pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Cetuximab (Erbitux) for Metastatic Colorectal Cancer

January 10, 2014

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Bristol-Myers Squibb Canada (BMS)** compared cetuximab +FOLFIRI to bevacizumab +FOLFOX for first-line treatment option for patients in Canada with *KRAS* wild-type epidermal growth factor receptor (EGFR) metastatic colorectal cancer (mCRC). Sensitivity analysis has been submitted comparing cetuximab +FOLFIRI to bevacizumab +FOLFIRI. The clinical trial CRYSTAL compares cetuximab + FOLFIRI with FOLFIRI alone, and therefore the economic evaluations versus bevacizumab+FOLFOX and bevacizumab+FOLFIRI have been based on indirect treatment comparison. Both cetuximab and bevacizumab are administered intravenously.

According to the pCODR Clinical Guidance Panel (CGP), the comparison with bevacizumab+ FOLFOX is appropriate, however the comparison with bevacizumab+FOLFIRI is also appropriate, since bevacizumab is used in combination with both FOLFORI and FOLFOX. Therefore the comparison versus bevacizumab+FOLFIRI needs to be included in the primary analysis as well. Moreover, FOLFOX is more expensive than FOLFIRI and therefore economic evaluation versus bevacizumab+FOLFOX only can undermine the economic implications of potential reimbursement of cetuximab+FOLFIRI. The CGP also considered that there is a benefit of cetuximab plus FOLFIRI in patients who would otherwise be ineligible or unsuitable for first-line bevacizumab use. In this population, FOLFIRI would be the most appropriate comparator. However; the submitter did not provide economic information assessing the cost-effectiveness of cetuximab+FOLFIRI in comparison to FOLFIRI alone in this population of patients.

Patient advocacy groups considered the following factors important in the review of cetuximab, which are relevant to the economic analysis: accessing therapies to help control their mCRC with respect to quality of life, progression free survival and overall survival. The caregivers' burden has also been raised with financial challenges relating to disability and cost of accessing treatments, including travel and parking costs. A full summary of the patient advocacy group input is provided in the pCODR Clinical Guidance Report.

- The submitted economic analysis explicitly considered improvements in overall survival, progression free survival, as well as quality of life information.
- The model has not considered caregivers' burden. While caregiver burden is an important issue, it is traditional for funding recommendations to be based primarily on economic models that take a health system perspective.

The **Provincial Advisory Group (PAG)** considered the comparison with bevacizumab in combination with FOLFOX/FOLFIRI based on direct evidence the resources used in KRAS testing and administration costs as important factors to consider in the economic analysis.

- The clinical efficacy inputs in the submitted model are based on indirect treatment comparison. Results from Fire 3 study directly comparing cetuximab +FOLFIRI to bevacizumab +FOLFIRI are available in abstract form and EGP conducted reanalysis by these inputs to the submitted model.
- PAG indicated that KRAS testing would need to be done earlier for patients, prior to initiating therapy, as opposed to current testing where KRAS test is performed beyond first-line therapy, which would represent change in the current testing

paradigm. The model does not take into consideration costs related to KRAS testing.

- PAG identified that the weekly administration of cetuximab would be a potential barrier, such that additional resources and clinic chair time would be required to prepare and administer cetuximab weekly, where concomitant chemotherapy and alternate treatments are administered every 2 or 3 weeks, however the CGP indicated that this can largely be mitigated by biweekly cetuximab administration which has already been adopted in practice in several jurisdictions. PAG also noted that cetuximab infusion is over one hour and would require more clinic chair time in comparison to the 10 minute bevacizumab infusion time.

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 $7189.51, assuming a body surface area of 1.7m^2. At the recommended subsequent weekly dose of 250mg/m^2, cetuximab costs $223.28 per day and $6251.75 per 28-day course. The cost provided does not assume any wastage of excess cetuximab.

