were designed to assess resectability and, in the absence of more robust data, the superiority of this regimen cannot be determined by these studies.

pERC deliberated upon the cost-effectiveness of cetuximab plus FOLFIRI based on a submitted model comparing it to bevacizumab plus FOLFIRI or to bevacizumab plus FOLFOX. pERC noted that in both comparisons, estimates were highly uncertain due to dependence on an indirect comparison and substantial uncertainty in rates of subsequent resection of metastatic disease. pERC considered that in both comparisons, it would be most appropriate to assume that conversion to resection was similar in the cetuximab and bevacizumab groups, or to exclude resection rates from the model, given the limitations of the clinical trial data for this outcome. Therefore, pERC determined that the cost-effectiveness of cetuximab plus FOLFIRI would likely be at the higher end of the EGP's range of best estimates. Consequently, cetuximab plus FOLFIRI could not be considered cost-effective at the submitted price compared with bevacizumab plus FOLFIRI or bevacizumab plus FOLFOX.

However, as a result of the Committee's deliberations on net clinical benefit, pERC considered it more relevant to assess cost-effectiveness in patients who are intolerant to or have a contraindication to bevacizumab. pERC considered that for these patients, FOLFIRI alone is the most relevant comparator, not bevacizumab plus FOLFIRI or bevacizumab plus FOLFOX. pERC noted that the manufacturer did not submit a comparison of cetuximab plus FOLFIRI with FOLFIRI alone in patients who are intolerant to or have a contraindication to bevacizumab. Therefore, pERC concluded that the cost-effectiveness of cetuximab plus FOLFIRI compared with FOLFIRI alone in this population was unknown.

pERC discussed the feasibility of implementing a recommendation for cetuximab. pERC noted that colorectal cancer is the second most common cause of cancer-related deaths and the burden of illness is large. pERC also noted that cetuximab is currently used later in the course of mCRC as a third-line treatment option for patients who have K-RAS wild type disease. Furthermore, pERC noted that the use of cetuximab earlier in treatment could potentially change treatment sequencing and treatment algorithms. pERC also noted that although K-RAS mutation testing has already been established and is currently done prior to the use of third-line therapy. Requiring testing prior to first-line mCRC therapy would substantially increase the need for testing and the total cost of testing.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from one patient advocacy group (Colorectal Cancer Association of Canada)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- pCODR's Provincial Advisory Group.
- one patient advocacy group (Colorectal Cancer Association of Canada)

The pERC Initial Recommendation was to not recommend funding cetuximab (Erbitux) for the first-line treatment of patients with K-RAS wild type unresectable metastatic colorectal carcinoma (mCRC). Feedback on the pERC Initial Recommendation indicated that the patient advocacy group disagreed with the initial recommendation while the pCODR's Provincial Advisory Group agreed with it.

Following the posting of the pERC Initial Recommendation and the end of the period during which stakeholders are able to provide feedback on the pERC initial recommendation, Bristol-Myers Squibb Canada requested a voluntary withdrawal of their submission for cetuximab (Erbitux) for mCRC. The submission was subsequently withdrawn. However, in order to obtain a pERC Final Recommendation that could be acted on by provinces, if needed, pCODR's Provincial Advisory Group (PAG) decided to continue with the submission using publically available information. This was done in accordance to *pCODR Procedures.*

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the efficacy and safety of cetuximab in combination with FOLFIRI (irinotecan, fluorouracil, leucovorin) as first-line treatment in patients who have epidermal growth factor receptor-expressing *K-RAS* wild-type metastatic colorectal cancer (mCRC).

Studies included

The pCODR systematic review included two randomized controlled trials, CRYSTAL (Van Cutsem 2009) and FIRE-3 (Heinemann 2013).

