



pan-Canadian Oncology Drug Review Final Clinical Guidance Report

Panitumumab (Vectibix) for Metastatic Colorectal Cancer

December 3, 2015

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FUNDING

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.

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 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of panitumumab in combination with FOLFOX (oxaliplatin, fluorouracil, leucovorin) as first-line treatment for patients who have non-mutated wild-type (WT) RAS metastatic colorectal cancer (WT RAS mCRC).

Panitumumab is a recombinant, fully human IgG2 monoclonal antibody that binds specifically to the human epidermal growth factor receptor (EGFR). Panitumumab has Health Canada approved indications:

- for the treatment of previously untreated patients with non-mutated (wild-type) RAS metastatic colorectal carcinoma (mCRC) in combination with FOLFOX.
- as monotherapy for the treatment of patients with EGFR-expressing mCRC with non-mutated (wild type) KRAS after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

Panitumumab is available at 100 (20 mg/mL) in 5mL single-use vials, respectively. The recommended dose of panitumumab is 6mg/kg of body weight given once every 2 weeks until disease progression.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two studies, the phase II trial PEAK¹ and the phase III trial PRIME.² Both studies were open-label, multi-centered, and randomized patients with previously untreated mCRC in a 1:1 ratio to receive either treatment with panitumumab plus FOLFOX versus FOLFOX plus bevacizumab (PEAK) or FOLFOX alone (PRIME). Patients in PEAK were treated with mFOLFOX6 and patients in PRIME were treated with FOLFOX4. Over 90% of patients in PEAK and PRIME had an ECOG performance status of 0 to 1. PEAK was restricted to performance status of 0 to 1 while PRIME included patients with a performance status of 0 to 2. The median age of patients ranged from 61 to 63 years.

Efficacy

The primary endpoint for both trials was progression-free survival (PFS). Secondary outcomes included overall survival (OS), response rates, metastases resection rates, and adverse events.

In the PEAK trial, in the pre-planned restricted analysis to patients with WT RAS tumours on extended RAS testing (n=170), the median PFS was 13 months in the panitumumab plus FOLFOX arm and 9.5 months in the bevacizumab plus FOLFOX arm (HR=0.65, 95% CI: 0.44-0.96, p=0.029).¹ In the PRIME trial, for the analysis restricted to patients with WT RAS tumours on extended RAS testing (n=512), the median PFS was 10.1 months in the panitumumab plus FOLFOX arm and 7.9 months in the FOLFOX arm (HR=0.72; 95%CI: 0.58-0.90, p=0.004).³

In PEAK, despite no improvement in PFS for the overall WT KRAS population (n=285), OS was higher in the panitumumab plus FOLFOX arm compared to the bevacizumab plus FOLFOX arm.¹ For patients with WT RAS tumours on extended RAS testing in the PEAK trial, PFS was

significantly and OS was not significantly higher in the panitumumab plus FOLFOX arm compared to the bevacizumab plus FOLFOX arm.¹ In PRIME for the overall WT KRAS population (n=656) and WT RAS population on extended RAS testing, PFS and OS was significantly higher in the panitumumab plus FOLFOX arm when compared to FOLFOX alone.^{2,3}

Both trials reported similar objective response rates and metastases (any site) resection rates between treatment arms. Health-related quality of life was not assessed in the PEAK trial and was assessed in the PRIME trial using the EQ-5D. There were no statistically or clinically significant differences in quality of life between treatment arms.⁴

Harms

In the PEAK trial, the incidence of any grade 3 or 4 adverse event was 90% and 83% in the panitumumab plus mFOLFOX6 and bevacizumab plus mFOLFOX6 arms, respectively.¹ In the PRIME trial, the incidence of any grade 3 or 4 adverse event was 84% and 69% in the panitumumab plus FOLFOX4 and FOLFOX4 arms, respectively.² In both studies, the incidence of adverse events in patients treated with panitumumab was higher than the control arms for skin toxicity/skin disorders, hypokalemia, mucositis/mucosal inflammation, and hypomagnesemia. Rates of treatment discontinuation due to adverse events were similar across treatment arms and both studies.

1.2.2 Additional Evidence

pCODR received input on panitumumab from one patient advocacy group (Colorectal Cancer Association of Canada). Provincial Advisory Group input was obtained from nine of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. No supplemental issues were identified during the development of the review.

1.2.3 Interpretation and Guidance

PEAK

In the small, randomized phase II PEAK trial comparing panitumumab plus FOLFOX to bevacizumab plus FOLFOX (n=285), the primary endpoint of PFS was similar between treatment arms. For the secondary endpoint of OS, despite no improvement in PFS, overall survival was higher with a median survival of 34.2 and 24.3 months in the panitumumab and bevacizumab arms, respectively (HR=0.62, 95% CI: 0.44-0.89, p=0.009). In the pre-planned prospective secondary analysis restricting to patients with WT RAS tumours on extended RAS testing (n=170), PFS was significantly higher and OS was not significantly higher in the panitumumab arm. Rates of grade 3 or higher adverse events were slightly higher in the panitumumab arm for skin toxicity, hypokalemia, mucositis, stomatitis, and hypomagnesemia. Health-related quality of life (HRQoL) was not measured in this trial.

PRIME

In the phase III PRIME trial comparing panitumumab plus FOLFOX to FOLFOX alone for patients with WT RAS on extended RAS testing (n=512), the median PFS was 10.1 and 7.9 months in the panitumumab plus FOLFOX and FOLFOX arms, respectively (HR=0.72, 95%CI: 0.58-0.90, p=0.004). The median OS was 25.8 and 20.2 months in the panitumumab plus FOLFOX and FOLFOX arms, respectively (HR=0.77, 95%CI: 0.64-0.94, p=0.009). These results were similar in the larger KRAS randomized population (n=656) on updated analyses. Adverse events that occurred more frequently in the panitumumab plus FOLFOX arm included skin toxicity, diarrhea, hypokalemia, fatigue, mucositis, and hypomagnesemia. This did not result in a statistically or clinically significant difference in overall health-related quality of life.

In both trials (PEAK and PRIME), response and metastatectomy rates were similar.

Other Considerations

There is not a large need for a new targeted therapy, of similar efficacy to the current standard, to add to a chemotherapy backbone in the first-line setting. About 10% of patients may have contraindications to multi-agent systemic therapy (i.e. to bevacizumab which include arterial or venous thrombosis, active fistulae, patients needing maximal systemic treatment within 28 days of prior or planned surgery, those with non-healing wounds, or uncontrolled brain metastases) and for whom panitumumab would be preferred.

The Clinical Guidance Panel felt there would unlikely be differences in outcomes between various antibody (panitumumab and cetuximab) and chemotherapy combinations in this setting. Panitumumab had similar modest benefits to the addition of another EGFR inhibitor, cetuximab, to combination chemotherapy in the first-line setting (see section 3.2 of Background Clinical Information).

