pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH 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 reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pCODR Expert Review Committee (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: Panitumumab (Vectibix) **Submitted Reimbursement Request:** In combination with chemotherapy, for the first-line treatment of mCRC patients with left-sided primary tumours that express wild-type (WT) *RAS*	
Submitted By: Amgen Canada Inc.	**Manufactured By:** Amgen Canada Inc.
NOC Date: August 31, 2015	**Submission Date:** September 8, 2017
Initial Recommendation: February 1, 2018	**Final Recommendation:** March 29, 2018

Approximate Per-Patient Drug Costs, per Month (28 Days) Submitted list price of $641.92 per 100 mg vial Note: Costs are calculated based on an average weight of 70 kg and body surface area of 1.7 m^2	**Panitumumab Regimen Costs:** $5,391.29 per 28-day course

pERC RECOMMENDATION

pERC does not recommend the reimbursement of panitumumab in combination with chemotherapy for the first-line treatment of metastatic colorectal cancer (mCRC) patients with left-sided primary tumours that express wild-type *RAS* and who would otherwise be candidates to receive bevacizumab.

pERC made this recommendation as the Committee was unable to conclude that there is a net clinical benefit with panitumumab plus FOLFOX compared with bevacizumab plus FOLFOX in this subgroup of mCRC patients with left-sided primary tumours that express wild-type *RAS*. There was considerable uncertainty in the progression-free and overall survival results from the subgroup analysis of left-sided tumours as well as manageable but not insignificant toxicities associated with panitumumab. pERC concluded that panitumumab plus FOLFOX partially aligned with patient values because it provides an alternative targeted therapy option, but with manageable yet considerable side effects and uncertain clinical effect.

The Committee noted that at the submitted price, panitumumab plus FOLFOX compared with available therapies cannot be considered cost-effective in this population. pERC also highlighted that the potential budget impact of panitumumab plus FOLFOX is likely underestimated and could be substantial.

Please note: This recommendation does not supersede the Panitumumab (Vectibix) mCRC - Final Recommendation (Published: December 3, 2015).

POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**No next steps were identified.**

SUMMARY OF pERC DELIBERATIONS

Metastatic colorectal cancer is the second most common cause of cancer deaths in Canada and is generally considered incurable. Approximately 70% of mCRCs are primary left-sided primary tumours which arise distal to the colonic splenic flexure. In mCRC regardless of therapy, right-sided primary tumours are considered an adverse prognostic factor. *BRAF* mutations, which are a known negative prognostic factor, are also more common among right-sided than left-sided primary tumours. Bevacizumab, an anti-angiogenic agent, together with oxaliplatin or irinotecan-based combination chemotherapy (bevacizumab plus FOLFOX or plus FOLFIRI), is standard first-line therapy in the management of WT *RAS* mCRC in Canada. While the majority of patients can tolerate bevacizumab, there is a small subgroup of patients (approximately 10%) who have contraindications to bevacizumab, such as active bleeding. These patients are currently treated with FOLFOX, FOLFIRI, or capecitabine; pERC previously recommended reimbursement of panitumumab plus FOLFOX for patients who are intolerant or have contraindications to bevacizumab. Panitumumab for patients ineligible for bevacizumab is reimbursed in some provinces, while reimbursement decisions are still pending in other provinces. pERC acknowledged a continued need for new and effective therapies for patients with mCRC that provide improvements in patient survival, have more favourable toxicity profiles, and improve quality of life.

However, the Committee concluded that the availability of bevacizumab in the first-line setting (in all provinces), bevacizumab in the second-line setting (in some provinces), panitumumab in the first-line setting for patients who have a contraindication or intolerance to bevacizumab (in some provinces), and panitumumab in the third-line setting (in all provinces), suggests that there is no unmet need for panitumumab in the first-line setting in this subgroup of mCRC patients with left-sided primary tumours that express WT *RAS*. However, pERC acknowledged that there is still a need for a choice of treatment options, including targeted therapies for the subgroup of mCRC patients with left-sided primary tumours that express WT *RAS*.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon the results of the retrospective analyses of two randomized controlled trials (PRIME and PEAK) included in the pCODR systematic review as well as contextual information that assessed the prognostic and predictive effect of tumour sidedness in WT *RAS* mCRC patients treated with anti-epidermal growth factor receptor and anti-vascular endothelial growth factor therapies. One of the retrospective analyses (Boeckx et al.) suggested that for patients with left-sided tumours, treatment with panitumumab plus FOLFOX compared with treatment with FOLFOX alone improved progression-free survival (PFS) and overall survival (OS). However, for patients with left-sided tumours treated with panitumumab plus FOLFOX compared with those treated with bevacizumab plus FOLFOX, there were no significant differences in PFS and OS. pERC reviewed the pCODR Methods Team's critical appraisal of the retrospective analysis (Boeckx et al.) which highlighted the following limitations:

- Based on an interaction test, there was no statistical difference in panitumumab's treatment effect on PFS and OS for patients with left- or right-sided tumours; this suggested that there is no differential treatment response to panitumumab based on tumour sidedness.
- The analyses were post hoc, descriptive, and retrospective, where the subgroups of tumour sidedness were not pre-specified in the PRIME and PEAK trial protocols.
- There was a lack of statistical adjustment for multiple testing, which increases the risk of type I error (i.e., reporting a treatment effect when there is no true difference).
- Subgroup analyses are often exploratory and hypothesis-generating, and firm conclusions on treatment effect cannot be drawn.
- The effect of panitumumab on tumour sidedness was not consistent across the PRIME and PEAK trials, and the trials did not report consistent results for patients with left-sided tumours versus those with right-sided tumours.

pERC agreed with the pCODR Methods Team and Clinical Guidance Panel that, based on widely used criteria (Oxman and Guyatt) to assess credibility of a subgroup analysis, there is uncertainty about whether there is a differential treatment response to panitumumab in WT *RAS* patients with left-

compared with those with right-sided tumours. pERC also acknowledged contextual information (Arnold et al. and Holch et al.) on the prognostic and predictive effect of tumour sidedness that suggested tumour sidedness may be a prognostic factor, but there is still some uncertainty with regard to the predictive effect of tumour sidedness on OS and PFS. Upon reconsideration of the Initial Recommendation, pERC reiterated that the analysis showed that tumour sidedness may be a prognostic factor but there is still uncertainty with regard to the predictive effect of tumour sidedness. A prognostic factor provides information about patient outcomes regardless of therapy, while a predictive factor provides information about the outcomes of a specific treatment. pERC also noted that although the submitted meta-analysis was well designed and of high quality, it was based on limited data from the subgroup analysis (Boeckx et al.) that assessed the comparative efficacy of panitumumab plus chemotherapy in patients with left and right-sided tumours, thus, pERC had concerns about this limited subgroup analysis data that was incorporated into the meta-analysis.

Additionally, pERC noted that panitumumab and bevacizumab had different toxicity profiles. Regardless of tumour sidedness, patients treated with panitumumab plus FOLFOX had more adverse events of rash, diarrhea, or hypomagnesemia. Significant toxicities, such as rash, can affect day-to-day quality of life (QoL), but QoL was not reported in the PEAK study. In the PRIME study, QoL was similar between treatment groups regardless of tumour sidedness. Upon reconsideration of the Initial Recommendation, pERC acknowledged feedback from the registered clinicians that indicated potential harm of panitumumab given to patients with right-sided tumours. pERC reiterated that the focus of the current review is for panitumumab in combination with chemotherapy, for the first-line treatment of mCRC patients with left-sided primary tumours that express WT *RAS*. pERC agreed with the pCODR Methods Team that although there appear to be differences across tumour-sidedness and treatment groups with respect to toxicity, these results should be interpreted with caution because of small sample sizes and number of adverse events in patients with right-sided tumours.

Based on the totality of evidence, pERC could not conclude that there was a net clinical benefit with panitumumab plus FOLFOX compared with bevacizumab plus FOLFOX. pERC agreed that until more robust data become available, the treatment effect of panitumumab in the subgroup of patients with left-sided WT *RAS* mCRC remains uncertain. pERC noted that additional evidence that is less prone to bias would be of value, and a larger sample size would increase the power to detect a difference in the treatment effect of panitumumab among mCRC patients with left-sided tumours that express WT *RAS.* Upon reconsideration of the Initial Recommendation, pERC acknowledged feedback from the submitter and registered clinicians that a larger RCT evaluating EGFR therapy in left-sided tumours is not anticipated or expected. The Committee reiterated that while a RCT would be preferred due to the low risk of bias (when properly conducted), other prospective study designs of sufficient sample size may be reasonable. Upon reconsideration of the Initial Recommendation, pERC also acknowledged feedback from the submitter that the consistency of results for anti-EGFR therapies as a class effect (e.g., panitumumab, cetuximab) in left-sided tumours across several clinical studies, meta-analyses, and guidelines is an important point of consideration. pERC reiterated that the current review is for panitumumab in combination with chemotherapy, for the first-line treatment of mCRC patients with left-sided primary tumours that express WT *RAS*. Therefore, the totality of evidence for panitumumab, not the overall class effect of anti-EGFR therapies which include panitumumab was assessed. pERC agreed with the pCODR Methods Team that although several studies and analyses were conducted to support panitumumab in left-sided tumours, all studies used the same sources of trial data for panitumumab (i.e., PEAK and PRIME); therefore, the additional analyses do not constitute new trial data for panitumumab, but additional analyses of the same data.