- CRYSTAL randomized patients to cetuximab plus FOLFIRI (irinotecan, leucovorin, fluorouracil) or to FOLFIRI alone
- FIRE-3 randomised patients to cetuximab plus FOLFIRI or bevacizumab plus FOLFIRI.

pERC noted that the current standard of care and most relevant comparator in the first-line treatment of metastatic colorectal cancer is bevacizumab plus FOLFIRI or plus FOLFOX. pERC also noted that in both studies K-RAS mutation status was determined retrospectively and, therefore, only post-hoc subgroup analyses were available on the K-RAS wild type population. In the FIRE-3 study, this subgroup data was only available as reported in a conference abstract, which limited the amount of detail pERC had available for deliberations.

The pCODR review also provided contextual information on:

- KRAS mutation testing in metastatic colorectal carcinoma
- Critical appraisal of indirect comparison of cetuximab plus FOLFIRI with bevacizumab plus FOLFIRI and bevacizumab plus FOLFOX (oxaliplatin, leucovorin, fluorouracil) in the treatment of metastatic colorectal carcinoma

Patient populations: unresectable K-RAS wild type

Overall, patient populations of CRYSTAL and FIRE 3 studies were similar in terms of age, gender, ECOG performance status and primary site at the colon.

Approximately 63% of patients (666 of 1,063) in the CRYSTAL study had K-RAS wild type metastatic colorectal carcinoma. The majority of patients had an ECOG performance status of 0 or 1 (53-55% and 41-43%, respectively), while 4% of patients had an ECOG performance status of 2. The primary site of tumors was colon (60%) and rectum (38%) and for all included patients, the tumors were not considered curatively resectable. The majority of patients (84-86%) had metastases at one or two sites, and 21% had metastasis confined to the liver.

Patients in FIRE-3 had an ECOG performance status of 0 or 1 in 94% to 98% of patients. There were 592 patients with KRAS wild-type tumours.

Key efficacy results: clinical benefit compared with bevacizumab plus FOLFIRI uncertain due to discordant PFS and overall survival results

Key efficacy outcomes deliberated on by pERC included progression free survival, overall survival and objective response rate. The primary outcome in the CRYSTAL study was progression-free survival in the ITT population and the primary outcome in FIRE-3 study was progression-free survival in the ITT population; the primary outcome was achieved in both studies.

pERC noted that in the FIRE-3 study, data on the K-RAS wild type population were only available in an abstract and that discordant results were observed between the overall survival and progression-free survival outcomes. In the KRAS wide-type population, the median overall survival was 28.8 months versus 25.0 months (HR 0.77; p=0.0164) in the cetuximab compared to bevacizumab arms, respectively. In contrast, the median progression-free survival in the K-RAS wild-type population was not statistically significant (10.3 vs. 10.4 months, HR=1.04; p=0.69) for the cetuximab and bevacizumab arms, respectively. The objective response rate was 62% and 57% in cetuximab and bevacizumab arm, respectively, in the KRAS wild-type population. Considering the discrepancies in these results and the

limited abstract data available on the KRAS wild-type population, pERC agreed with the pCODR Clinical Guidance Panel that the clinical benefit of cetuximab compared with bevacizumab is uncertain. However, pERC noted that an ongoing study, CALGB-C80405, is expected to provide more robust information in the future on the effectiveness of cetuximab plus FOLFIRI compared with bevacizumab plus FOLFIRI. Upon reconsideration of the pERC Initial Recommendation, pERC discussed the feedback received from the patient advocacy group regarding the significance of the results from the FIRE-3 study that appeared to show discordant results in terms of OS and PFS outcomes. pERC considered that the discrepancy in the data creates uncertainty about the true clinical benefit patients may be achieving from treatment with cetuximab plus FOLFIRI. As such, pERC expects that the results of the ongoing study, CALGB-C80405, should provide more robust evidence on the effectiveness of cetuximab plus FOLFIRI in comparison to bevacizumab plus FOLFIRI.