Although randomized trials comparing bevacizumab and panitumumab when combined with FOLFIRI have not been conducted, the Clinical Guidance Panel felt it was reasonable to extrapolate the results from the PRIME and PEAK trials and results would likely be similar regardless of chemotherapy backbone. Some patients for whom bevacizumab is initially contraindicated may later become eligible for bevacizumab after treatment with panitumumab (for example resolution of temporary contraindications of post-operative bleeding). It would be clinically reasonable to give bevacizumab with second-line chemotherapy, however this option is not currently consistently publicly funded in Canada. However, once an EGFR inhibitor has been given to progression, the CGP is of the opinion, EGFR inhibitors should not be used in any later lines of therapy. Selection for treatment with an EGFR inhibitor should be done with extended RAS testing and there is currently no clear role for BRAF testing. EGFR inhibitors cause net harm in patients with RAS mutations and should not be given.

1.3 Conclusions

Bevacizumab - Eligible Patients

The Clinical Guidance Panel concluded that, while non-inferior, there is not a net overall clinical benefit to panitumumab + FOLFOX in the first-line treatment of WT RAS metastatic colorectal cancer compared to the current standard first-line targeted agent bevacizumab + FOLFOX/FOLFIRI. Rather, the efficacy of each of these agents is similar when added to chemotherapy in the first-line setting. The Panel based this conclusion on a small randomized phase II trial (PEAK) evaluating panitumumab + FOLFOX compared with bevacizumab + FOLFOX as well as other trials comparing similar drug combinations.

In reaching this conclusion, the Clinical Guidance Panel considered that:

- In its primary analysis based on initial entry criteria at the time of WT KRAS tumours, this Phase II trial demonstrated that the addition of panitumumab to FOLFOX has similar efficacy to the addition of bevacizumab to the same chemotherapy backbone in terms of progression-free survival, the primary endpoint of the study, and found a statistically significant improvement in overall survival, an endpoint for which the study was not powered. On restriction to the extended WT RAS subpopulation, PFS was increased by 3.5 months but OS was no longer statistically significantly different but was not sufficiently powered.
- The Panel was unable to comment on patient HRQoL as this was not measured in the PEAK trial.

- Adverse event profiles differed between panitumumab and bevacizumab but are at levels patients often consider to be acceptable. The dermatological effects of panitumumab likely result in more noticeable day-to-day on-treatment toxicity compared to bevacizumab.
- The Clinical Guidance Panel felt there were limitations with the PEAK trial as it was a small phase II study and there was no independent assessment of the primary endpoint of PFS.
- The need for a new targeted therapy, of similar efficacy to the current standard, to add to a chemotherapy backbone in the first line setting is not great. There are a small number of patients who are candidates for multi-agent systemic therapy who may have contraindications, usually relative contraindications, to bevacizumab.
- Other trials testing similar combinations of drugs have also generally found the efficacy of EGFR inhibitors and bevacizumab to be similar when combined with chemotherapy in this setting.

Bevacizumab - Ineligible Patients

The Clinical Guidance Panel concluded that there is a moderate net overall clinical benefit to panitumumab + FOLFOX compared to FOLFOX alone. The Clinical Guidance Panel based this decision on one high-quality randomized controlled trial (PRIME).

In reaching this conclusion, the Clinical Guidance Panel considered that:

- The PRIME trial demonstrated a clinically and statistically significant benefit in progression free survival and overall survival for panitumumab + FOLFOX compared with FOLFOX alone. This finding is consistent with other trials comparing similar combinations of drugs.
- In the PRIME trial, there were no significant differences in HrQoL for the panitumumab and FOLFOX arms.
- The addition of panitumumab to the chemotherapy backbone resulted in the expected increase in toxicity, but this toxicity is usually considered a reasonable trade-off for the benefit derived.
- At this point in time, these results are most relevant for the small population of patients with WT RAS metastatic colorectal cancer who are candidates for first-line multi-agent systemic therapy but for whom bevacizumab is contraindicated.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding panitumumab (Vectibix) for metastatic colorectal cancer (mCRC). The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website, www.cadth.ca/pcodr.

This Clinical Guidance is based on: a systematic review of the literature regarding panitumumab (Vectibix) for mCRC conducted by the Gastrointestinal Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on panitumumab (Vectibix) for mCRC and a summary of submitted Provincial Advisory Group Input on panitumumab (Vectibix) for mCRC are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

In 2015 the Canadian Cancer Society estimates that there were 25,100 new cases of colorectal cancer diagnosed, and 9,300 people died from the disease.⁵ Most of this latter group would have had spread of their cancer from the colon into vital organs, most commonly the liver or lungs. In a minority of patients with a few isolated sites of metastatic disease, surgery can sometimes be curative. Unfortunately, for the majority metastatic disease is incurable.

When colorectal cancer is at an incurable stage, the primary treatment is with systemic therapy. This is given with goals of extending survival and ameliorating or delaying symptoms, but it is with only palliative, not curative intent. Recent studies involving treatment with multiple lines of chemotherapy routinely report median survivals of over 24 months.⁶ The standard first-line of therapy in Canada is fluoropyrimidine-based chemotherapy combined with bevacizumab. These drugs can be combined with oxaliplatin and/or irinotecan to make the common regimens FOLFOX, FOLFIRI, capeOx, and capeIRI. Sequencing oxaliplatin and irinotecan in first- versus second-line regimens are considered to be clinically equivalent approaches.^{7,8}

Bevacizumab is a monoclonal antibody that blocks angiogenesis through binding to the vascular endothelial growth factor (VEGF) receptor. Bevacizumab has been shown in multiple studies to increase overall survival in metastatic colorectal cancer by approximately 1.5 months when given in combination with chemotherapy in the first-line setting.⁹⁻¹¹

Cetuximab and panitumumab are monoclonal antibodies to the epidermal growth factor receptor (EGFR). The presence of RAS mutations in the tumour, observed in 40% of colorectal cancers,¹² is a negative predictor of EGFR benefit.

Currently, the use of cetuximab and panitumumab in Canada is primarily limited to the third-line setting for patients with non-mutated, 'wild-type' (WT) RAS tumours.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the efficacy and safety of panitumumab in combination with oxaliplatin-based chemotherapy as first-line treatment for patients with wild-type (WT) RAS mCRC.

Refer to Table 2 in Section 6.2.1 for outcomes of interest and appropriate comparators.

2.1.3 Highlights of Evidence in the Systematic Review

Two randomized controlled trials comparing the efficacy and safety of panitumumab in combination with oxaliplatin-based chemotherapy to an appropriate comparator as first-line treatment for patients with WT RAS mCRC were identified and included in this systematic review.^{1,2} For a more detailed description of trial design characteristics refer to Tables 3 and 4 in the Systematic Review (section 6.3.2.1).