FOLFIRI (Irinotecan, Leucovorin, Fluorouracil) costs $10.00, $0.50 and $1.50 per 20mg/ml, 10mg/ml and 50mg/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, 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 $3010.36 per 28-day cycle.

1.2 Summary of Results

1.2.1 Results of cetuximab+ FOLFIRI comparison with bevacizumab+FOLFOX

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $76,591and $233,500 when cetuximab+ FOLFIRI is compared with bevacizumab+FOLFOX. However, there is large uncertainty around the cost-effectiveness estimates, as described below, that has not been resolved.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The EGP's best estimate of:

- the extra cost [ΔC] of cetuximab+ FOLFIRI when compared with bevacizumab+FOLFOX is between $8,631 and $10,909. Key costs considered in the analysis included drug costs, administration costs and costs associated with resection, follow up visits costs and non-drug mCRC costs.
- the extra clinical effect (ΔE) of cetuximab+ FOLFIRI when compared with bevacizumab+FOLFOX is between 0.0467 and 0.1127 QALYs. Key clinical effects included benefit from higher resection rates, and survival benefit.

The EGP based these estimates on the model submitted by Bristol-Myers Squibb Canada and reanalyses conducted by the EGP.

- The lower estimate of the range (ICER of $76,591) assumed R0 resection rates for cetuximab+ FOLFIRI as observed in CRYSTAL trial, and R0 resection rates for the comparator based on indirect treatment comparison, with relative risks applied to the chemo arm from CRYSTAL, as well as adjusted administration time for fluorouracil to 1 hour, as opposed to 6 hours used in the submitters' base case. The extra costs associated with cetuximab+ FOLFIRI were $8,631 and the extra QALYs associated with cetuximab+ FOLFIRI were 0.1127.
- The upper estimate of the range (ICER of $33,500) assumed equal R0 resection rates across comparators as per CRYSTAL study to account for the large uncertainty around this parameter, as well as the sensitivity of the analysis to this parameter. Adjusted administration time for fluorouracil of 1 hour, as opposed to 6 hours used in the submitters' base case has also been applied to this reanalysis. The extra costs associated with cetuximab+ FOLFIRI were $10,909 and the extra QALYs associated with cetuximab+ FOLFIRI were 0.0467.

The estimates above do not address all the limitations identified by the EGP, especially the issues around OS and PFS inputs that have been based on naive indirect treatment comparison and the uncertainty around the extrapolation techniques. The CGP concluded that the indirect comparison have severe limitations that leads to substantial uncertainty around the conclusion, and therefore, there is currently insufficient evidence to evaluate the clinical benefit of fist-line cetuximab in combination with chemotherapy as compared with the current standard of first-line bevacizumab in combination with chemotherapy.

EGP conducted several additional reanalysis. If the same assumptions around R0 rates are implemented, by shortening the time- horizon to 10 years, the cost-effectiveness range increases to $93,141 to $259,502 per QALY, or if administration costs are based on BC cancer agency (BCCA), the range increases to $102,494 to $294,767.

Therefore, there is large uncertainty around the cost-effectiveness estimates that has not been resolved, resulting with wide range of the EGP estimate. As shown above, the results are extremely sensitive to the R0 resection rates applied in the model. If further evidence shows that the treatment of cetuximab+ FOLFIRI does not result with fewer R0 resection rates compared to bevacizumab+FOLFOX, than the cost-effectiveness ratio is likely to be to the upper estimate of the EGP range.

Results of some of the EGP's sensitivity analyses exploring the impact R0 rates and other parameters on the ICUR's are provided in the table below.

Scenario	cetuximab+FOLFIRI vs bevacizumab +FOLFOX
	ICUR ($/QALY)
R0 rates based on ITC with RR applied on CRYSTAL rates, 5 years	**$115,073**
R0 rates based on ITC with RR applied on CRYSTAL rates, 1 hours 5FU administration	**$76,591**
Equal 5.1% R0 rates across treatments, time horizon of 10 years,	**$259,502**
Equal 5.1% R0 rates across treatments, 1 hours 5FU administration	**$233,500**
Exclusion of R0 rates from the model	$256,410

The EGPs estimates differed from the submitted estimates.

