CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Panitumumab (Vectibix) for Left-Sided metastatic Colorectal Cancer

March 29, 2018

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The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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TABLE OF CONTENTS

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

Two main economic analyses were submitted to **pCODR by Amgen Canada Inc.** for patients with primary left-sided wild-type (WT) rat sarcoma-2 (RAS) metastatic colorectal cancer (mCRC): those who receive bevacizumab and those who do not receive bevacizumab in the first-line setting.

- For patients who receive bevacizumab in the first-line setting, 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.
- For patients who do not receive bevacizumab in the first-line setting, the submitter provided a model, which compared panitumumab in combination with FOLFOX to either FOLFOX alone or FOLFIRI alone in the first line setting.

The submitter provided the option of using FOLFIRI as the backbone chemotherapy (instead of FOLFOX).

Table 1. Submitted Economic Model

Funding Request/Patient Population Modelled	First-line treatment of left-sided WT RAS mCRC
Type of Analysis	CUA and CEA
Type of Model	Partitioned survival
Comparator	For patients who receive bevacizumab (see Table 2), the comparator was bevacizumab plus FOLFOX. For patients who do not receive bevacizumab (see Table 3), the comparator was FOLFOX alone.
Year of costs	2017
Time Horizon	Lifetime
Perspective	Government
Cost of Panitumumab *Accessed IMS Brogan on January 11, 2018	At the list price, panitumumab costs $641.92 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 $192.55 per day and $5391.29 per 28-day course.
Cost of Comparator	Bevacizumab costs $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 $4,200.00 per 28-day course. Oxaliplatin costs $10.20/mg. At the recommended dose of 85 mg/m2 day 1 every 2 weeks, the cost of oxaliplatin is $105.28 per day and $2947.80 per 28-day course. Leucovorin costs $0.05/mg. At the recommended dose of 200 mg/m2 day 1 and 2 every 2 weeks, the cost of leucovorin is $2.43 per day and $68.00 per 28-day course. Fluorouracil costs $0.003/mg. At the recommended dose of bolus, 400 mg/m2 and 2400 mg/m2 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 costs $0.50/mg. At the recommended dose of 180

	mg/m2 day 1 every 2 weeks, the cost of irinotecan is $10.93 per day and $306.00 per 28-day course. Capecitabine costs $0.46 per 150 mg tablet and $1.53 per 500 mg tablet. At the recommended dose of 1000 mg/m2 PO BID days 1-14 every 3 weeks, the cost of capecitabine is $6.97 per day and $195.20 per 28-day course.
Model Structure	A partitioned survival with the following periods: first-line progression-free survival, second-line progression-free survival, third-line progression-free survival, time to death given no second-line treatment (i.e. best supportive care only after first line), time to death given no third-line treatment (ie. best supportive care only after second line), time to death following third-line treatment.
Key Data Sources	Boeckx retrospective review of PRIME and PEAK Network meta-analysis

Table 2. Management strategy used in economic model for patients who receive bevacizumab first line, as taken from pCODR submission

Management Strategy	First Line	Second Line	Third Line
Panitumumab	Panitumumab + FOLFOX	Bevacizumab + FOLFIRI	BSC alone
Comparator	Bevacizumab + FOLFOX	FOLFIRI alone	Panitumumab + BSC

BSC = best supportive care; FOLFIRI = 5-fluorouracil, irinotecan, and leucovorin; FOLFOX = 5-fluorouracil, oxaliplatin, and leucovorin.

Table 3. Management strategy for patients who do not receive bevacizumab first line, as taken from pCODR submission

Management Strategy	First Line	Second Line	Third Line
Panitumumab	Panitumumab + FOLFOX	Bevacizumab + FOLFIRI	BSC alone
Comparator	FOLFOX alone	Bevacizumab + FOLFIRI	Panitumumab + BSC

BSC = best supportive care; FOLFIRI = 5-fluorouracil, irinotecan, and leucovorin; FOLFOX = 5-fluorouracil, oxaliplatin, and leucovorin.

1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate.