PRIME was a phase III trial and PEAK was a phase II trial. Both trials were open-label, multi-centred, and randomized patients with previously untreated mCRC in a 1:1 ratio to receive treatment with panitumumab and FOLFOX chemotherapy versus either FOLFOX alone (PRIME) or FOLFOX combined with bevacizumab (PEAK).

KRAS wild-type (WT) tumour status was required for trial entry into the PEAK trial but not in the PRIME trial. In PRIME, trial entry required the availability of paraffin-embedded tumour tissue for central biomarker analysis. During the course of patient enrolment the significance of tumour biomarker status on treatment outcomes became apparent. The design of the trial was subsequently amended to prospectively compare treatment outcomes by KRAS (exon 2) tumour status.

PRIME included patients with an ECOG performance status of 0 to 2, while PEAK included patients with a performance status of 0 to 1.

Panitumumab was administered at the same dose and schedule in both trials: 6 mg/kg intravenously over one hour every two weeks. FOLFOX4 was the chemotherapy regimen used in the PRIME trial, while mFOLFOX6 was the chemotherapy regimen used in the PEAK trial. In both trials, treatment regimens were given until disease progression, unacceptable toxicity or withdrawal of consent. FOLFOX4 and FOLFOX6 are standard regimens used in the mCRC setting.

It is important to highlight that the comparator arm in the PRIME trial, FOLFOX chemotherapy, is not the current standard of care in Canada, and therefore the generalizability of the trial results should be interpreted within this context.

The primary outcome in both trials was progression-free survival (PFS). Secondary outcomes in each trial included overall survival (OS), objective tumour response (ORR), metastasis resection rate, and adverse events.

Both trials were open label. As such, they are at risk for a number of biases that can affect the internal validity of a trial (e.g., patient selection for eligibility, performance bias due to knowledge of assigned treatment). However, assessments of PFS (the primary outcome) and ORR were conducted via a blinded independent central review in PRIME, which reduces the potential for biased results. Bias is of greater concern in the PEAK trial considering both the investigators assessing these outcomes and data analysts were not blinded to treatment assignment.

In PRIME, ascertainment of KRAS tumour status was obtained for 93% of the 1183 patients randomized to the trial; thus efficacy analyses included this patient population.

Additional data analyses were performed in both trials to examine treatment effects in patients with and without mutations beyond KRAS exon 2. In both trials extended RAS analyses included all randomized patients with available tumour biomarker information; and assessment of tumour biomarker status was blinded and performed in a central laboratory prior to any efficacy analyses.

In PRIME, the extended RAS analysis was prospectively planned but performed retrospectively using the original PRIME trial data.³ Extended RAS tumour status was unevaluable in 123 patients (10%) and these patients were excluded from analyses. A total of 512 patients were WT RAS in this trial. It is important to emphasize that the extended analyses were exploratory in nature and included no formal hypothesis testing, and therefore results should be interpreted with caution and considered hypothesis generating, requiring further validation in prospective trials.

In the PEAK trial, the extended RAS analysis was evaluated prospectively as a secondary objective of the trial.¹ Extended RAS tumour status was unevaluable in 58 patients (22%) and these patients were excluded from analyses. A total of 170 patients were WT RAS in this trial. The efficacy results associated with this small subgroup should be interpreted in consideration of its small sample size.

Amgen sponsored both trials, and employees/stockholders were involved in all aspects of conducting the trials and data analyses. The extent to which the use of independent investigators and data analysts may have influenced the results and reporting of the trials is unknown.

The randomization procedure achieved balance for most patient and disease characteristics at baseline between trial arms of both trials. For a more detailed description of baseline patient characteristics refer to Table 5 in the Systematic Review (section 6.3.2.1).

The key efficacy outcomes for both trials are summarized in Table 1. Both trials reported statistically significant improvements in PFS in favour of the panitumumab-containing arms compared to control arms among patients with WT RAS tumours. Similarly, the updated analyses of OS in both trials showed longer survival in favour of the panitumumab-containing arms compared to control arms among patients with WT RAS tumours; however, the observed benefit was only statistically significant in the PRIME trial. Both trials reported similar rates of ORR and metastases (any site) resection between trial arms. Statistical comparisons for these outcomes were generally not reported.

Health-related quality of life (HRQoL) was assessed in the PRIME trial as a tertiary outcome of interest.⁴ The EuroQoL 5-Dimensions (EQ-5D) was used to measure patient-reported HRQoL between trial arms. Of the 656 WT KRAS patients randomized in the PRIME trial, 88% of these patients (n=576) were included in the primary analysis of HRQoL. The observed difference in EQ-5D measures between treatment arms was considered neither statistically nor clinically significant.^{4,13}

In both trials, all patients (WT KRAS) who received at least one dose of study treatment were included in analyses of safety. No statistical comparisons of the rates of adverse events between trial arms were reported in either trial. For a more detailed description of harms outcomes refer to Table 8 in the Systematic Review (section 6.3.2.2).

In the PRIME trial,² the incidence of any grade 3 or 4 adverse events was 85% in the panitumumab-FOLFOX4 arm and 69% in the FOLFOX4 control arm. The incidence of the following adverse events was higher in patients treated with panitumumab compared with control: skin toxicity/skin disorders (36% vs. 2%), diarrhea (18% vs. 9%), hypokalemia (10% vs. 5%), fatigue (9% vs. 3%), mucositis/mucosal inflammation (6% vs. <1%) and

hypomagnesemia (6% vs. <1%). The incidence of fatal adverse events and fatal treatment-related adverse events were similar between trial arms.

In the PEAK trial,¹ the incidence of any grade 3 or 4 adverse events was 90% in the panitumumab-mFOLFOX6 arm and 83% in the bevacizumab-mFOLFOX6 arm. The incidence of the following adverse events was higher in patients treated with panitumumab compared with control: skin toxicity/skin disorders (32% vs.1%), hypokalemia (11% vs. 5%), mucositis/mucosal inflammation (7% vs. 1%), stomatitis (5% vs. <1%), and hypomagnesemia (7% vs. 0). Treatment with bevacizumab was associated with a higher incidence of hypertension (7%) compared to treatment with panitumumab (0). The incidence of grade 3 or 4 fatal adverse events and fatal treatment-related events was similar between trial arms.

