pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Panitumumab (Vectibix) for Metastatic Colorectal Cancer

December 3, 2015

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INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
154 University Avenue, Suite 300
Toronto, ON
M5H 3Y9

Telephone: 613-226-2553
Toll Free: 1-866-988-1444
Fax: 1-866-662-1778
Email: requests@cadth.ca
Website: www.cadth.ca/pcodr

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

Two main economic analyses were **submitted to pCODR by Amgen Canada Inc.** for patients with wild-type (WT) rat sarcoma-2 (RAS) metastatic colorectal cancer (mCRC): those who are bevacizumab-ineligible and those who are bevacizumab-eligible.

- In the bevacizumab-ineligible population, the submitter provided a model, which compared panitumumab in combination with FOLFOX to either FOLFOX alone or FOLFIRI alone in the first line setting.
- In the bevacizumab-eligible population, the submitter provided a model, which compared panitumumab in combination with FOLFOX to either bevacizumab in combination with FOLFOX or bevacizumab in combination with FOLFIRI in the first-line setting.

Panitumumab as well as FOLFOX, FOLFIRI and bevacizumab are administered intravenously.

According to the pCODR Clinical Guidance Panel (CGP), the comparisons for both the bevacizumab ineligible and eligible populations are appropriate.

Patients considered the following factors important in the review of panitumumab, which are relevant to the economic analysis: access to therapies, disease control, quality of life, progression-free survival and overall survival. All these factors have been incorporated into the economic model.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for panitumumab, and which are relevant to the economic analysis:

- *Appropriateness of comparator*: The PRIME[1] trial which compared panitumumab plus FOLFOX to FOLFOX alone is not current standard of care. The PEAK[2] trial comparing panitumumab plus FOLFOX to bevacizumab plus FOLFOX is more relevant. Both of these analyses are presented here in this report.
- *Sequencing of treatments*: Sequencing of treatments may vary in the provinces. For example, bevacizumab plus FOLFOX or FOLFIRI is funded for second-line treatment some provinces and panitumumab monotherapy is funded for third-line treatment in most provinces. The EGP examined the impact of these scenarios in their one-way scenario analyses.
- *Drug administration*: In provinces that fund third-line panitumumab, there is familiarity for the patients and centres administering the drugs with panitumumab which is an enabler to implementation. Further, panitumumab is given in combination with FOLFOX, with the same schedule as FOLFOX, which is an enabler for patients.
- *Drug wastage*: In smaller centres where vial sharing may be difficult, PAG noted that there may be incremental costs to drug wastage. The EGP examined the impact of wastage in its analysis.
- *Increased incremental costs*: The cost of panitumumab, the need for RAS testing and the longer infusion times are all possible barriers to implementation.

Panitumumab costs $615.96 per 100mg vial with a strength of 20mg/mL. At the recommended dose of 6 mg/kg day 1 every 2 weeks, with a body weight of 70 kg, the cost of panitumumab is $184.78 per day and $5174.06 per 28-day course. Bevacizumab cost $600.00 per 100mg vial. At the recommended dose of 5 mg/kg day 1 every 2 weeks, with a

body weight of 70 kg, the cost of bevacizumab is $150.00 per day and $4200.00 per 28-day course.

Oxaliplatin cost $10.20/mg. At the recommended dose of 85 mg/m^2 day 1 every 2 weeks, the cost of oxaliplatin is $105.28 per day and $2947.80 per 29-day course. Leucovorin cost $0.05/mg. At the recommended dose of 200 mg/m^2 day 1 and 2 every 2 weeks, the cost of leucovorin is $2.43 per day and $68.00 per 28-day course. Fluorouracil cost $0.003/mg. At the recommended dose of bolus, 400 mg/m^2 and 2400 mg/m^2 on day 1 and continued over 3 days every 2 weeks, the cost of fluorouracil is $2.77 per day and $77.52 per 28-day course. Irinotecan cost $0.50/mg. At the recommended dose of 180 mg/m^2 day 1 every 2 weeks, the cost of irinotecan is $10.93 per day and $306.00 per 28-day course.