- Relevant issues identified in the conclusions of the CGP included:
  - *With respect to the NMA, the NMA was deemed to be overall well designed and of high quality, but given findings demonstrating uncertainty in the comparative efficacy of chemotherapy plus panitumumab in patients with left-sided tumours, the results of the NMA were difficult to interpret.*
  - *The retrospective efficacy analysis of left-sided tumors for the PRIME study showed a statistically significant OS and PFS benefit of panitumumab over chemotherapy; however, there was no evidence of a statistical difference between treatment effect and tumor sidedness.*

- *The retrospective analysis of left-sided tumors for the PEAK study showed that there was no significant treatment difference observed by sidedness between panitumumab plus FOLFOX versus bevacizumab plus FOLFOX.*
- *Though bevacizumab plus chemotherapy may be a clinically appropriate therapy following panitumumab plus chemotherapy, it is not currently available in all provinces as second-line treatment.*
- *Extended RAS testing should be used to guide decisions and may not be routinely available prior to commencement of first-line therapy.*

Summary of registered clinician input relevant to the economic analysis
Registered clinicians considered panitumumab plus chemotherapy is superior in survival benefits for the subgroup of patients with RAS wild-type left-sided mCRC. They noted that RAS testing is required to determine eligibility for treatment with panitumumab. Panitumumab has adverse events that include skin toxicity, diarrhea and fatigue.

Summary of patient input relevant to the economic analysis
Patients considered symptom management, improvement in quality of life, and disease control as important factors. These were incorporated into the economic analysis through adverse events, utilities and progression-free survival.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis
PAG considered the following factors (enablers or barriers) important to consider if implementing a funding recommendation for panitumumab which are relevant to the economic analysis:

- *Sequencing of therapies following first-line panitumumab.*
- *Use of FOLFIRI as the combination chemotherapy regimen.*

Sequencing of therapies following first-line panitumumab were considered with the treatment management approach assessing first-, second-, and third-line treatment in this setting. FOLFIRI was provided as an option for the chemotherapy regimen.

1.3 Submitted and EGP Reanalysis Estimates

A. Patients who receive bevacizumab in the first line

Table 4. Submitted and EGP Estimates for patients who receive bevacizumab in the first line

Estimates (range/point)	Submitted	EGP Reanalysis Lower bound	EGP Reanalysis Upper bound
ΔE (LY)	0.414	0.406	0.083
ΔE (QALY)	0.327	0.322	0.068
First-line PFS	0.043	0.147	0.147
Second-line PFS	0.381	0.255	-0.001
No second-line TTD	0.000	0.000	0.000
Third-line PFS	-0.095	-0.079	-0.079
No third-line TTD	-0.001	-0.001	0.000
After third-line TTD	-0.001	-0.001	0.000
ΔC ($)	$36,118	$40,686	$18,594
ICER estimate - deterministic ($/QALY)	$110,414	$126,389	$275,255

B. Patients who do not receive bevacizumab in the first line

Table 5. Submitted and EGP Estimates for patients who do not receive bevacizumab in the first line

Estimates (range/point)	Submitted	EGP Reanalysis Lower bound	EGP Reanalysis Upper bound

ΔE (LY)	0.413	0.230	0.231
ΔE (QALY)	0.331	0.184	0.185
First-line PFS	0.432	0.266	0.266
Second-line PFS	-0.006	-0.003	-0.002
No second-line TTD	-0.001	0.000	0.000
Third-line PFS	-0.093	-0.078	-0.079
No third-line TTD	-0.001	0.000	0.000
After third-line TTD	0.000	0.000	0.000
ΔC ($)	$47,486	$44,471	$57,311
ICER estimate - deterministic ($/QALY)	$143,559	$241,444	$309,975

The key assumptions and limitations with the submitted economic evaluation were:

- Use of "time to death" estimates instead of direct overall survival data to estimate survival. "Time to death" estimates time from progression to death for each line of therapy (first, second, and third) instead of overall survival estimates from clinical trials using the treatment management strategy approach in the model. The use of the treatment management strategy approach (and not a more direct approach with one input for overall survival), precluded the ability to modify the estimates around overall survival of patients (as three time-to-death parameters are used and are dependent on their underlying data). This estimation limits the generalizability of the model for several reasons: the exclusion of modeling an endpoint collected in a trial (i.e., overall survival) and the exclusion of certain sub-groups when determining time to death data.
- The submitter used a treatment management strategy approach for patients receiving bevacizumab in the first-line setting and those not receiving bevacizumab in the first-line setting. This approach takes into consideration the survival on each line of therapy, including subsequent lines of therapy and those progressing without receiving further lines of therapy. It should be noted that in the submitted base case, bevacizumab is used in the second-line following panitumumab in first-line; however, bevacizumab is not currently funded in the second-line in most provinces. These sequencing changes substantially impacted the ICER.
- Treatment duration was unable to be modified directly in the model. The Submitter calibrated treatment duration curves to progression-free survival curves, using PRIME data (for both those who receive bevacizumab and those who do not receive bevacizumab in the first-line setting), to match the mean number of treatment administrations.