pERC deliberated on patient group input, indicating that it is important to access therapies to help patients control their mCRC with respect to OS, PFS, and QoL. Patients who had direct experience with panitumumab noted toxicities such as rashes, neuropathy, nausea, fatigue, hair loss, mouth sores, and shortness of breath. pERC discussed patient input about skin toxicities such as rash, which can have a significant impact on day to day life; however, patients who provided input noted that skin toxicities were managed with medication and that panitumumab provided disease control. Upon reconsideration of the Initial Recommendation, pERC reiterated that the patient group indicated that panitumumab provided significant disease regression, ability to go onto further surgical options, and status of no evidence of disease. The Committee noted it was unclear whether patients with direct experience with panitumumab had left-sided or right-sided tumours. Upon reconsideration of the Initial Recommendation, pERC acknowledged feedback from the patient group that indicated all patients who had direct experience with panitumumab had left-sided tumours. pERC agreed with patient input that upfront *RAS* testing would be

needed if panitumumab was reimbursed in this setting and the Committee was concerned about the turnaround time for *RAS* testing results in order to guide treatment decisions. pERC was unable to conclude that there was a net clinical benefit with panitumumab plus FOLFOX compared with the standard of care bevacizumab plus FOLFOX as there was uncertainty in the efficacy results from the subgroup analysis of left-sided tumours, along with manageable but not insignificant skin toxicities, and no reported QoL in the PEAK study. The Committee concluded that panitumumab plus FOLFOX only partially aligned with patient values because it provides an alternative targeted therapy option but with manageable but not insignificant side effects and uncertain clinical effect. Upon reconsideration of the Initial Recommendation, pERC reiterated that there is still a need for a choice of treatment options for this patient population. However, based on the currently available evidence, pERC was still unable to conclude there was a net clinical benefit with panitumumab plus FOLFOX compared with the standard of care bevacizumab plus FOLFOX given uncertainty in the efficacy results from the subgroup analysis of left-sided tumours, manageable but not insignificant skin toxicities, and no reported QoL.

pERC noted that registered clinicians reported that current provincially funded options include bevacizumab plus FOLFOX or FOLFIRI, FOLFOX alone, FOLFIRI alone, and capecitabine. pERC agreed that these treatment options are commonly used as first-line agents. pERC noted that clinician input indicated that panitumumab was an improvement over existing first-line treatment for mCRC and had improved survival for the subgroup of patients with left-sided mCRC. However, the Committee also discussed the methodological limitations in the retrospective analyses highlighted by the pCODR Methods Team. Clinicians providing input noted that, relative to bevacizumab plus chemotherapy, adverse events with panitumumab plus chemotherapy include skin toxicity, diarrhea, electrolyte abnormalities such as hypomagnesemia, and fatigue. Overall, pERC found that there was insufficient evidence of effectiveness of panitumumab plus FOLFOX compared with available therapies for patients with left-sided WT *RAS* mCRC.

Upon reconsideration of the Initial Recommendation, pERC acknowledged feedback from the registered clinicians, patient group, and submitter that the recommendation was not in line with the consensus statement recently published in Current Oncology on the predictive effect of primary tumour location in the treatment of mCRC. pERC noted, while respectful of efforts and opinions of key opinion leaders in Canada, pCODR is a health technology assessment body that examines the comparative effectiveness of different treatment strategies looking at multiple dimensions while aiming to provide a balance between the values, needs, preferences, and perspectives of patients and those of society. The Committee's decisions must be equitable, transparent, timely, and accountable to patients, health care funders, and the public to ensure that effective treatment options are considered for public funding. Based on the totality of the currently available evidence, including the methodological limitations of the subgroup analyses of left-sided tumours highlighted by the pCODR Methods Team, pERC concluded that its lack of confidence in the estimate of effect was unchanged from the Initial Recommendation.

pERC deliberated on the cost-effectiveness of panitumumab based on the submitted models. pERC noted that, based on the submitter's estimates of cost-effectiveness, panitumumab could not be considered cost-effective compared with: 1) FOLFOX alone for patients who do not receive bevacizumab in the first-line; or 2) bevacizumab plus FOLFOX for patients who do receive bevacizumab in the first-line. Given pERC was uncertain of the clinical effectiveness of panitumumab in this setting, pERC agreed with the Economic Guidance Panel (EGP) reanalysis exploring different sources of the PFS hazard ratios.

pERC also noted that not all provinces fund bevacizumab in the second-line setting. There was a large change in the magnitude of the incremental cost-effectiveness ratio (ICER) and subsequent conclusions of the cost-effectiveness results due to sequencing of the treatment management strategy. Specifically, in the panitumumab treatment strategy approach for patients who receive bevacizumab in the first-line, the removal of bevacizumab in the second line (and use of FOLFIRI alone) results in the panitumumab treatment strategy approach being both less effective and more costly. pERC noted that the effectiveness of panitumumab was largely dependent on bevacizumab use in the second line, which increased the uncertainty of the cost-effectiveness results. Overall, pERC concluded that, at the submitted price, panitumumab plus FOLFOX cannot be considered cost-effective compared with FOLFOX alone or bevacizumab plus FOLFOX.