1.2 Summary of Results

The EGP was unable to provide best estimates for all comparators in the bevacizumab-ineligible and bevacizumab-eligible population as the submitter did not provide models with the option to modify the time horizon upon request. The EGP conducted their own modifications of the models and truncated the length over which costs and benefits were accrued. The submitter noted it was not possible because of downstream therapies and potential survival gained with subsequent therapies. However, continuing to accrue benefit from downstream therapies when there is little likelihood of patients surviving to that time frame is not reasonable and may favour panitumumab. Other reviews of mCRC have noted that time horizons of 3 – 5 years are reasonable, which is supported by the CGP.

Bevacizumab-ineligible patients

According to the economic analysis that was submitted by Amgen Canada Inc., when panitumumab +FOLFOX is compared with FOLFOX:

- the extra cost of panitumumab is $43,859 (ΔC). Costs considered in the analysis included drug acquisition costs, drug administration costs, RAS testing, resource costs and liver resection costs.
- the extra clinical effect of panitumumab is 0.250 quality-adjusted life years gained (ΔE). The clinical effect considered in the analysis was based on progression-free survival, time to death, and utilities.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $175,202.

The EGP was unable to determine a best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) when panitumumab, in combination with FOLFOX, is compared with FOLFOX or FOLFIRI.

The EGP conducted reanalyses based on the model submitted by Amgen Canada Inc.

For panitumumab + FOLFOX vs FOLFOX alone, the reanalysis conducted by the EGP using the submitted model showed that when:

- Wastage was included, the extra cost of panitumumab is $48,440 ($\Delta C_1$), and the extra clinical effect is 0.250 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $193,501 (from $175,202).

- Liver resection rates are equal for both treatment arms and are set at a rate of 17.1%, the extra cost of panitumumab is $42,455 ($\Delta C_2$) and the extra clinical effect is 0.200 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $212,762 (from $175,202).
- The utility for best supportive care is lowered to 0.636, the extra cost of panitumumab is $43,859 ($\Delta C_3$), and the extra clinical effect of panitumumab is 0.251 (ΔE_3), which decreases the estimated incremental cost-effectiveness ratio to $174,440 (from $175,202).
- As the 95% confidence interval for hazard ratio for progression-free survival was a significant driver of the ICER and a plausible range within which to expect to find results, the EGP examined the upper and lower bound:
    - When the lower 95% confidence interval for the progression-free survival hazard ratio for panitumumab + FOFLOX vs FOLFOX is used, the extra cost of panitumumab is $52,087 ($\Delta C_4$), and the extra clinical effect of panitumumab is 0.489 (ΔE_4), which decreases the estimated incremental cost-effectiveness ratio to $106,481 (from $175,202).
    - When the upper 95% confidence interval for the progression-free survival hazard ratio for panitumumab + FOFLOX vs FOLFOX is used, the extra cost of panitumumab is $36,117 ($\Delta C_5$), and the extra clinical effect of panitumumab is 0.061 (ΔE_5), which increases the estimated incremental cost-effectiveness ratio to $588,014 (from $175,202).

According to the economic analysis that was submitted by Amgen Canada Inc., when panitumumab +FOLFOX is compared with FOLFIRI:

- the extra cost of panitumumab is $52,264 ($\Delta C$). Costs considered in the analysis included drug acquisition costs, drug administration costs, RAS testing, resource costs and liver resection costs.
- the extra clinical effect of panitumumab is 0.250 quality-adjusted life years gained (ΔE). The clinical effect considered in the analysis was based on progression-free survival, time to death, and utilities.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $208,778.

For panitumumab + FOLFOX vs FOLFIRI alone, the reanalysis conducted by the EGP using the submitted model showed that when:

- Wastage was included, the extra cost of panitumumab is $58,174 ($\Delta C_1$), and the extra clinical effect is 0.250 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $232,384 (from $208,778).
- Liver resection rates are equal for both treatment arms and are set at a rate of 17.1%, the extra cost of panitumumab is $50,860 ($\Delta C_2$) and the extra clinical effect is 0.200 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $254,884 (from $208,778).
- The utility for best supportive care is lowered to 0.636, the extra cost of panitumumab is $52,264 ($\Delta C_3$), and the extra clinical effect of panitumumab is

0.251 (ΔE_3), which decreases the estimated incremental cost-effectiveness ratio to $207,869 (from $208,778).