pERC also discussed the results of the CRYSTAL study, even though FOLFIRI alone is not currently considered the most appropriate comparator in the first-line treatment of mCRC. pERC noted that statistically significant improvements in overall survival and progression-free survival were observed favouring cetuximab plus FOLFIRI. As of the May 31, 2009 data cut-off, the median overall survival of patients with KRAS wild-type tumours was 23.5 months versus 20 months in the cetuximab plus FOLFIRI arm and FOLFIRI alone arm, respectively (HR=0.80; p=0.0093). Median progression-free survival in patients with KRAS wild-type tumours was 9.9 months versus 8.4 months in the cetuximab plus FOLFIRI arm versus FOLFIRI alone arm, respectively (HR=0.70; p=0.0012) while in the ITT population, which was the primary outcome, median PFS was 8.9 versus 8.0 months in the cetuximab plus FOLFIRI arm versus FOLFIRI alone arm, respectively (HR=0.85; p=0.048). Therefore, pERC acknowledged that the addition of cetuximab to FOLFIRI was associated with a clinical benefit in the CRYSTAL study. However, pERC noted that because FOLFIRI alone does not reflect the current first-line standard of care in Canada, there are limitations in determining the applicability of this study to Canadian patients.

pERC also discussed the potential for cetuximab to convert initially unresectable patients to resectability after treatment with cetuximab. In the CRYSTAL study, patients with *KRAS* wild-type disease, R0 resections were achieved in 5.1% on cetuximab + FOLFIRI compared with 2% on FOLFIRI alone (OR 2.65 [95% CI 1.08, 6.49], p=0.027). Results were similar or slightly lower in the ITT populations. However, pERC noted that this was a post-hoc analysis and neither study was powered to evaluate conversion to resectability. Also, both studies included any patients who were unresectable, not just those who were potentially resectable. pERC noted that in order to obtain relevant information on conversion to resectability, a study would need to be designed that evaluated resectability as a primary or key secondary outcome in patients with mCRC who are potentially resectable, and criteria for potential resectability would need to be defined. Therefore, pERC was unable to conclude that cetuximab provides a clinical benefit by converting more patients to resectability. Upon reconsideration of the pERC initial recommendation, pERC discussed the feedback received from the Patient Advocacy Group regarding the post-hoc analysis assessing resectability rates in patients receiving cetuximab. pERC further confirmed that as the study was not designed to assess conversion to resection; (the study population consisted of a mix of resectable and unresectable patients and there was no clear definition of resectability)the data presented is not sufficient to make a conclusion on the potential clinical benefit associated with patients being converted to resectability.

Considering all of these factors, pERC was unable to conclude that there is a net clinical benefit of cetuximab as a first-line therapy for all patients with K-RAS wild type mCRC but acknowledged that there is a clinical need for cetuximab as a first-line therapy in patients who are intolerant to or have a contraindication to bevacizumab. pERC noted that patients would continue to have access to cetuximab later in the management of mCRC as a third-line treatment but the Committee was not confident that there was sufficient evidence to change this treatment strategy to provide access to cetuximab in the first-line treatment of patients with K-RAS wild-type mCRC.

Quality of life: similar between cetuximab plus FOLFIRI and FOLFIRI alone

pERC noted that in CRYSTAL, there were no statistically significant differences between cetuximab plus FOLFIRI and FOLFIRI alone for any of the quality of life measures including global health status and other functional scores including physical, role, emotional, cognitive and social. No quality of life data were reported in the FIRE-3 study.

Safety: well known and manageable toxicities

pERC reviewed the adverse events from the CRYSTAL study and noted that the information aligned with the expected toxicity profile of cetuximab, which is well-known as this agent is already used to treat mCRC patients as a third-line therapy. Established adverse effects related to cetuximab include acneiform rash, diarrhea and hypomagnesemia. In the CRYSTAL study, the grade 3 or 4 adverse events more frequently observed with cetuximab + FOLFIRI compared with FOLFIRI alone were skin reaction, acne-like rash, infusion reaction and palmar-plantar erythrodysesthesia. In FIRE-3, cetuximab was associated with more acneiform exanthema (grade 3-4) and neutropenia while bevacizumab was associated with hypertension.