Table 1: Summary of key efficacy outcomes in included trials of panitumumab in combination with oxaliplatin-based chemotherapy as first-line treatment in patients with wild-type (WT) RAS metastatic colorectal cancer (KRAS and extended WT RAS populations).						
Treatment Arms	PFS		Updated OS ^B		Objective Response Rate %	Metastases Resection Rate %
	Median (mos)	HR (95 %CI)	Median (mos)	HR (95% CI)		
PRIME Trial WT KRAS^{2,3}						
Panitumumab + FOLFOX4 (n=325)	9.6	0.80 ^A (0.66-0.97)	23.8	0.83 (0.70-0.98)	55	8.3
FOLFOX4 (n=331)	8.0	p=0.02	19.4	p=0.03	48	7
PRIME Trial extended WT RAS³						
Panitumumab + FOLFOX4 (n=259)	10.1	0.72 ^C (0.58-0.90)	25.8	0.77 (0.64-0.94)	59	NR
FOLFOX4 (n=253)	7.9	p=0.004	20.2	p=0.009	46	
PEAK Trial WT KRAS¹						
Panitumumab + mFOLFOX6 (n=142)	10.9	0.87 ^D (0.65-1.17)	34.2	0.62 (0.44-0.89)	57.8	10
Bevacizumab + mFOLFOX6 (n=143)	10.1	p=0.353	24.3	p=0.009	53.5	8
PEAK Trial extended WT RAS¹						
Panitumumab + mFOLFOX6 (n=88)	13	0.65 ^E (0.44-0.96)	41.3	0.63 (0.39-1.02)	63.6	NR
Bevacizumab + mFOLFOX6 (n=82)	9.5	p=0.029	28.9	p=0.058	60.5	
Abbreviations: CI - confidence interval; HR - hazard ratio; mos - months; n = number; NR - not reported; OS - overall survival; p = p-value; PFS - progression-free survival; WT KRAS - wild-type KRAS; WT RAS - wild-type RAS.						
Notes:						
^A Median follow-up times were 13.2 and 12.5 months in panitumumab and control arms, respectively.						
^B Median follow-up times were not reported.						
^C Median follow-up times were 14.5 and 13.5 months in panitumumab and control arms, respectively.						
^D Median follow-up times were not reported.						
^E Median follow-up times were 16.3 and 16.2 months in the panitumumab and control arms, respectively.						

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify any further relevant literature providing supporting information for this review.

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review.

2.1.6 Other Considerations

Please see below for a summary of specific input received from the patient advocacy groups. Cited responses are not correct for spelling or grammar.

See Section 4 and 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.

Patient Advocacy Group Input

From a patient perspective, mCRC is a fatal disease for which there is no known cure other than tumour control or reduction coupled with surgery (in some cases). Respondents expressed their desire to continue accessing therapies to help control their mCRC with respect to quality of life, progression free survival and overall survival. Depending upon the metastatic site impacted, symptoms of mCRC include severe abdominal pain, vomiting, dizziness, shortness of breath, coughing, fatigue, loss of appetite and bloating. Over 50% of respondents reported fatigue and weakness as being a commonly experienced side effect of their treatments. Others respondents noted nausea, neuropathy, diarrhea, constipation and digestive disorders. For the three respondents with experience with panitumumab, it was reported that they found the therapy was able to shrink or control their colorectal cancer. For one respondent, the cancer returned. Some of the therapy's common adverse events included: rash, fatigue, numbness, nerve damage, pain in feet and hands. Respondents noted that all side effects were considered acceptable, including the rash, which respondents report, was relatively easy to control. Respondents reported welcoming this side effect as it is an indication of response. All respondents confirmed the therapy was easy to administer/receive as it allowed for synchronization with chemotherapy dosing and minimized the number of required clinic visits. Respondents also reported they were able to maintain a normal quality of life while taking panitumumab.

PAG Input

Input on the panitumumab review was obtained from all of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of panitumumab:

Clinical factors:

- In some provinces, FOLFIRI is the standard of care for first-line treatment of mCRC
- Alternate treatment option with a different toxicity profile for these patients.

Economic factors:

- Drug wastage
- Testing for RAS mutation would need to be conducted in all patients in the first-line setting

2.2 Interpretation and Guidance

PEAK

In the small randomized phase II PEAK trial comparing panitumumab to bevacizumab, each in combination with FOLFOX, the initial analysis of all patients entered into the trial with WT KRAS tumours found the primary endpoint of PFS to be similar in the two arms at about 10 months. Despite no improvement in PFS, OS was found to have increased from 24.3 to 34.2 months ($p=0.009$). On the pre-planned prospective secondary analysis restricted to patients with WT RAS tumours on extended RAS testing, the current standard for RAS testing, PFS was prolonged at 13 months among the 88 patients treated with panitumumab, compared to 9.5 months for the 82 who received bevacizumab ($p<.03$). Overall survival was 41.3 months in the panitumumab arm and 28.9 months in the bevacizumab arm, and this bordered on statistical significance ($p=0.06$). Post-progression crossover to the other antibody appeared to be similar in both arms. Rates of grade 3 or higher adverse events were slightly more frequent in patients treated with panitumumab compared with controls: skin toxicity (32% vs.1%), hypokalemia (11% vs. 5%), mucositis (7% vs. 1%), stomatitis (5% vs. <1%), and hypomagnesemia (7% vs. 0). Treatment with bevacizumab was associated with a higher incidence of hypertension (7% vs. 0%). HRQoL data was not captured in this trial.

PRIME

The PRIME phase III trial ($n=1183$) randomized participants to FOLFOX with or without panitumumab. Among those with WT RAS on extended RAS testing (a pre-specified retrospective analysis), the addition of panitumumab prolonged median PFS from 7.9 to 10.1 months ($p=0.004$) and median overall survival from 20.2 to 25.8 months ($p=0.009$). Results were similar among the initial larger KRAS randomized population on updated analyses. Certain adverse events occurred more frequently in the panitumumab arm: skin toxicity (36% vs. 2%), diarrhea (18% vs. 9%), hypokalemia (10% vs. 5%), fatigue (9% vs. 3%), mucositis (6% vs. <1%) and hypomagnesemia (6% vs. <1%). This did not, however, result in a detectable difference in overall HRQoL.

Other outcomes such as response and metastatectomy rates did not differ in either trial (PEAK or PRIME) in any important or consistent way. On balance, the literature cited in Section 3 Background Clinical Information looking at other similar combinations shows that the addition of an EGFR inhibitor (i.e. cetuximab) to first line chemotherapy provides a modest benefit, and that this benefit is similar to the addition of bevacizumab. The Clinical Guidance Panel is of the opinion that there are unlikely to be differences in outcomes between the various antibody and chemotherapy combinations that are important in non-curative settings.