- As the 95% confidence interval for hazard ratio for progression-free survival was a significant driver of the ICER and a plausible range within which to expect to find results, the EGP examined the upper and lower bound:
    - When the lower 95% confidence interval for the progression-free survival hazard ratio for panitumumab + FOFLOX vs FOLFOX is used, the extra cost of panitumumab is $60,492 ($\Delta C_4$), and the extra clinical effect of panitumumab is 0.489 (ΔE_4), which decreases the estimated incremental cost-effectiveness ratio to $123,663 (from $208,778).
    - When the upper 95% confidence interval for the progression-free survival hazard ratio for panitumumab + FOLFOX vs FOLFOX is used, the extra cost of panitumumab is $44,522 ($\Delta C_5$), and the extra clinical effect of panitumumab is 0.061 (ΔE_5), which increases the estimated incremental cost-effectiveness ratio to $724,858 (from $208,778).

Bevacizumab-eligible patients

The EGP was unable to determine a best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) when panitumumab, in combination with FOLFOX, is compared with bevacizumab in combination with FOLFOX or FOLFIRI.

According to the economic analysis that was submitted by Amgen Canada Inc., when panitumumab +FOLFOX is compared with bevacizumab + FOLFOX:

- the extra cost of panitumumab is $13,096 (ΔC). Costs considered in the analysis included drug acquisition costs, drug administration costs, RAS testing, resource costs and liver resection costs.
- the extra clinical effect of panitumumab is 0.113 quality-adjusted life years gained (ΔE). The clinical effect considered in the analysis was based on progression-free survival, time to death, and utilities.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $116,184.

The EGP conducted reanalyses based on the model submitted by Amgen Canada Inc.

For panitumumab + FOLFOX vs bevacizumab + FOLFOX, the reanalysis conducted by the EGP using the submitted model showed that when:

- Wastage was included, the extra cost of panitumumab is $13,807 ($\Delta C_1$), and the extra clinical effect is 0.113 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $122,494 (from $116,184).
- Liver resection rates are equal for both treatment arms and are set at a rate of 17.1%, the extra cost of panitumumab is $11,692 ($\Delta C_2$) and the extra clinical effect is 0.062 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $188,804 (from $116,184).
- The utility for best supportive care is lowered to 0.636, the extra cost of panitumumab is $13,096 ($\Delta C_3$), and the extra clinical effect of panitumumab is

0.113 (ΔE_3), which decreases the estimated incremental cost-effectiveness ratio to $115,415 (from $116,184).

- As the 95% confidence interval for hazard ratio for progression-free survival was a significant driver of the ICER and a plausible range within which to expect to find results, the EGP examined the upper and lower bound:
    - When the lower 95% confidence interval for the progression-free survival hazard ratio for panitumumab + FOFLOX vs FOLFOX is used, the extra cost of panitumumab is $21,324 ($\Delta C_4$), and the extra clinical effect of panitumumab is 0.352 (ΔE_4), which decreases the estimated incremental cost-effectiveness ratio to $60,656 (from $116,184).
    - When the upper 95% confidence interval for the progression-free survival hazard ratio for panitumumab + FOLFOX vs FOLFOX is used, the extra cost of panitumumab is $5,353 ($\Delta C_5$), and the extra clinical effect of panitumumab is -0.131 (no clinical benefit—less benefit than comparator) (ΔE_5), thus making the treatment strategy dominated (costs more, less effective).

According to the economic analysis that was submitted by Amgen Canada Inc., when panitumumab +FOLFOX is compared with bevacizumab + FOLFIRI:

- the extra cost of panitumumab is $22,657 (ΔC). Costs considered in the analysis included drug acquisition costs, drug administration costs, RAS testing, resource costs and liver resection costs.
- the extra clinical effect of panitumumab is 0.113 quality-adjusted life years gained (ΔE). The clinical effect considered in the analysis was based on progression-free survival, time to death, and utilities.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $201,005.

For panitumumab + FOLFOX vs bevacizumab + FOLFIRI, the reanalysis conducted by the EGP using the submitted model showed that when:

- Wastage was included, the extra cost of panitumumab is $24,900 ($\Delta C_1$), and the extra clinical effect is 0.113 (ΔE_1), which increases the estimated incremental cost-effectiveness ratio to $220,908 (from $201,005).
- Liver resection rates are equal for both treatment arms and are set at a rate of 17.1%, the extra cost of panitumumab is $21,253 ($\Delta C_2$) and the extra clinical effect is 0.062 (ΔE_2), which increases the estimated incremental cost-effectiveness ratio to $343,195 (from $201,005).
- The utility for best supportive care is lowered to 0.636, the extra cost of panitumumab is $22,657 ($\Delta C_3$), and the extra clinical effect of panitumumab is 0.113 (ΔE_3), which decreases the estimated incremental cost-effectiveness ratio to $199,675 (from $201,005).
- As the 95% confidence interval for hazard ratio for progression-free survival was a significant driver of the ICER and a plausible range within which to expect to find results, the EGP examined the upper and lower bound:

- When the lower 95% confidence interval for the progression-free survival hazard ratio for panitumumab + FOFLOX vs FOLFOX is used, the extra cost of panitumumab is $30,885 ($\Delta C_4$), and the extra clinical effect of panitumumab is 0.352 (ΔE_4), which decreases the estimated incremental cost-effectiveness ratio to $87,852 (from $201,005).
- When the upper 95% confidence interval for the progression-free survival hazard ratio for panitumumab + FOFLOX vs FOLFOX is used, the extra cost of panitumumab is $14,914 ($\Delta C_5$), and the extra clinical effect of panitumumab is -0.076 (no clinical benefit—less benefit than comparator) (ΔE_5), thus making the treatment strategy dominated (costs more, less effective).

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 EGP was unable to provide a best estimate for all comparators in both the bevacizumab-ineligible and bevacizumab-eligible population, largely due to the lack of the option to modify the time horizon. Though a lifetime horizon is recommended when doing economic modeling, an appropriate lifetime needs to be chosen for a given patient population. In this case, the CGP has identified in this review, and other mCRC reviews, that 3-5 years is an appropriate time horizon. The EGP did ask for a model with the ability to modify this, and it was not provided. However, the submitter provided a rationale that by changing the time horizon, the model would end up with extra survival attributed to subsequent lines of therapy.

Though the EGP was not able to provide a best estimate, they were able to identify two inputs that had a large impact on the ICER: the progression-free survival hazard ratio of panitumumab + FOLFOX vs FOLFOX and liver resection rates. The 95% confidence intervals for the progression-free survival hazard ratio for panitumumab had a large impact on the ICER. Liver resection rates, though not significantly different in the clinical trial, were assumed to be different in the submitter's main analysis. When equal resection rates were examined, there was an impact on the ICER. The EGP had also wished to modify the utility associated with liver resection rates, based on other utilities identified in the literature, however, the cell functionality for this input was not working; the impact did not appear to be as large as the liver resection rates themselves and in the interest of the review timeline, this was not pursued further.

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

Yes, factors important to patients – survival, quality of life – were taken into account in the economic model.

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

The model provided may not be adequate. The EGP had requested a model that allowed for the modification of the time horizon, and the submitter was not able to do this.

However, the submitter provided a rationale that by changing the time horizon, the model would end up with extra survival attributed to subsequent lines of therapy. Further, there were some inputs that were not functioning correctly in the model (i.e. the EGP was also unable to modify these); the impact of the utility associated with liver resection rates did not appear to be as large as the liver resection rates themselves and in the interest of the review timeline, this was not pursued further. Finally, the using a design of a partitioned survival analysis may overestimate the benefit of survival in the post-progression state.

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 95% confidence interval for the progression-free survival hazard ratio of panitumumab+FOLFOX had a large impact on the results. The CGP had indicated that there may not be any net clinical benefit in bevacizumab-eligible patients when compared to bevacizumab (although not inferior), and that the benefit may be modest in bevacizumab-ineligible patient when compared to FOLFOX alone; the magnitude of change on the ICER with the modification in the hazard ratio is large.

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?

Many of the data inputs were adequate, however, the EGP felt that liver resection rates did not warrant being different for the two treatment arms. Further, in the clinical trial, no significant differences were found in liver resection rates between the two treatment arms; the CGP confirmed that there is no clinical reason that they should be different. The EGP had also wished to modify the utility associated with liver resection rates, based on other utilities identified in the literature, however, the cell functionality for this input was not working; the impact did not appear to be as large as the liver resection rates themselves and in the interest of the review timeline, this was not pursued further.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The BIA was most sensitive to the number of metastatic CRC cases, whether or not bevacizumab is provided in the second-line after panitumumab and the market uptake in bevacizumab-ineligible patients.

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

The number of mCRC patients eligible for treatment is an assumption, along with the number of patients who are tested for RAS (a requirement prior to panitumumab treatment). Further, the submitter assumed that only 95% of patients would have the cost covered of panitumumab, where, if the drug was recommended for reimbursement, the number would likely be 100%.