According to the economic analysis that was submitted by Bristol-Myers Squibb Canada when cetuximab+ FOLFIRI is compared with bevacizumab+ FOLFOX

- the extra cost of cetuximab+FOLFIRI is $5,868. Costs considered in the analysis included drug costs, administration costs, costs due to treatment of adverse events, cost of resection, follow up visits costs and non-drug mCRC costs.
- the extra clinical effect of cetuximab+FOLFIRI is 0.21 quality-adjusted life years (QALYs), (0.24 life years gained (LY)), this was largely driven by the favorable R0 resection rates associated with cetuximab.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $28,546 per QALY ($23,768 per LY).

1.2.2 Results of cetuximab+ FOLFIRI comparison with bevacizumab+FOLFIRI

The EGP's estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is at least $181,345 when cetuximab+ FOLFIRI is compared with bevacizumab+FOLFIRI.

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The EGP's estimate of:

- the extra cost [ΔC] of cetuximab+ FOLFIRI when compared with bevacizumab+FOLFIRI is at least $39,485. Key costs considered in the analysis included drug costs, administration costs and costs associated with resection, follow up visits costs and non-drug mCRC costs.
- the extra clinical effect (ΔE) of cetuximab+ FOLFIRI when compared with bevacizumab+FOLFIRI is 0.218 QALYs. Key clinical effects included survival benefit based on Fire 3 study and from estimated higher resection rates

The EGP based these estimates on the model submitted by Bristol-Myers Squibb Canada and reanalyses conducted by the EGP.

These estimates are based on EGP reanalysis implementing the OS and PFS inputs as reported in Fire 3 study which directly compares cetuximab+FOLFIRI and bevacizumab+FOLFIRI, as well as adjusted administration time for fluorouracil to 1 hour, as opposed to 6 hours used in the submitters' base case.

Similar to above, the estimates above do not address all the limitations identified by the EGP, especially the uncertainty around comparative R0 resection rates. The R0 rates from Fire 3 have not yet been reported, and the indirect treatment comparison on R0 resection rates has many methodological limitations, which leads to large uncertainty around these parameters. Based on the EGP reanalysis, using conservative approach of equal R0 efficacy rates among treatments, the cost effectiveness ratio could go up to $9M per QALY.

Results of some of the EGP's sensitivity analyses exploring the impact R0 rates and other parameters on the ICUR's are provided in the table below.

Scenario	cetuximab+FOLFIRI vs bevacizumab +FOLFIRI ICUR ($/QALY)
R0 rates based on ITC with RR applied on CRYSTAL rates, 5 years	**$271,114**
R0 rates based on ITC with RR applied on CRYSTAL rates, 1 hours 5FU administration	**$402,356**
Equal 5.1% R0 rates across treatments, time horizon of 10 years,	**$645,529**
Equal 5.1% R0 rates across treatments, 1 hours 5FU administration	**$2,754,430**
Exclusion of R0 rates from the model	$2,724,173

According to the economic analysis that was submitted by Bristol-Myers Squibb Canada, when cetuximab+ FOLFIRI is compared with bevacizumab+ FOLFIRI:

- the extra cost of cetuximab+FOLFIRI is $37,376. Same as above, costs considered in the analysis included drug costs, administration costs, costs due to treatment of adverse events, cost of resection, follow up visits costs and non-drug mCRC costs.
- the extra clinical effect of cetuximab+FOLFIRI is 0.24 quality-adjusted life years (QALYs), (0.28 LYs) similarly to above largely driven by the favorable R0 resection rates associated with cetuximab.

So, the submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $159,282 per QALY ($133,259/LY).

1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of ΔC, ΔE and the ICER differ from the Submitter's, what are the key reasons?