The burden of suffering that metastatic colorectal cancer has on patients and their caregivers is large and better therapies are clearly desired. The need for a new targeted therapy, of similar efficacy to the current standard, to add to a chemotherapy backbone in the first line setting is not great, however. There are a small number of patients who are candidates for multi-agent systemic therapy who may have contraindications, usually relative contraindications, to bevacizumab. These might include those with or at high-risk of bleeding, arterial thrombosis (such as extensive atherosclerotic disease), venous clotting, or fistulae. Uncontrolled hypertension could worsen with treatment with bevacizumab. Conceivably, there may be patients requiring immediate initiation of maximal systemic therapy but who are unable to wait 4 weeks from major surgery. The fact that RAS testing would still need to be done prior to initiating treatment with panitumumab makes this scenario not practically feasible. Overall, the number of patients WT for RAS, for whom panitumumab would be clearly preferred, and for whom the modest benefits provided by

the addition of targeted therapy to chemotherapy are important, would be expected to be small (<10%).

Addressing questions from the PAG, although randomized trials have not been carried out comparing bevacizumab and panitumumab when combined with FOLFIRI, the Clinical Guidance Panel is of the opinion that it is not unreasonable to extrapolate from the data described above, the results would likely be similar regardless of chemotherapy backbone. Some patients for whom bevacizumab is initially contraindicated may later become eligible for bevacizumab after treatment with panitumumab due to resolution of temporary contraindications (post-operative bleeding). Consequently, if panitumumab is given with chemotherapy first-line, in eligible patients it would be clinically reasonable to give bevacizumab with second-line chemotherapy, even though this option is not currently consistently publicly funded in Canada. Once an EGFR inhibitor has been given to progression, however, EGFR inhibitors should not be used in any later lines of therapy. Selection for treatment with an EGFR inhibitor should be done with extended RAS testing. There is currently no clear role for BRAF testing in making these decisions. EGFR inhibitors cause net harm in patients with RAS mutations and should not be given for those patients.

2.3 Conclusions

Bevacizumab - Eligible Patients

The Clinical Guidance Panel concluded that, while non-inferior, there is not a net overall clinical benefit to panitumumab + FOLFOX in the first-line treatment of WT RAS metastatic colorectal cancer compared to the current standard first-line targeted agent bevacizumab + FOLFOX/FOLFIRI. Rather, the efficacy of each of these agents is similar when added to chemotherapy in the first-line setting. The Panel based this conclusion on a small randomized phase II trial (PEAK) evaluating panitumumab + FOLFOX compared with bevacizumab + FOLFOX as well as other trials comparing similar drug combinations.

In reaching this conclusion, the Clinical Guidance Panel considered that:

- In its primary analysis based on initial entry criteria at the time of WT KRAS tumours, this Phase II trial demonstrated that the addition of panitumumab to FOLFOX has similar efficacy to the addition of bevacizumab to the same chemotherapy backbone in terms of progression-free survival, the primary endpoint of the study, and found a statistically significant improvement in overall survival, an endpoint for which the study was not powered. On restriction to the extended WT RAS subpopulation, PFS was increased by 3.5 months but OS was no longer statistically significantly different but was not sufficiently powered.
- The Panel was unable to comment on patient HRQoL as this was not measured in the PEAK trial.
- Adverse event profiles differed between panitumumab and bevacizumab but are at levels patients often consider to be acceptable. The dermatological effects of panitumumab likely result in more noticeable day-to-day on-treatment toxicity compared to bevacizumab.
- The Clinical Guidance Panel felt there were limitations with the PEAK trial as it was a small phase II study and there was no independent assessment of the primary endpoint of PFS.
- The need for a new targeted therapy, of similar efficacy to the current standard, to add to a chemotherapy backbone in the first line setting is not great. There are a small number of patients who are candidates for multi-agent systemic therapy who may have contraindications, usually relative contraindications, to bevacizumab.

- Other trials testing similar combinations of drugs have also generally found the efficacy of EGFR inhibitors and bevacizumab to be similar when combined with chemotherapy in this setting.

Bevacizumab - Ineligible Patients

The Clinical Guidance Panel concluded that there is a moderate net overall clinical benefit to panitumumab + FOLFOX compared to FOLFOX alone. The Clinical Guidance Panel based this decision on one high-quality randomized controlled trial (PRIME).

In reaching this conclusion, the Clinical Guidance Panel considered that:

- The PRIME trial demonstrated a clinically and statistically significant benefit in progression free survival and overall survival for panitumumab + FOLFOX compared with FOLFOX alone. This finding is consistent with other trials comparing similar combinations of drugs.
- In the PRIME trial, there were no significant differences in HrQoL for the panitumumab and FOLFOX arms.
- The addition of panitumumab to the chemotherapy backbone resulted in the expected increase in toxicity, but this toxicity is usually considered a reasonable trade-off for the benefit derived.
- At this point in time, these results are most relevant for the small population of patients with WT RAS metastatic colorectal cancer who are candidates for first-line multi-agent systemic therapy but for whom bevacizumab is contraindicated.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Gastrointestinal Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

In 2015 the Canadian Cancer Society estimates that there were 25,100 new cases of colorectal cancer diagnosed, and 9,300 people died from the disease.⁵ Most of this latter group would have had spread of their cancer from the colon into vital organs, most commonly the liver or lungs. In a minority of patients with a few isolated sites of metastatic disease, surgery can sometimes be curative. Unfortunately, for the majority metastatic disease is incurable.

3.2 Accepted Clinical Practice

When colorectal cancer is at an incurable stage, the primary treatment is with systemic therapy. This is given with goals of extending survival and ameliorating or delaying symptoms, but it is with only palliative, never curative intent. With supportive care alone, the median survival is approximately 6-12 months. Recent studies involving treatment with multiple lines of chemotherapy routinely report median survivals of over 24 months.⁶ The standard first-line of therapy in Canada is fluoropyrimidine-based chemotherapy combined with bevacizumab.¹⁴

Chemotherapy

Fluoropyrimidines available in Canada are intravenous 5-fluorouracil (5-FU), usually given with leucovorin, and its oral prodrug, capecitabine. These drugs can be combined with oxaliplatin and/or irinotecan to make the common regimens FOLFOX, FOLFIRI, capeOx, and capeIRI. Sequencing oxaliplatin and irinotecan in first- versus second-line regimens are considered to be clinically equivalent approaches.^{7,8}

Targeted Agents

Vascular endothelial growth factor inhibitors (VEGFi)

Bevacizumab is a monoclonal antibody that blocks angiogenesis through binding to the vascular endothelial growth factor (VEGF) receptor. Bevacizumab has been shown in multiple studies to increase overall survival in metastatic colorectal cancer by approximately 1.5 months when given in combination with chemotherapy in the first-line setting.⁹⁻¹¹

Epidermal Growth Factor Receptor inhibitors (EGFRi)

Cetuximab and panitumumab are monoclonal antibodies to the epidermal growth factor receptor (EGFR) that inhibit its downstream signaling pathways, such as the RAS pathway. Cetuximab is chimeric whereas panitumumab is a fully humanized antibody. Common toxicities with this class of agents include significant skin rash, diarrhea, and hypomagnesemia. Severe anaphylactic reactions can also occur, but are more common with cetuximab due to its mouse component.