pERC considered the feasibility of implementing a reimbursement recommendation for panitumumab. As noted in the Provincial Advisory Group (PAG) input, bevacizumab is reimbursed, in combination with FOLFOX or FOLFIRI, for the first-line treatment of mCRC. In some provinces, bevacizumab is reimbursed in second-line treatment, in combination with FOLFOX or FOLFIRI, for patients who have not received

bevacizumab in the first-line setting. pERC agreed that, if panitumumab were an option in the first-line setting for patients with left-sided mCRC, the number of patients requiring extended *RAS* testing in the first-line setting may be larger, given it would not be reserved for patients who may be candidates for third-line treatment with panitumumab. Upon reconsideration of the Initial Recommendation, pERC acknowledged feedback from the registered clinicians and patient group on the consideration of *RAS* testing prior to panitumumab in the reimbursement decision. pERC considered that adoption feasibility is one of the quadrants of pERC's deliberative framework, alongside clinical benefit, patient-based values, and cost-effectiveness. pERC reiterated that *RAS* testing is not standard of care for first-line mCRC and would be required prior to initiation of panitumumab. pERC noted that timely availability of *RAS* testing would be an important factor for feasibility of implementing a reimbursement recommendation for panitumumab. pERC noted in the budget impact analysis that when the treatment duration of panitumumab was increased to align with the submitted economic model, the budget impact was no longer cost-saving and represented an incremental cost. pERC also had concerns that patients in provinces where bevacizumab is only available in the first-line setting would lose overall access to bevacizumab in their mCRC treatment strategy in exchange for access to panitumumab in first-line instead of third-line. Upon reconsideration of the Initial Recommendation, pERC acknowledged that the pCODR Clinical Guidance Panel agreed with feedback from registered clinicians that the downstream implications of bevacizumab in second-line is an important consideration but funding of bevacizumab is out of scope for this review and would require a separate submission to pCODR.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review
- Other literature in the *Clinical Guidance Report* that provided 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 of Canada
- Input from registered clinicians
- Input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- One patient advocacy group, Colorectal Cancer of Canada
- Registered clinicians
- The PAG
- The submitter, Amgen Canada Inc.

The pERC Initial Recommendation was to not recommend reimbursement of panitumumab in combination with chemotherapy, for the first-line treatment of mCRC patients with left-sided primary tumours that express wild-type (WT) RAS. Feedback on the pERC Initial Recommendation indicated that the PAG agreed with the Initial Recommendation. The patient advocacy group, registered clinicians, and submitter disagreed with the Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of panitumumab in combination with chemotherapy compared with an appropriate comparator for the first-line treatment of metastatic colorectal cancer (mCRC) patients with left-sided primary tumours that express wild-type *RAS.*

Studies included: Two retrospective analyses of two RCTs (PRIME and PEAK)

The pCODR systematic review included two retrospective analyses using data from two open-label randomized controlled trials (PEAK and PRIME), which evaluated the efficacy and safety of panitumumab plus FOLFOX compared with bevacizumab plus FOLFOX (PEAK) or FOLFOX alone (PRIME). Panitumumab was administered at a dose of 6 mg/kg of body weight given once every two weeks until disease progression. The pCODR Clinical Guidance Panel noted that FOLFOX6 (PEAK) and FOLFOX4 (PRIME) are standard regimens used in the first-line mCRC setting.

The retrospective, descriptive, post hoc analysis by Boeckx et al. investigated the association between tumour sidedness and panitumumab efficacy in wild-type *RAS* mCRC patients enrolled in the PRIME and PEAK trials. Patients were considered as *RAS* wild-type carrier status if they did not have a mutation in the K*RAS*/N*RAS* exon 2/3/4 region. Patients were only included if they had data on a primary tumour location. Tumours were classified as right-sided if they were located in the cecum to transverse colon while they were classified as left-sided if they were located in the splenic flexure to the rectum.

The other retrospective analysis was conducted by Geissler et al. and presented in abstract form only. This analysis explored the effect of tumour sidedness on panitumumab efficacy using data from the PRIME and PEAK trials. Similar to Boeckx et al., patients were considered *RAS* wild-type carriers if they did not have a mutation in the K*RAS*/N*RAS* exon 2/3/4 region. It was not reported how tumour sidedness was classified.

Patient populations: Wild-type *RAS*, majority of patients with left-sided tumours

Patients were enrolled in the PEAK and PRIME trials based on K*RAS* (exon 2) tumour status; subsequently extended *RAS* analysis was conducted to identify other *RAS* mutation beyond exon 2 (K*RAS* Exon 3 and 4; N-*RAS* Exon 2, 3, and 4). In the PRIME trial, 1,183 patients were randomly assigned to treatment with panitumumab plus FOLFOX4 or FOLFOX4. Among these patients, 512 were retrospectively identified as *RAS* wild-type carriers (panitumumab + FOLFOX4, n = 259; FOLFOX4, n = 253). In the PEAK trial, 170

patients with wild-type *RAS* were randomly assigned to either panitumumab plus mFOLFOX6 (n = 88) or bevacizumab plus mFOLFOX6 (n = 82).

The Boeckx et al. retrospective analysis included wild-type *RAS* patients from the PRIME (N = 505) and PEAK (N =170) trials. Tumour sidedness was determined in a total of 83% of patients from the PRIME (n = 416/505) and PEAK (n = 143/170) trials. The majority of patients in both trials had a left-sided tumour with 79% of patients in PRIME and 75% of patients in PEAK. Patient characteristics appeared to be similar across tumour sidedness and treatment groups. However, this was difficult to assess, given the small sample size. *BRAF* wild-type carrier status was overall higher in the left-sided tumour populations of PRIME and PEAK compared with right-sided tumour populations regardless of treatment group (range of 92.3% to 98.1% of left-sided tumours versus 59.1% to 92.9% of right-sided tumours). Sites of metastasis also varied by tumour sidedness and treatment groups with no consistent trend across treatment groups and trials.