1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the submitted economic model:

- **Time horizon**. The EGP chose a time horizon of 5 years for their reanalysis instead of the submitted time horizon of a lifetime. This shorter time horizon was chosen to align with other metastatic colorectal cancer submissions and to reflect the natural history of the condition, as confirmed by the CGP that the vast majority of patients do not live beyond 5 years.
- **Use of trial data from PRIME and PEAK in Boeckx and not data from the network-meta analysis**. The network meta-analysis had several limitations that limited its generalizability (see limitations and Section 7.2 CGR for details).Though both clinical trials were not designed to detect survival differences in the left-sided population, a retrospective analysis conducted by Boeckx assessed the impact of left-sidedness tumours on effectiveness of panitumumab. Given the limitations of the NMA, the EGP thus chose to use trial data, adjusted for left-sidedness in their re-analysis.
- **Number of treatment cycles**. It was not possible to specify a specific treatment duration in the submitted economic model. It was only possible to calibrate the curve to either reflect a mean number of cycles or to follow the progression-free survival curve. As the number of treatment cycles has an impact on the ICER and it was unknown what the mean (rather than

median) number of cycles were in the clinical trial, the EGP chose an upper bound of no calibration (i.e. PFS curve) in its reanalysis as a conservative estimate.

Management strategy. In the submitted treatment management strategy approach, patients who receive panitumumab (plus FOLFOX) in the first-line, then receive bevacizumab (plus FOLFIRI) in the second-line, followed by best supportive care (BSC) alone. However, bevacizumab is not funded in every province across Canada (see Table of Limitations). To explore the impact this would have on the ICER for these provinces, bevacizumab was removed in the second line for the panitumumab treatment strategy, and patients were treated only with FOLFIRI only in the second line (for both treatment arms).

The treatment management strategy used in the reanalysis is as follows:

First Line	Second Line	Third Line
Panitumumab+FOLFOX	FOLFIRI Alone	BSC Alone
Bevacizumab+FOLFOX	FOLFIRI Alone	Panitumumab+BSC

Table 6. EGP Reanalysis Estimates for panitumumab vs bevacizumab for patients who receive bevacizumab in the first line

	ΔC	ΔE QALYs	ICUR (QALY)	
Baseline (deterministic)	$36,118	0.327	**$110,414**	-----
EGP's Reanalysis for the Best Case Estimate - Lower Bound				
Description of Reanalysis	ΔC	ΔE QALYs	ICUR (QALY)	Δ from baseline submitted ICER
Time horizon - 5 years	$35,424	0.219	**$161,551**	$51,137
Use of trial data for PFS hazard ratio	$41,378	0.429	**$96,346**	-$14,068
Best case estimate - lower bound (deterministic)	$40,686	0.322	**$126,389**	$15,975
Best case estimate - lower bound (probabilistic)	$41,020	0.327	**$125,414**	$15,000
EGP's Reanalysis for the Best Case Estimate - Upper Bound				
Time horizon - 5 years	$35,424	0.219	**$161,551**	$51,137
Use of trial data for PFS hazard ratio	$41,378	0.429	**$96,346**	-$14,068
Number of treatment cycles - PFS curve	$39,448	0.327	**$120,595**	$10,181
No bevacizumab in second line (Panitumumab → FOLFIRI alone → BSC alone)	$9,483	-0.051	**Dominated**	-----
Best case estimate - upper bound (deterministic)	$18,594	0.068	**$275,255**	$164,841
Best case estimate - upper bound (probabilistic)	$15,598	0.072	**$215,472**	$105,058

The treatment management strategy used in the reanalysis is as follows:

First Line	Second Line	Third Line
Panitumumab+FOLFOX	FOLFIRI Alone	BSC Alone
FOLFOX Alone	FOLFIRI Alone	Panitumumab+BSC

Table 7. EGP Reanalysis Estimates for panitumumab vs chemotherapy for patients who do not receive bevacizumab in the first line