The presence of a RAS mutation in the tumour, observed in 40% of colorectal cancers,¹² is a negative predictor of EGFRi benefit. Consequently, because of toxicity patients are on balance harmed by EGFRi treatment if their tumour harbours a RAS mutation, and hence these drugs are contraindicated in this setting.

It should be noted that EGFRis combined with bevacizumab and chemotherapy produce outcomes that are inferior to using either targeted agent alone. Consequently, the two types of targeted agents should not be combined.

Chemotherapy + Targeted Agents

Chemotherapy + VEGFis

Oxaliplatin-based regimens tend to be the most popular first-line choice in the United States because of slightly better perceived day-to-day tolerability, even though there is a cumulative peripheral neurotoxicity that usually eventually limits the duration of treatment. In Canada, funding rules around bevacizumab sometimes result in it having to be discontinued when the oxaliplatin is stopped, even for toxicity. As a result, irinotecan regimens are strategically more commonly used here. Additionally, because approximately a third of patients do not proceed to second-line chemotherapy, it is economically preferable to start with the less expensive irinotecan-containing regimens.

Chemotherapy + EGFRis

Currently, the use of cetuximab and panitumumab in Canada is primarily limited to the third-line setting for patients with non-mutated, 'wild-type' (WT) RAS tumours. A large international randomized trial has demonstrated that cetuximab provides similar efficacy outcomes to bevacizumab when combined with first-line chemotherapy in patients with WT RAS tumours,¹⁵ but its increased toxicity and cost make it the less desirable choice.¹⁶ The CRYSTAL trial demonstrated an improvement in PFS and, in a retrospective analysis of WT KRAS enrollees, OS at 23.5 versus 20.0 months, $p=.009$) with the addition of cetuximab to FOLFIRI in first-line treatment of mCRC.¹⁷ A pooled analysis of the COIN and OPUS trials that compared FOLFOX with or without cetuximab found improved PFS but similar OS with the addition of cetuximab.¹⁸ Most relevant, the large Phase III CALGB/SWOG 80405 trial found similar efficacy when either cetuximab or bevacizumab was added to first line chemotherapy (at the treating physician's discretion 73% received FOLFOX and 27% FOLFIRI) among over 3000 patients with WT KRAS tumours.¹⁵ The European FIRE-3 trial compared cetuximab with bevacizumab when added to FOLFIRI in WT KRAS patients. PFS was similar in each arm. An OS advantage was observed for the cetuximab arm, but this trial has been criticized for having low rates of post-progression treatment, which could explain the OS result.¹⁹

There had been hope that cetuximab with chemotherapy might have an advantage for patients with borderline resectable metastases due to a perceived higher response rate, but this has proven not to be the case.²⁰

The combination of panitumumab with first-line oxaliplatin-containing chemotherapy is the topic of the current submission.

3.3 Evidence-Based Considerations for a Funding Population

The relevant funding population for panitumumab with FOLFOX is patients with non-mutated (i.e. wild-type (WT)) RAS tumours undergoing first-line chemotherapy for metastatic colorectal cancer. KRAS and extended RAS testing are currently completed in later lines of mCRC therapy to identify patients appropriate for third-line treatment with panitumumab. As RAS mutation is observed in 40% of colorectal cancers, the remaining 60% will be non-mutated, WT RAS tumours. Testing beyond KRAS exon-2 will further reduce the mCRC patient population eligible for EGFR therapy by an additional 10%.¹² As mentioned in Section 3.1, approximately 9,300 patients die from colorectal cancer in Canada each year and most of these patients would at some point have been eligible to consider palliative

chemotherapy. Given what we know about panitumumab's toxicity and cost, it would be the preferred choice in patients for whom bevacizumab is for some reason contraindicated, such as those with impaired post-operative wound healing, high-risk of arterial or venous thrombosis, or active fistulae.

Targeted agents have not been found to provide benefit in non-metastatic colorectal cancer.

3.4 Other Patient Populations in Whom the Drug May Be Used

Panitumumab is currently used as third-line treatment for patients with metastatic wild-type RAS colorectal cancer.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Colorectal Cancer Association of Canada (CCAC), provided input on panitumumab (Vectibix) for the treatment of patients with WT RAS mCRC in first line treatment setting in combination with FOLFOX, and their input is summarized below.

CCAC conducted an online survey on April 10 - April 19, 2015 of colorectal cancer patients and caregivers in Canada and abroad to gather information about patient and caregiver experiences with the drug under review, and received 82 responses. CCAC reported that three respondents have experienced with panitumumab in first line therapy and one accessed the therapy in second line. These respondents were contacted through CCAC's database of registered colorectal cancer patients and their respective caregivers residing primarily in Canada and a small number abroad. The survey used free-form commentary and scoring options (ten point scale) and limited closed-ended questions (agree/disagree, yes/no, patient/caregiver). In addition, to better provide the patient and caregiver perspective, CCAC conducted interviews with patients and caregivers from the CCAC support groups as well as obtaining publications focusing on the therapy in question. Specifically, two patient respondents were interviewed for the purpose of this submission and have offered their input, herein referenced as Patient I and Patient II. CCAC also included a Quality of Life (QoL) survey of 1,001 Canadians aged 18 and over that was conducted in March 2011.

From a patient perspective, metastatic colorectal cancer (mCRC) is a fatal disease for which there is no known cure other than tumour control or reduction coupled with surgery (in some cases). Respondents expressed their desire to continue accessing therapies to help control their mCRC with respect to quality of life, progression free survival and overall survival. Depending upon the metastatic site impacted, symptoms of mCRC include severe abdominal pain, vomiting, dizziness, shortness of breath, coughing, fatigue, loss of appetite and bloating. Over 50% of respondents reported fatigue and weakness as being a commonly experienced side effect of their treatments. Others respondents noted nausea, neuropathy, diarrhea, constipation and digestive disorders. For the three respondents with experience with panitumumab, it was reported that they found the therapy was able to shrink or control their colorectal cancer. For one respondent, the cancer returned. Some of the therapy's common adverse events included: rash, fatigue, numbness, nerve damage, pain in feet and hands. Respondents noted that all side effects were considered acceptable, including the rash, which respondents report, was relatively easy to control. Respondents reported welcoming this side effect as it is an indication of response. All respondents confirmed the therapy was easy to administer/receive as it allowed for synchronization with chemotherapy dosing and minimized the number of required clinic visits. Respondents also reported they were able to maintain a normal QoL while taking panitumumab.