In the Geissler et al. analysis, tumour sidedness could be determined in 559 patients in the PRIME and PEAK trials. In this analysis, 78% of patients had a left-sided tumour (N = 435). It was reported patients with left-sided tumours were more likely to have a *BRAF* wild-type carrier status (94%) as compared with those with a right-sided tumour (68%).

Key efficacy results: Clinical benefit of panitumumab plus FOLFOX uncertain

The key efficacy outcomes deliberated on by pERC included progression-free survival (PFS), the primary end point of the PEAK and PRIME studies, and overall survival (OS). These results were assessed in the Boeckx et al. retrospective analysis.

Based on the PRIME trial, patients with a left-sided tumour who were treated with panitumumab plus FOLFOX had a longer median PFS than those treated with FOLFOX alone (12.9 versus 9.2 months, hazard ratio (HR) 0.72; 95% confidence interval (CI), 0.57 to 0.90; *P* = 0.0048). There was no difference in PFS between patients with a right-sided tumour who were treated with panitumumab plus FOLFOX compared with FOLFOX alone. Based on PEAK, there was no significant treatment difference in PFS between panitumumab plus FOLFOX and bevacizumab plus FOLFOX. Similar PFS results were seen with right-sided tumours for panitumumab plus FOLFOX compared with bevacizumab plus FOLFOX.

Based on the PRIME trial, patients with a left-sided tumour who were treated with panitumumab plus FOLFOX had a longer median OS than those treated with FOLFOX alone (30.3 versus 23.6 months, HR, 0.73; 95% CI, 0.57 to 0.93; *P* = 0.0112). There was no difference in OS between patients with a right-sided tumour who were treated with panitumumab plus FOLFOX compared with FOLFOX alone. Based on PEAK, patients with a left-sided tumour who were treated with panitumumab plus FOLFOX compared with bevacizumab plus FOLFOX had similar OS. Similar OS results were seen with right-sided tumours for panitumumab plus FOLFOX compared with bevacizumab plus FOLFOX.

Compared with the larger WT *RAS* population reviewed in a previous pCODR review of panitumumab for first-line mCRC, these results differed: PFS and OS were not significantly improved among patients with left-sided tumours for panitumumab plus FOLFOX compared with bevacizumab plus FOLFOX. Considering the discrepancies in these results, pERC concluded that the clinical benefit of panitumumab compared with bevacizumab remains uncertain.

Patient-reported outcomes: No deterioration in overall quality of life

Quality of life (QoL) outcomes were not collected in the PEAK study but were collected in the PRIME study. In the PRIME trial, QoL was measured using the EuroQoL 5-Dimensions (EQ-5D) Health State Index (HSI) and the visual analogue scale (VAS). Results suggested that overall QoL was not statistically or clinically significantly different between the panitumumab plus FOLFOX and FOLFOX alone groups. Similar results were seen when stratified by tumour sidedness for WT *RAS* patients with mCRC; there were no statistically significant differences in changes from baseline for the EQ-5D HSI and EQ-5D VAS between panitumumab plus FOLFOX and FOLFOX alone for patients with a left- or right-sided tumour.

Limitations: Uncertainty in treatment effect of panitumumab in left-sided tumours

Boeckx et al. and Geissler et al. represent post hoc, retrospective, descriptive analyses. The pCODR Methods Team noted that these post hoc analyses should be interpreted with caution because they are more subject to multiplicity (i.e., multiple testing), which increases the risk of type I error (i.e.,

reporting a treatment effect when there is no true difference). Furthermore, subgroups are often exploratory in nature and hypothesis-generating.

According to PRIME data, patients with a left-sided tumour who were treated with panitumumab had improved OS as compared with those with a right-sided tumour; these results were not replicated in the PEAK trial. An interaction test to determine whether the treatment effect of panitumumab on PFS differs among patients with left- or right-sided tumours had a *P* value of 0.9637 and 0.2398 (PRIME and PEAK, respectively), which indicates that the effect of panitumumab on PFS did not differ between patients with left-sided or right-sided tumours. An interaction test to determine whether the treatment effect on OS of panitumumab differs among patients with left- or right-sided tumours had a *P* value of 0.2734 and 0.9503 (PRIME and PEAK, respectively). Since the p-value for interaction was greater than 0.05, it is not possible to reject the hypothesis that the effect of panitumumab on OS was the same for patients with left-sided or right-sided tumours. This indicates that the effect of panitumumab on OS did not differ between patients with left-sided or right-sided tumours. The pCODR Methods Team noted that this suggests there is no statistical difference in treatment effect on PFS and OS for patients with left- or right-sided tumours.

According to the pCODR Methods Team, based on criteria to assess the credibility of a subgroup analysis, there is uncertainty in whether there is a differential treatment response to panitumumab in WT *RAS* patients with left- or right-sided tumours. Overall, pERC agreed with the pCODR Methods Team that the effect of panitumumab on tumour sidedness was not consistent across the PRIME and PEAK trials.