Comparator information: indirect comparison with bevacizumab plus FOLFOX uncertain

pERC noted that both pCODR's Provincial Advisory Group and the pCODR Clinical Guidance Panel considered bevacizumab plus FOLFIRI or bevacizumab plus FOLFOX to be the current standard of care for patients with epidermal growth factor receptor-expressing *K-RAS* wild-type metastatic colorectal cancer (mCRC). While the FIRE-3 study provided a comparison with bevacizumab plus FOLFIRI, the comparative efficacy with bevacizumab plus FOLFOX was assessed in an indirect comparison. pERC noted that the conclusions drawn from such indirect comparisons are not as robust as those from direct, head-to-head comparisons and, therefore, the findings must be interpreted with caution. It was noted that this indirect comparison had severe limitations, which led to substantial uncertainty, such as including non-randomized non-comparative study design and making unadjusted indirect comparisons.

Need: more effective and tolerable treatment options

Colorectal cancer represents a significant burden of illness in Canada as the second most common cause of cancer-related deaths. The majority of patients with mCRC present with unresectable metastatic colorectal cancer. pERC noted that the current standard of care and most relevant comparator in the first-line treatment of unresectable metastatic colorectal cancer is bevacizumab plus FOLFIRI or bevacizumab plus FOLFOX. The pCODR Clinical Guidance Panel considered that a large majority of patients will still die of mCRC Therefore, there remains a need for more effective therapies. Although pERC was unable to conclude that there is a net clinical benefit of cetuximab as a first-line therapy for all patients with wild type K-RAS mCRC, pERC acknowledged that there is a clinical need for cetuximab as a first-line therapy in patients who are intolerant to, or have a contraindication to bevacizumab and require an effective therapy.

Upon reconsideration of the pERC initial recommendation, pERC discussed the feedback received from the Patient Advocacy Group regarding the need for a treatment option for patients intolerant to bevacizumab. pERC reiterated that they still did not have information to inform the cost-effectiveness of cetuximab plus FOLFIRI compared with FOLFIRI alone in patients intolerant to or with a contraindication to bevacizumab. pERC further emphasized the discordant data from the FIRE-3 study comparing cetuximab with bevacizumab and confirmed that the ongoing study CALGB-C80405 is likely to provide more robust information on the comparative effectiveness of cetuximab versus bevacizumab in the future.

PATIENT-BASED VALUES

Values of patients with metastatic colorectal cancer: disease control and maintaining quality of life

pERC reviewed input from one patient advocacy group and concluded that treatment with cetuximab plus FOLFIRI would align with patient values. From a patient perspective, accessing therapies to help control their mCRC with respect to quality of life, progression free survival and overall survival is extremely important. The most frequently reported disease-related symptoms were fatigue, abdominal pain, bloody stools and painful diarrhea or constipation, all of which significantly impact quality of life. Fatigue, pain, weakness and diarrhea were rated to be the most important and difficult symptoms to control by the majority of patients. pERC noted that patients valued having more effective treatment options and, based on the CRYSTAL study considered that cetuximab could be another first-line treatment option that

would provide a greater clinical benefit than treatment with FOLFIRI alone while providing a similar quality of life.

Patient values on treatment: choice of effective but tolerable treatment options

pERC reviewed input from one patient advocacy group and concluded that treatment with cetuximab plus FOLFIRI would align with patient values. pERC noted that patients value effective but tolerable treatments. However, patients are willing to accept considerable toxicity if a treatment provides an important clinical benefit. Patients reported that it would be very important to have access to additional treatments even though the benefits might only be short term and despite adverse treatment effects. Based on the collected patient input, the majority of patients would accept a cancer therapy despite it having a severe toxicity profile. Patients also value being able to choose, together with their oncologist, the best therapeutic option for the management of their disease. Patient input also noted that patients experience adverse events such as peripheral neuropathy and gastrointestinal events from other treatments and patients value having more tolerable treatment options. Patients indicated that the currently available first and second line treatment with bevacizumab plus FOLFIRI or FOLFOX has proven to successfully shrink tumours and stop the progression of the disease for a period of time for a subset of the population. However, there are some patients who were unable to tolerate, or have a contraindication to bevacizumab as well as oxaliplatin, and, therefore, would like to have an alternative such as cetuximab plus FOLFIRI. pERC acknowledged that there is a need for cetuximab in patients who are intolerant to or have a contraindication to bevacizumab. Upon reconsideration of the pERC initial recommendation, pERC discussed feedback received from the Patient Advocacy group regarding the need for a treatment option for patients that are intolerant to or have a contraindication to bevacizumab. However, pERC recognized that there is still no economic analysis addressing this patient population, which would be required to assess the cost-effectiveness of cetuximab in this setting.