Please see below for a summary of specific input received from the patient advocacy group. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission, without modification.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with mCRC

CCAC indicated that depending upon the metastatic site impacted, symptoms of metastatic colorectal cancer (mCRC) include severe abdominal pain, vomiting, dizziness, shortness of breath, coughing, fatigue, loss of appetite and bloating. CCAC noted that the most frequently reported disease-related symptoms included: bloody stools, pain/cramping, diarrhea/constipation, bowel obstruction, fatigue, and nausea.

According to CCAC, respondents identified the following aspects colorectal cancer as being the most important and difficult to control were:

- Fatigue
- Bowel obstruction/abnormal bowel movements
- Pain
- Anxiety/insomnia/fear
- Shortness of breath
- Bleeding

Survey respondents stated the limitations resulting from those symptoms included but are not limited to the following:

- Work cessation
- Confined to nearby bathroom
- Inability to exercise
- Inability to socialize
- Inability to participate in household responsibilities
- Inability to travel

Respondents were also provided with an opportunity to list any physical or psychological limitations resulting from their colorectal cancer. CCAC reported that 47% of respondents reported depression, anxiety, fear and memory loss; and 21% of respondents reported fatigue and weakness. The balance of responses included the following:

- Frequent and/or abnormal bowel movements
- Neuropathy
- Pain
- Mobility Challenges
- Diarrhea and constipation

4.1.2 Patients' Experiences with Current Therapy for mCRC

According to CCAC, standard treatment for mCRC, which is received by approximately 50% of the colorectal cancer population, involves chemotherapy based on fluoropyrimidines, oxaliplatin, and irinotecan used in combination i.e. FOLFIRI and FOLFOX, and sequentially; and monoclonal antibodies (MAB) targeting vascular endothelial growth factor (VEGF) such as bevacizumab. In patients with RAS wild type (WT) tumours, monoclonal antibodies targeting epidermal growth factor receptor (EGFR) such as cetuximab and panitumumab are also used. CCAC reported that patients with WT RAS tumours comprise roughly 50% of mCRC cases, which may affirm the effect of anti-EGFR agents such as panitumumab when administered in combination with FOLFOX in first line therapy.

Current therapies such as FOLFIRI and FOLFOX administered in first and second line in combination with a biologic therapy have proven to successfully shrink tumours and provide progression free survival (PFS) for a limited period of time. According to the survey results, respondents did have access FOLFIRI, FOLFOX and the biologic therapies to help shrink their metastatic disease. 70% of respondents maintained these therapies were effective at controlling their symptoms resulting from their colorectal cancer and reported the following:

- *" Yes, symptoms subsided after chemotherapy"*
- *" Yes, symptoms subsided after combined chemotherapy and surgery"*

Notwithstanding, respondents reported treatment-related adverse effects with their current therapies. Over 50% of respondents reported fatigue and weakness as being a commonly experienced side effect of their treatments. Others respondents noted nausea, neuropathy, diarrhea, constipation and digestive disorders.

57% of respondents surveyed maintained that some of those treatment-related adverse events were more difficult to tolerate than others. The respondents reported neuropathy, diarrhea, fatigue and weakness, pain, and weight loss as the most difficult adverse effects to control. Diarrhea, nausea, and vomiting were the most frequently reported side effects of irinotecan which can cause severe dehydration and necessitate cessation of therapy as well.

When respondents were asked if they could choose a treatment based on each drug's known toxicity profile, 80% of respondents reported that it would be very important to do so.

CCAC found that disparities exist across Canada as they relate to access to treatments both to the therapy itself and in some cases, the line of treatment in which it is available. This is evidenced in the QoL Survey results which show regional disparities in the confidence levels of Canadians regarding access to therapies. Over 50% of respondents surveyed believe that geographical location impacts their quality of treatment when diagnosed with cancer.

Respondents reported that it would be very important to access additional treatments whose benefits might only be short term despite treatment adverse effects. A survey conducted by the CCAC in March 2011 indicated that respondents were interested in treatment even in end of life situations when the benefit was just a few weeks, provided, there was good QoL.

33% of respondents surveyed reported out of pocket expenses associated with the management of their disease. They cited travel and accommodation, parking, over the counter medications, and treatment accessories as the most highly incurred expenditures when accessing their drug therapies.

When asked if patients would be willing to pay out of pocket to access new drug therapies for the treatment of their mCRC, 57.9% of respondents replied "Yes". Some of the open-ended replies are reported below:

- *"Yes, if it improved my survival rate"*
- *"Yes, if it is affordable"*

When respondents were asked if some of their needs were not being met, the following open ended replies were noted:

- *"There are some therapies that can improve treatment. It seems over time some drugs become ineffective and newer effective therapies are not covered therefore unavailable."*
- *"Need a chemo drug that will be a cure vs. just delaying things."*

Based on discussion with the CCAC support group, respondents identified an unmet clinical need for personalized targeted treatment of their mCRC in the first line. Patients and caregivers are currently inundated with the progress made in the personalized treatment of cancer and how it could offer to improve patient outcomes. Support group members fail to see how their personal disease characteristics form the basis of treatment selection in the first line management of their mCRC.

CCAC indicated that since predictive biomarkers (i.e. RAS mutation status) are available for panitumumab to support drug selection for individual patients, in settings where tumour shrinkage is a relevant therapeutic goal, panitumumab in combination with FOLFOX might be the preferred option for first line treatment. The availability of predictive biomarkers (KRAS and NRAS status) offers the possibility of an improved likelihood of achieving an overall response. It is important to note this is a benefit not available with bevacizumab since there is a lack of predictive biomarkers currently available to support patient selection for this drug.

4.1.3 Impact of mCRC and Current Therapy on Caregivers

CCAC indicated that the impact of mCRC on caregivers and families is significant. Caregivers provide supportive care to the patient in managing adverse side effects, providing emotional support and assuming additional unpaid work duties in the home.

Additionally, caregivers of mCRC patients are fraught with financial challenges relating to disability and cost of accessing treatments in those provinces that have reimbursement restrictions. Travel and parking costs are also assumed by the caregiver when accessing drug therapies.

96% of respondents surveyed identified the following difficulties in caring for patients with colorectal cancer:

- *"Inability to attend to family/household responsibilities"*
- *"Watching a loved one suffer"*
- *"Lack of support/information"*
- *"Fear that one isn't being supportive enough"*
- *"Limited financial resources"*
- *"Stress"*

75% of respondents surveyed reported the following challenges in dealing with adverse effects from the current therapies:

- *"Emotional stress"*
- *"Physical stress"*
- *"Patient non-compliance"*
- *"Watching the patient suffer"*
- *"Lack of support for caregivers"*

In addition to the above, respondents reported that accessing drug therapies significantly impacts a caregiver's daily routine. This included:

- *"Taking time off work"*
- *"Assuming the patient's previous roles in the household"*
- *"Learning to cope with the patient's symptoms and needs"*
- *"Fear, feelings of helplessness"*

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Panitumumab

Based on the information collected by CCAC, respondents expressed their desire to continue accessing therapies to help control their mCRC with respect to quality of life, progression free survival and overall survival.