Safety: Well-known and manageable toxicities

pERC reviewed the adverse events (AEs) observed in the PEAK and PRIME studies and noted that the information aligned with the expected toxicity profile of panitumumab, which is well-known as this agent is already used to treat patients with mCRC as first- and third-line therapies. Safety outcomes were stratified by tumour sidedness for WT *RAS* patients with mCRC. Regardless of therapy in PRIME and PEAK, more patients with a right-sided tumour had any serious AE or an AE that led to a discontinuation as compared with those with a left-sided tumour. Compared with FOLFOX alone or bevacizumab plus FOLFOX, patients with left-sided or right-sided tumours who were treated with panitumumab plus FOLFOX were more likely to experience rash, diarrhea, or hypomagnesemia.

Comparator information: Bevacizumab with combination chemotherapy

The current standard of care in the first-line treatment of advanced or metastatic CRC is bevacizumab with oxaliplatin or irinotecan-based combination chemotherapy. pERC noted that both pCODR's Provincial Advisory Group (PAG) and Clinical Guidance Panel considered bevacizumab plus FOLFOX or bevacizumab plus FOLFIRI to be the current standard of care for patients with WT *RAS* mCRC. The PEAK study provided a comparison with bevacizumab plus FOLFOX and the PRIME study provided a comparison with FOLFOX alone.

Contextual information: Prognostic and predictive effect of tumour sidedness

The pCODR Methods Team critically appraised a meta-analysis and pooled analysis that explored the efficacy of panitumumab plus chemotherapy versus active therapies for the first-line treatment of mCRC patients with left- and right-sided primary tumours that express WT *RAS.* The prognostic and predictive effect of tumour sidedness in WT *RAS* mCRC patients treated with anti–epidermal growth factor receptor (EGFR) and anti–vascular endothelial growth factor therapies was assessed. Overall, the analyses showed that tumour sidedness may be a prognostic factor but there is still some uncertainty with regard to the predictive effect of tumour sidedness. However, the class effect of anti-EGFRs was assessed rather than the independent effects of cetuximab or panitumumab. Upon reconsideration of the Initial Recommendation, pERC reiterated that the analysis showed that tumour sidedness may be a prognostic factor but there is still uncertainty with regard to the predictive effect of tumour sidedness. pERC also noted that, although the submitted meta-analysis was well designed and of high quality, it was based on limited data from the subgroup analysis (Boeckx et al.) that assessed the comparative efficacy of panitumumab plus chemotherapy in patients with left and right-sided tumours, thus, pERC had concerns about this limited subgroup analysis data that was incorporated into the meta-analysis.

Need and burden of illness: Additional treatment options for patients

Metastatic colorectal cancer is the second most common cause of cancer deaths in Canada and is generally considered incurable. Approximately 70% of mCRCs are primary left-sided tumours, which are

primary tumours distal to the colonic splenic flexure. In mCRC regardless of therapy, right-sided primary tumours are considered an adverse prognostic factor. *BRAF* mutations, which are known negative prognostic factors, are also more common among right-sided than left-sided primary tumours. Bevacizumab combined with oxaliplatin and irinotecan-based combination chemotherapies are standard first-line therapies in the management of mCRC. Approximately 10% of patients have a contraindication or intolerance to bevacizumab (e.g., active bleeding) and these patients would be treated only with combination chemotherapy such as FOLFOX, FOLFIRI, or capecitabine alone. Panitumumab plus FOLFOX is available in some provinces for patients who are intolerant or have contraindications to bevacizumab. pERC acknowledged a continued need for new and effective therapies for patients with mCRC that provide improvements in patient survival, have more favourable toxicity profiles, and improve quality of life. However, the Committee agreed that the availability of bevacizumab in the first-line setting (in all provinces), bevacizumab in the second-line setting (in some provinces), panitumumab in the first-line setting for patients who have a contraindication or intolerance to bevacizumab (in some provinces), and panitumumab in the third-line setting (in all provinces), indicates that there is no unmet need for panitumumab in this subgroup of mCRC patients with left-sided primary tumours that express WT *RAS*.

Registered clinician input: Effective in patients with left-sided tumours

The Committee deliberated on two clinician inputs: one joint clinician input from Cancer Care Ontario and one joint clinician input from Colorectal Cancer Canada. According to their input, current provincially funded options include bevacizumab plus FOLFOX or FOLFIRI, FOLFOX alone, FOLFIRI alone, and capecitabine. pERC agreed that these treatment options are commonly used as first-line agents. pERC acknowledged that clinician input indicated that panitumumab was an improvement over existing first-line treatment for mCRC and had improved survival for the subgroup of patients with left-sided mCRC. Clinicians providing input noted that relative to bevacizumab plus chemotherapy, AEs with panitumumab plus chemotherapy include skin toxicity, diarrhea, and fatigue. Clinician input indicated that EGFR inhibitors such as panitumumab or cetuximab would replace bevacizumab as first-line treatment for WT *RAS* left-sided mCRC patients. Second-line treatment for patients would be bevacizumab plus chemotherapy. Clinician input also acknowledged that *RAS* testing is mandatory and must be available at presentation of mCRC. The input also noted the definition of left- versus right-sided tumours varies but the common cut point is the splenic flexure.