ECONOMIC EVALUATION

Economic model submitted: cost-utility and cost-effectiveness

The pCODR Economic Guidance Panel assessed a cost-utility analysis comparing cetuximab plus FOLFIRI with bevacizumab plus FOLFOX as a first line treatment for patients with KRAS wild-type, EGFR-expressing mCRC. An additional analysis comparing cetuximab plus FOLFIRI with bevacizumab plus FOLFIRI was also assessed.

The economic evaluations involving bevacizumab plus FOLFOX and bevacizumab plus FOLFIRI are based on an indirect comparison, which included the CRYSTAL study, and the pCODR Economic Guidance Panel validated some of the analyses using data from the FIRE-3 study.

Basis of the economic model: clinical and economic inputs

Costs considered in the analysis included drug costs, administration costs, costs of treating adverse events, cost of resection, follow up visits costs and non-drug mCRC costs.

Key clinical effects included progression-free survival, overall survival and liver resection rates. The resection rates were a key driver of the analysis. Clinical efficacy outcomes for the comparison versus bevacizumab plus FOLFOX were based on two randomized controlled trials, CRYSTAL (Van Cutsem 2009) and N016966 (Saltz 2008) while the analysis versus bevacizumab plus FOLFIRI was based on the randomized controlled trial N016966 (Saltz 2008) and the open-label non-comparative non-randomized study, BEAT (Van Cutsem 2009).

Drug costs:

At the list price, cetuximab costs $367.75 per 100 mg single use vial. At the recommended initial (loading) dose of 400mg/m^2, the average cost per day is $256.77 and the average cost per 28-day course is $7,189.51. At the recommended subsequent, weekly dose of 250mg/m^2, cetuximab costs $223.28 per day and $6,251.75 per 28-day course. The cost provided does not assume any wastage of excess cetuximab.

Bevacizumab costs $125.00/5 mg. At the recommended dose (5 mg/kg, 90-min infusion; 5 mg/kg, 60-min infusion 2 weeks later; 5 mg/kg, 30-min infusion every 2 weeks) the average cost per day is $125.00 and the average cost per 28-day course is $3,500.00.
FOLFIRI (irinotecan, leucovorin, fluorouracil) costs $10.00, $0.50 and $1.50 per 20 mg/ml, 10 mg/ml and 50 mg/ml vials, respectively. At the recommended dose of 180 mg/m^2 (irinotecan), 400 mg/m^2 (leucovorin) and 400 mg/m^2 (Fluorouracil), FOLFIRI costs $14.38 per day and $402.56 per 28-day cycle.

FOLFOX (oxaliplatin, leucovorin, fluorouracil) costs $10.20, $0.50 and $1.50 per 1mg/mL, 10mg/ml and 50mg/ml vials, respectively. At the recommended dose of 85 mg/m^2 (oxaliplatin), 400 mg/m^2 (leucovorin) and 400 mg/m^2 (fluorouracil), FOLFOX costs $107.51 per day and $3,010.36 per 28-day cycle.