1.5 Future Research

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

Providing an economic model where the option to modify the time horizon would allow the EGP to provide a best estimate. This would allow the EGP to examine the drug in the context of similar inputs to other drugs for the same population of patient with mCRC. The EGP had also wished to modify the utility associated with liver resection rates, based on other utilities identified in the literature, however, the cell functionality for this input was not working; the impact did not appear to be as large as the liver resection rates themselves and in the interest of the review timeline, this was not pursued further.

Is there economic research that could be conducted in the future that would provide valuable information related to panitumumab for metastatic colorectal cancer?

The use of individual patient data in a future economic analysis could improve the precision of survival inputs. Also, as liver resection rates are a driver of the ICER, calculating sample size to ensure that there is adequate power to detect a difference would be helpful. Further, Markov modeling in order to account for post-progression survival, and the impact of subsequent therapies, may provide more insight into the cost-effectiveness of mCRC therapies.

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 Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Gastrointestional 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 panitumumab (Vectibix) for metastatic colorectal cancer. A full assessment of the clinical evidence of panitumumab (Vectibix) 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.cadth.ca/pcodr).

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.

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.cadth.ca/pcodr). 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. Douillard JY, Oliner KS, Siena S, et al. Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. *The New England journal of medicine.* Sep 12 2013;369(11):1023-1034.

2. Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Apr 20 2008;26(12):2013-2019.

3. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Apr 1 2008;26(10):1626-1634.

4. Adam R, Wicherts DA, de Haas RJ, et al. Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Apr 10 2009;27(11):1829-1835.

5. Peeters M, Price T, Cervantes A, al. e. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI along as second-line treatment in patients with metastatic colorectal cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2010;28(31):4706-4713.

6. Van Cutsem E, Peeters M, Siena S, al. e. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care along in patients with chemotherapy-refractory metastatic colorectal cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007;25(13):1658-1664.

7. Evans WK, Wolfson MC, Flanagan WM, et al. Canadian Cancer Risk Management Model: evaluation of cancer control. *International journal of technology assessment in health care.* Apr 2013;29(2):131-139.

8. Dranitsaris G, Truter I, Lubbe MS, Cottrell W, Spirovski B, Edwards J. The application of pharmacoeconomic modelling to estimate a value-based price for new cancer drugs. *Journal of evaluation in clinical practice.* Apr 2012;18(2):343-351.

9. Mittmann N, Au HJ, Tu D, et al. Prospective cost-effectiveness analysis of cetuximab in metastatic colorectal cancer: evaluation of National Cancer Institute of Canada Clinical Trials Group CO.17 trial. *Journal of the National Cancer Institute.* Sep 2 2009;101(17):1182-1192.

10. Wang J, Zhao Z, Barber B, Sherrill B, Peeters M, Wiezorek J. A Q-TWiST analysis comparing panitumumab plus best supportive care (BSC) with BSC alone in patients with wild-type KRAS metastatic colorectal cancer. *British journal of cancer.* Jun 7 2011;104(12):1848-1853.

11. Gazelle GS, McMahon PM, Beinfeld MT, Halpern EF, Weinstein MC. Metastatic colorectal carcinoma: cost-effectiveness of percutaneous radiofrequency ablation versus that of hepatic resection. *Radiology.* Dec 2004;233(3):729-739.

12. Ewara EM, Zaric GS, Welch S, Sarma S. Cost-effectiveness of first-line treatments for patients with KRAS wild-type metastatic colorectal cancer. *Current oncology (Toronto, Ont.).* Aug 2014;21(4):e541-550.

13. Lawrence D, Maschio M, Leahy KJ, Yunger S, Easaw JC, Weinstein MC. Economic analysis of bevacizumab, cetuximab, and panitumumab with fluoropyrimidine-based chemotherapy in the

first-line treatment of KRAS wild-type metastatic colorectal cancer (mCRC). *Journal of medical economics.* Dec 2013;16(12):1387-1398.

14. Graham CN, Hechmati G, Hjelmgren J, et al. Cost-effectiveness analysis of panitumumab plus mFOLFOX6 compared with bevacizumab plus mFOLFOX6 for first-line treatment of patients with wild-type RAS metastatic colorectal cancer. *European journal of cancer (Oxford, England : 1990).* Nov 2014;50(16):2791-2801.