PATIENT-BASED VALUES

Values of patients with metastatic colorectal cancer: Disease control and survival

One patient group, Colorectal Cancer of Canada, provided input on panitumumab for the treatment of patients with left-sided mCRC. Patient input indicated there are a number of symptoms associated with mCRC that affect quality of life including bloody stools, abdominal discomfort, fatigue, constipation and diarrhea, weight loss, and bowel obstruction. Psychological limitations resulting from mCRC included depression, anxiety, and fear. Caregiver respondents indicated significant impact on their lives in terms of financial, physical, and psychological challenges when caring for their loved ones. With current therapies, patients noted fatigue and nausea as commonly experienced side effects. Mouth sores were reported as the most difficult to tolerate.

Patient values on treatment: Effective but tolerable treatment options

pERC noted that 10 patients who provided input had direct experience with panitumumab. The most common reported side effects for panitumumab in combination with chemotherapy were rashes, neuropathy, nausea, fatigue, hair loss, mouth sores, and shortness of breath. Patients reported that panitumumab helped shrink patients' disease. Upon reconsideration of the Initial Recommendation, pERC reiterated that the patient group indicated that panitumumab provided significant disease regression, ability to go onto further surgical options, and status of no evidence of disease. Seven patients rated their QoL on the treatment on a scale of 1 to 10: of whom three patients identified QoL as 8 out of 10, three identified it as 7 out of 10, and one patient rated quality of life as 5 on days 5 through 7 of treatment and 7 on the rest of the days. Patients also noted that panitumumab plus chemotherapy resolved pain or pressure symptoms from metastases. Overall pERC acknowledged that patients indicated it is important to access therapies to help control their mCRC with respect to OS, PFS, and QoL.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis, partitioned-survival analysis

The pCODR Economic Guidance Panel (EGP) assessed two cost-utility analyses comparing panitumumab for patients with primary left-sided WT *RAS* mCRC who receive bevacizumab and those who do not receive bevacizumab in the first-line setting. For those who receive bevacizumab in the first-line setting, panitumumab plus FOLFOX was compared with bevacizumab plus FOLFOX or FOLFIRI. For those who do not receive bevacizumab in the first-line setting, panitumumab plus FOLFOX was compared with FOLFOX or FOLFIRI alone. The comparisons were based on the Boeckx et al. retrospective review of PRIME and PEAK and a submitted network meta-analysis. The submitted model was a partitioned-survival model with the following periods: first-line PFS, second-line PFS, third-line PFS, 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 (i.e., best supportive care only after second line), and time to death following third-line treatment.

Basis of the economic model: Clinical and economic inputs

Costs included in the models were cost of treatment, cost of *RAS* testing, cost of managing AEs, cost of disease monitoring, and cost of best supportive care. pERC noted that the cost estimates were based on published literature including Boeckx et al. and expert opinion.

Key clinical effects considered in the analysis included PFS, time to death, and utilities.

Drug costs: Cost of treatment

Panitumumab costs $641.92 per 100 mg vial with a strength of 20 mg/mL. At the recommended dose of 6 mg/kg beginning on day 1 and repeating every two weeks, with a body weight of 70 kg, the cost of panitumumab is $192.55 per day and $5,391.29 per 28-day course.

Bevacizumab costs $600.00 per 100 mg vial. At the recommended dose of 5 mg/kg beginning on day 1 and repeating 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/m^2 beginning on day 1 and repeating every two weeks, the cost of oxaliplatin is $105.28 per day and $2,947.80 per 28-day course. Leucovorin costs $0.05/mg. At the recommended dose of 200 mg/m^2 beginning on day 1 and repeating every two 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/m^2 and 2,400 mg/m^2 beginning on day 1 and continued over three days every two 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/m^2 day 1 every two weeks, the cost of irinotecan is $10.93 per day and $306.00 per 28-day course.

Cost-effectiveness estimates: Time horizon, management strategy (bevacizumab in second-line treatment)

pERC discussed the submitter's and the EGP's best estimates of the incremental cost-effectiveness ratio (ICER) of panitumumab plus chemotherapy compared with chemotherapy alone and bevacizumab plus chemotherapy for patients with primary left-sided WT *RAS* mCRC. The Committee considered estimates provided by the submitter and reanalysis estimates provided by EGP and noted uncertainty regarding the extrapolation over a lifetime time horizon and treatment management strategy (i.e., use of bevacizumab plus chemotherapy in the second-line setting). The EGP noted that the utilization of a single treatment strategy may not be applicable to all provinces in Canada as bevacizumab is not reimbursed in the second line in most provinces. In both economic models (patients who do receive bevacizumab in the first line and patients who do not receive bevacizumab in the first line) the factors that most influenced the ICER were the time horizon, cost of panitumumab, number of treatment cycles, treatment management strategy, and source of the PFS hazard ratio (network meta-analysis versus the Boeckx et al. retrospective analysis of left-sided tumours in the PEAK and PRIME studies). pERC noted a large change in the magnitude of the ICER and subsequent conclusions of the cost-effectiveness results due to sequencing of the treatment management strategy. In the panitumumab treatment strategy for patients receiving bevacizumab in the first-line setting, the removal of bevacizumab in the second line (FOLFIRI alone is used), results approach both less effective and more costly. pERC noted that the effectiveness of panitumumab was largely dependent on bevacizumab use in the second line, which increased the uncertainty of the clinical and cost-effectiveness of panitumumab in this setting.