Cost-effectiveness: cost-effectiveness unknown versus FOLFIRI in patients intolerant to bevacizumab

pERC deliberated upon the cost-effectiveness of cetuximab plus FOLFIRI based on a submitted model comparing it to bevacizumab plus FOLFIRI or to bevacizumab plus FOLFOX. pERC noted that in both comparisons, estimates were highly uncertain due to dependence on an indirect comparison and substantial uncertainty in rates of subsequent resection of metastatic disease. pERC considered that in both comparisons, it would be most appropriate to assume that conversion to resection was similar in the cetuximab and bevacizumab groups, or to exclude resection rates from the model, given the limitations of the clinical trial data for this outcome. Therefore, pERC considered that the cost-effectiveness of cetuximab plus FOLFIRI would likely be at the higher end of the EGP's range of best estimates. Therefore, cetuximab plus FOLFIRI could not be considered cost-effective at the submitted price compared with bevacizumab plus FOLFIRI or bevacizumab plus FOLFOX.

However, as a result of the Committee's deliberations on net clinical benefit, pERC considered it more relevant to assess cost-effectiveness in patients who are intolerant to or have a contraindication to bevacizumab. pERC considered that for these patients, FOLFIRI alone is the most relevant comparator, not bevacizumab plus FOLFIRI or bevacizumab plus FOLFOX. pERC noted that the manufacturer did not submit a comparison of cetuximab plus FOLFIRI with FOLFIRI alone in patients who are intolerant to or have a contraindication to bevacizumab. Therefore, pERC concluded that the cost-effectiveness of cetuximab plus FOLFIRI compared with FOLFIRI alone in this population was unknown.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: impact on treatment algorithms and K-RAS mutation testing

pERC discussed the feasibility of implementing a recommendation for cetuximab. pERC noted that colorectal cancer is the second most common cause of cancer-related deaths and the burden of illness is large. pERC also noted that cetuximab is currently used later in the course of mCRC as a third-line treatment option for patients who have K-RAS wild type disease. pERC noted that the use of cetuximab earlier in treatment could potentially change treatment sequencing and treatment algorithms. If cetuximab were funded in the first-line setting, sequential therapy with bevacizumab as second-line therapy and third-line therapy for patients who would have previously received cetuximab in this setting would need to be further evaluated.

pERC also noted that K-RAS mutation testing has already been established and is done prior to third-line therapy. However, requiring testing prior to first-line mCRC therapy would substantially increase the need for testing and the total cost of testing. This is because more resources and time would be required to coordinate testing in a larger patient population and could possibly delay access to first-line treatment.

DRUG AND CONDITION INFORMATION

Drug Information	• monoclonal antibody • 100mg vial • 400 mg/m^2, 120-min infusion; followed by 250 mg/m^2, 60-min infusion every week
Cancer Treated	• Epidermal growth factor receptor-expressing *K-RAS* wild-type metastatic colorectal cancer (mCRC) • First-line setting
Burden of Illness	• Colorectal cancer is the second most common cause of cancer-related death in Canada • Majority of patients with mCRC present with unresectable metastatic colorectal cancer
Current Standard Treatment	• Bevacizumab plus FOLFIRI (irinotecan, leucovorin, fluorouracil) • Bevacizumab plus FOLFOX (oxaliplatin, leucovorin, fluorouracil)
Limitations of Current Therapy	• A large majority of patients will die of their disease. • There remains a need for more effective cancer therapies. • Some patients unable to tolerate bevacizumab plus FOLFIRI or FOLFOX

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Chaim Bell, Economist
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Wasney, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Peter Venner, Oncologist
Dr. Tallal Younis, Oncologist

Dr. Maureen Trudeau chaired the meeting in her capacity as Vice-Chair of pERC. All members participated in deliberations and voting on the initial recommendation except:

- Dr. Bill Evans who was not present for the meeting
- Dr Anthony Fields and Dr. Scott Berry who were excluded from voting due to a conflict of interest
- Carole McMahon who did not vote due to her role as a patient member alternate

Dr. Maureen Trudeau chaired the meeting in her capacity as Vice-Chair of pERC. All members participated in deliberations and voting on the final recommendation except:

- Dr Anthony Fields and Dr. Scott Berry who were excluded from voting due to a conflict of interest
- Carole McMahon who did not vote due to her role as a patient member alternate

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of cetuximab (Erbitux) for metastatic colorectal cancer, through their declarations, seven members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, two of these members were excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation document.

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