The key reasons for differences between the submitter's and Economic Guidance Panel's estimates relate to assumptions around R0 resection rates that appear to be main driver of the cost effectiveness results. The R0 rates used to inform the model have been based on simplistic indirect comparison, subject to methodological limitations, which resulted with large inconsistency between R0 rates for cetuximab +FOLFIRI among the submitted ITC-based results and the results from the CRYSTAL study and therefore high degree of uncertainty. The CGP found the R0 rates from CRYSTAL study to be more appropriate in an upfront unresectable mCRC population, which are also comparable with the rates from NO16966 study in similar patient population.

Were factors that are important to patients adequately addressed in the submitted economic analysis?

Yes. Patient advocacy groups considered the following factors important in the review of cetuximab, which are relevant to the economic analysis: accessing therapies to help control their mCRC with respect to quality of life, progression free survival, overall

survival and spoke about the caregivers' burden, including travel costs. These factors were addressed in the economic analysis when possible and appropriate.

Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?

Yes, the model structure was adequate and no changes in structure are needed.

For key variables in the economic model, what assumptions were made by the Submitter in their analysis that have an important effect on the results?

The assumptions around the R0 resection rates as implemented in the submitted model appear to have the most important effect on the results. R0 resection indicates complete removal of the tumor and therefore patients achieving R0 resection are disease-free and have quality of health and mortality rates as for the general population. The favorable R0 resection rate for cetuximab used to inform the model have been based on simplistic indirect comparison, subject to many methodological limitations, which resulted with large inconsistency between R0 rates for cetuximab +FOLFIRI among the submitted ITC-based results (12.5%)and the actual results from the CRYSTAL study (5.1%). The CGP found the R0 rates from CRYSTAL study to be more appropriate in an upfront unresectable mCRC population, which are also comparable with the rates from NO16966 study conducted in similar patient population.

Comparative clinical efficacy in terms of overall survival and progression free survival of cetuximab + FOLFIRI and bevacizumab+ FOLFOX was based on simplistic indirect treatment comparison based on two phase III RCT, CRYSTAL[1] and N016966[2]. In addition, the comparative clinical efficacy of cetuximab + FOLFIRI and bevacizumab+ FOLFIRI was based on indirect treatment comparison based on the phase III RCT N016966[2] and the open-label non-comparative non RCT trial BEAT[3]. The CGP report concluded that the indirect comparison have severe limitations that leads to substantial uncertainty around the conclusion, and therefore, there is currently insufficient evidence to evaluate the clinical benefit of fist-line cetuximab in combination with chemotherapy as compared with the current standard of first-line bevacizumab in combination with chemotherapy.

Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the EGP would have chosen and were they adequate for answering the relevant question?

There is large uncertainty around the clinical effects used in the submitted model. The indirect treatment comparison has many methodological limitations. Also, there is a lot of uncertainty around the long term benefit, since it is based on extrapolation with no formal statistical goodness of fit test, nor the impact of alternative distributions has been explored. The impact of alternative distributions has not been explored. With the exception of the administration costs, the rest of the cost inputs seem adequate and the EGP would have used similar data.

1.4 Summary of Budget Impact Analysis Assessment

The manufacturer submitted a budget impact analysis for Canadian settings providing estimates of the increased costs for the three years subsequent to the listing of cetuximab as 1st line treatment for KRAS wild-type epidermal growth factor receptor (EGFR)-expressing mCRC. The submitted budget impact analysis seems well-designed with standard methods to calculate incidence and prevalence. The model uses estimates of current market share for bevacizumab, and cetuximab, as well as forecasted market

growth for cetuximab, based on manufacturer's market research studies. It has been estimated that market share of cetuximab for first line will be 5.5%, 8.4% and 9.1% in year 1, 2 and 3.

What factors most strongly influence the budget impact analysis estimates?

The results from the submitted sensitivity analyses showed that the results will be most sensitive to drug costs and cetuximab estimated market share, which is to be expected.