Overall, pERC agreed with the EGP's best estimates of the ICER when panitumumab plus chemotherapy was compared with bevacizumab plus chemotherapy and chemotherapy alone. This estimate corresponds to an ICER based on treatment duration, which follows the PFS curve and consideration that bevacizumab is not reimbursed in every province across Canada for second-line treatment (i.e., replacement of bevacizumab with FOLFIRI alone in the panitumumab treatment strategy approach). Consequently, pERC concluded that panitumumab was not cost-effective at the submitted price.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: High drug cost, large budget impact
pERC considered the feasibility of implementing a funding recommendation for panitumumab. pERC noted that the budget impact analysis indicated that there was cost savings associated with panitumumab. pERC noted that when the treatment duration of panitumumab was increased to align with the submitted economic model, the budget impact was no longer cost-saving and represented an incremental cost. pERC noted that the factor that most influenced the budget impact analysis was the number of cycles per line of panitumumab treatment. A key limitation identified of the budget impact analysis was that if the current funding request for panitumumab is granted patients with right-sided tumours would lose provincially reimbursed access to panitumumab. Another limitation of the budget impact analysis was that subsequent lines of therapy, including use of panitumumab in later lines of therapies, are not considered.

As noted in PAG input, bevacizumab is reimbursed, in combination with FOLFOX or FOLFIRI, for the first-line treatment of mCRC. In some provinces, bevacizumab is reimbursed in second-line treatment, in combination with FOLFOX or FOLFIRI, for patients who have not received bevacizumab in the first-line setting. PAG noted in the previous review of panitumumab in the first-line treatment of *KRAS* wild-type mCRC, the Committee recommended panitumumab for patients who have contraindications or intolerance to bevacizumab. pERC agreed that if panitumumab were an option in the first-line setting for patients with left-sided mCRC, the number of patients requiring extended *RAS* testing in the first-line setting may be larger, given it would not be reserved for patients who may be candidates for third-line treatment with panitumumab.

DRUG AND CONDITION INFORMATION

Drug Information	• Monoclonal antibody • 100, 200 and 400 mg vial • 6 mg/kg of body weight every 2 weeks until disease progression
Cancer Treated	• Metastatic colorectal cancer (mCRC) patients with left-sided primary tumours that express wild-type *RAS* • First-line setting • 70% of mCRCs are primary left-sided tumours
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 • Primary right-sided tumours a negative prognostic factor
Current Standard Treatment	• Bevacizumab plus FOLFIRI (irinotecan, leucovorin, fluorouracil) • Bevacizumab plus FOLFOX (oxaliplatin, leucovorin, fluorouracil) • Panitumumab plus FOLFOX (oxaliplatin, leucovorin, fluorouracil) • Bevacizumab plus capecitabine • FOLFIRI • FOLFOX
Limitations of Current Therapy	• A large majority of patients will die of mCRC • There remains a need for more effective cancer therapies • Some patients are unable to tolerate bevacizumab plus FOLFIRI or FOLFOX

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

pERC Membership During Deliberation of the Initial Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice Chair)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Craig Earle, Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Dr. Kelvin Chan, Dr. Winson Cheung, and Dr. Craig Earle, who were not present for the meeting
- Cameron Lane, who did not vote due to his role as a patient member alternate.

pERC Membership During Deliberation of the Final Recommendation

Dr. Maureen Trudeau, Oncologist (Chair)	Leela John, Pharmacist
Dr. Catherine Moltzan, Oncologist (Vice Chair)	Dr. Anil Abraham Joy, Oncologist
Dr. Kelvin Chan, Oncologist	Dr. Christine Kennedy, Family Physician
Lauren Flay Charbonneau, Pharmacist	Cameron Lane, Patient Member Alternate
Dr. Matthew Cheung, Oncologist	Christopher Longo, Health Economist
Dr. Winson Cheung, Oncologist	Valerie McDonald, Patient Member
Dr. Avram Denburg, Pediatric Oncologist	Carole McMahon, Patient Member
Dr. Craig Earle, Oncologist	Dr. Marianne Taylor, Oncologist

All members participated in deliberations and voting on the Final Recommendation, except:

- Dr. Kelvin Chan, Dr. Craig Earle, and Dr. Christine Kennedy who were not present for the meeting
- Cameron Lane, who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of pERC 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 panitumumab (Vectibix) for left-sided metastatic colorectal cancer, through their declarations, no members had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members was excluded from voting.

Information sources used

pERC 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 its 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*. Amgen Canada Inc., as the primary data owner, did not agree to the disclosure of clinical information, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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