	ΔC	ΔE QALYs	ICUR (QALY)	
Baseline (deterministic)	$47,486	0.331	**$143,559**	-----
EGP's Reanalysis for the Best Case Estimate - Lower Bound				
Description of Reanalysis	ΔC	ΔE QALYs	ICUR (QALY)	Δ from baseline submitted ICER
Time horizon - 5 years	$46,896	0.265	**$177,134**	$33,575
Use of trial data for PFS hazard ratio	$44,866	0.221	**$202,780**	$59,223
Best case estimate - lower bound (deterministic)	$44,471	0.184	**$241,444**	$97,885
Best case estimate - lower bound (probabilistic)	$44,428	0.186	**$239,274**	$95,715
EGP's Reanalysis for the Best Case Estimate - Upper Bound				
Time horizon - 5 years	$46,896	0.265	**$177,134**	$33,575
Use of trial data for PFS hazard ratio	$44,866	0.221	**$202,780**	$59,223
Number of treatment cycles - PFS curve	$61,036	0.331	**$184,525**	$40,966
No bevacizumab in second line (Panitumumab → FOLFIRI alone → BSC alone versus FOLFOX alone → FOLFIRI alone → Panitumumab + BSC)	$47,609	0.333	**$143,054**	-$505
Best case estimate - upper bound (deterministic)	$57,311	0.185	**$309,975**	$166,416
Best case estimate - upper bound (probabilistic)	$44,498	0.186	**$238,748**	$95,189

1.5 Evaluation of Submitted Budget Impact Analysis

The factor that most influenced the budget impact analysis was the number of cycles per line of treatment. When the number of cycles of panitumumab is increased from 12 to 16 (as per the economic model with a mean of 16 cycles of treatment), without changing treatment duration of any other included therapies, the total three-year budget impact increased from cost savings to an incremental cost. Increasing the yearly growth of the number of patients from 0% to 5% increased the budget impact.

Key limitations of the BIA model include the assumption that if the current funding request for panitumumab is granted, patients with right-sided tumors will lose public access to the drug. Should this not be the case, there would be no incremental budget impact for patients who do not receive bevacizumab and for patients who do receive bevacizumab, assuming that 15% of patients with right-sided tumors would receive panitumumab, the budget impact increases to $6,915,034. Another limitation of the budget impact is that subsequent lines of therapy, including the use of panitumumab in later lines of therapy, are not considered.

1.6 Conclusions

The EGP's best estimate of ΔC and ΔE for panitumumab plus chemotherapy when compared to bevacizumab plus chemotherapy (patients who do receive bevacizumab in the first-line) is:

- Between $126,389/QALY and $275,255/QALY

- The extra cost of panitumumab is between $18,594 and $41,020 (ΔC). The factors that most influence incremental costs include the source of the PFS hazard ratio (network meta-analysis vs. Boeckx retrospective analysis of left-sided tumours in the PEAK study), the treatment management strategy and the cost of panitumumab.
- The extra clinical effect of panitumumab is between 0.072 and 0.327 (ΔE). The factors that most influence incremental effects include the time horizon, the source of the hazard ratio (network meta-analysis vs. Boeckx retrospective analysis of left-sided tumours in the PEAK study) and the management strategy.

The EGP's best estimate of ΔC and ΔE for panitumumab plus chemotherapy when compared to chemotherapy (patients who do not receive bevacizumab in the first-line) is:

- Between $241,444/QALY and $309,975/QALY
- The extra cost of panitumumab is between $44,471 and $57,311 (ΔC). The main factors that most influence incremental costs include the treatment management strategy, the number of treatment cycles and the cost of panitumumab.
- The extra clinical effect of panitumumab is between 0.184 and 0.185 (ΔE). The factors that most influence incremental effects include the time horizon, the source of hazard ratio (network meta-analysis vs PRIME study) and the management strategy.

Overall conclusions of the submitted model:

- The model has several key assumptions and limitations that limited the generalizability of the results.
- The EGP was able to correct for some of these limitations but not all (assessing the impact of overall survival on the results).
- The utilization of a single treatment management strategy may not be applicable to all provinces in Canada as bevacizumab is not funded in the second-line in most provinces.

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 left sided metastatic colorectal cancer. A full assessment of the clinical evidence of panitumumab (Vectibix) for left sided 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 non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

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.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.

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