What are the key limitations in the submitted budget impact analysis?

The main limitation of the analysis seems to be the fact that it assumes use of cetuximab with FOLFOX and FOLFIRI in 58% and 42% of the patients respectively, although cetuximab +FOLFIRI only is under pCODR review. In addition, the administration costs and KRAS testing costs are not included in the analysis.

1.5 Future Research

What are ways in which the submitted economic evaluation could be improved?

More sophisticated indirect comparison among cetuximab and bevacizumab, based on Kaplan–Meier graphs instead relative risk of time to event would have been more appropriate and may have reduced the uncertainty of clinical efficacy inputs.

The economic evaluation of could have been largely improved by conducting more sensitivity analysis around the uncertainty of the input parameters as well as the assumptions used in the model. More robust probabilistic sensitivity analysis would have been helpful to fully capture the uncertainty around the estimates.

Is there economic research that could be conducted in the future that would provide valuable information related to cetuximab for metastatic Colorectal Cancer (mCRC)?

A head to head clinical study direct comparing first line of cetuximab +FOLFIRI and bevacizumab +FOLFOX would have improved the evidence around the clinical efficacy inputs and eliminated the need for indirect treatment comparison which itself has inherent uncertainties. Also, once the results from the Fire 3 study are fully available, including the R0 resection rates, conducting an economic analysis using those estimates would be helpful.

2. DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the *pCODR Disclosure of Information Guidelines*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Final Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Gastrointestinal Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-effectiveness of cetuximab (Erbitux) for metastatic colorectal cancer. A full assessment of the clinical evidence of cetuximab (Erbitux) for metastatic colorectal cancer is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no information redacted from this publicly available Guidance Report.

This Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.pcodr.ca). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

REFERENCES

1. Van Cutsem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009 Apr 2;360(14):1408-17.

2. Saltz LB, Clarke S, Diaz-Rubio E, Scheithauer W, Figer A, Wong R, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a andomized phase III study. J Clin Oncol. 2008 Apr 20;26(12):2013-9.

3. Van Cutsem E, Rivera F, Berry S, Kretzschmar A, Michael M, DiBartolomeo M, et al. Safety and efficacy of first-line bevacizumab with FOLFOX, XELOX, FOLFIRI and fluoropyrimidines in metastatic colorectal cancer: the BEAT study. Ann Oncol. 2009 Nov;20(11):1842-7.

4. Tournigand C, Andre T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol. 2004 Jan 15;22(2):229-37.

5. Adam R, Wicherts DA, de Haas RJ, Ciacio O, Levi F, Paule B, et al. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? J Clin Oncol. 2009 Apr 10;27(11):1829-35.

6. Asseburg C, Frank M, Köhne CH, Hartmann JT, Griebsch I, Mohr A, et al. Cost-effectiveness of targeted therapy with cetuximab in patients with K-*ras* wild-type colorectal cancer presenting with initially unresectable metastases limited to the liver in a German setting. Clin Ther. 2011 Apr;33(4):482-97.

7. Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE. LBA3506: randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS wild-type metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3). J Clin Oncol [Internet]. 2013 [cited 2013 Jul 9];31(suppl). Available from: http://meetinglibrary.asco.org/print/1158611 (Presented at Annual Meeting of the American Society of Clinical Oncology (ASCO), Chicago, May 31 - June 4, 2013).

8. Stintzing S, Jung A, Rossius L, Modest DP, von Weikersthal LF, Decker T, et al. Analysis of KRAS/NRAS and BRAF mutations in FIRE-3: a randomized phase III study of FOLFIRI plus cetuximab or bevacizumab as first-line treatment for wild-type (WT) KRAS (exon 2) metastatic colorectal cancer (mCRC) patients. Abstract presented at: European Cancer Congress 2013. 2013 September 27 - October 1; Amsterdam, The Netherlands. Abstract LBA17.