82% of respondents expressed a desire to be afforded the opportunity to have choice in the selection of the best therapeutic option in the treatment of their mCRC. In particular, patient support group members stated that patients should receive the best therapeutic option based on the patient's individual disease characteristics.

CCAC also found that 31% of surveyed respondents have identified access to drugs in their province as limited/restrictive.

Below were some of the key statements from respondents as to why the funding of panitumumab is important:

- *"Options = HOPE=longer survival times"*
- *"I have Lynch Syndrome so even though I have been cured of my original cancer, I may get it again and will need access to the best treatments"*
- *"One never knows what's around the corner after having CRC"*
- *"Underwent surgery only but if cancer comes back may require chemical therapy and to give other patients access to the best medicine"*

One respondent felt that panitumumab would be *"better option for patients with liver dominant disease"*.

CCAC indicated that in patients with relative contraindications to bevacizumab such as hypertension, recent surgery, thrombosis, panitumumab may offer a good option for the initiation of systemic therapy.

According to CCAC, three respondents reported having accessed panitumumab in first line therapy and one accessed the therapy in second line. The therapy was funded:

- *"As a part of a clinical trial"*
- *"Through the government"*

Respondents reported the following positive and negative effects with their treatment:

Positive effects included:

- *"Shrank my cancer and allowed the tumour to be removed"*
- *"Shrunk and controlled the tumours"*

Negative effects included:

- *"It gave me a rash"*
- *"The cancer returned"*

Some of the therapy's common adverse events reported by respondents included:

- *"Rash, fatigue, numbness"*
- *"Nerve damage"*
- *"Tiredness, hair thinning, numbness in fingers"*
- *"Pain in my feet and hands"*

One respondent reported no side effects resulting from the therapy.

According to CCAC, all side effects were considered acceptable, including the rash, which respondents report, was relatively easy to control. Respondents have reported welcoming this side effect as it is an indication of response.

All respondents confirmed the therapy was easy to administer/receive as it allowed for synchronization with chemotherapy dosing and minimized the number of required clinic visits. Two respondents went on to receive bevacizumab + FOLFIRI in second line therapy, and two respondents reported that panitumumab was able to better shrink their cancer in comparison to the other therapies received.

Respondents also reported they were able to maintain a normal QoL while taking panitumumab. With respect to a patient's long term health and well-being, respondents indicated that the therapy was capable of "*providing normalized daily life*" and "*health and well-being was high*". One respondent stated: "*I am still young, love to work and travel. This combination has helped me improve my results significantly, and my daily life is much more normal now.*"

CCAC also conducted extensive interviews with two mCRC patients from one of the CCAC support groups. Patient #1 is a 67 year old male who was interviewed on April 23rd, 2015. He was diagnosed with mCRC (metastatic disease confined to liver and primary colon tumour intact) in January 2014. The patient has a history of transient ischemic attacks and was, therefore, not a candidate for first line BEV therapy. Instead, he was prescribed FOLFOX therapy to help shrink his disease. The patient experienced ongoing and ultimately severe neurotoxicity which necessitated dose reductions in the oxaliplatin and eventually cessation of the therapy altogether. The patient then commenced FOLFIRI therapy in January 2015 and is currently undergoing same. As a result of participating in the COMPACT study, the patient's molecular testing results revealed he was RAS WT and potentially a candidate for anti-EGFR therapy. The patient's greatest desire has been to eventually qualify for surgical resection of his primary and liver metastases.

In his words, patient #1 stated: "*My goal has always been to get to surgery to remove my disease. I feel I have the best chance of beating this cancer if it can be surgically taken out. Not having qualified for Avastin was disappointing to me; but to learn that there is another biologic therapy that could help better shrink my disease from the get go and not have access to it till third line therapy, was even more disappointing. I want the best possible therapies to help cure me. Why do I have to wait for a biologic treatment to be administered in third line when it might help me more in first line? Perhaps having accessed Vectibix with FOLFOX in first line might have shrunk my disease enough to qualify for surgery. I will never know...*"

Patient #2 is a 55-year-old female who was diagnosed with mCRC (metastatic disease to lungs and liver; primary intact) in February 2013. She was interviewed on April 23rd, 2015. Her first line treatment consisted of bevacizumab + FOLFIRI, in which she achieved disease stability for almost a year. Disease progression then necessitated cessation of the bevacizumab + FOLFIRI. She then accessed FOLFOX alone. Funding restrictions in her province would not permit continued therapy with bevacizumab. Again, she was able to achieve disease stability with FOLFOX for nine months with intermittent chemo breaks due to drug induced toxicities compromising QoL significantly. She experienced peripheral neuropathy, mouth sores (preventing food ingestion) and fatigue. Disease progression in December 2014 once again necessitated moving on to third line therapy. Due to ongoing QoL issues, her oncologist recommended panitumumab monotherapy, for which she was a candidate based on her recently determined KRAS WT status. According to the patient, she has been responding to panitumumab with disease regression.

In her words, she stated: *“Vectibix is the first therapy that has shrunk my tumours in the lungs and liver! I feel much better now and am so happy these tumours are finally shrinking. I wish I would have been able to access Vectibix when I first started treatment for my cancer. Maybe together with chemo, vectibix could have shrunk my tumours more because Avastin didn’t do as great a job as I had hoped. Vectibix seems to be working much better for me..... Shouldn’t patients be afforded the best therapy for their colorectal cancer?”*

4.3 Additional Information

According to CCAC, patients and caregivers believe that not only are additional therapies required for the treatment of metastatic colorectal cancer (mCRC), but a choice of when those therapies are administered is also warranted.

In addition, CCAC noted that since every patient with cancer is unique, therefore, the focus should be on identifying treatment options for patients based on their cancer’s genetic makeup. As reported by patients in CCAC’s support group meetings, patients encourage the use of therapies designed to genetically target their cancer and would wish to avail themselves of such therapies in first line, when their cancer is most vulnerable. Their hope is to administer the most effective therapy to help shrink their disease upon commencing treatment. Tumor specific genetic markers allow for more accurate selection of patients who are likely to have a response to a particular therapy and may prevent toxic effects in those who are unlikely to benefit. The predictive biomarkers (KRAS and NRAS) available for panitumumab could support the selection of this therapy in mCRC patients. Of particular relevance, is the subset of patients with borderline resectable liver metastases. Preoperative conversion therapy is of paramount importance in patients wishing to explore potentially curative intent resection. Employment of the most effective first line therapy would aid to improve attempted curative resection rates and rates of successful complete resection.

In view of the above, CCAC is of the opinion that the RAS WT mCRC population would greatly benefit from panitumumab + FOLFOX treatment in upfront therapy, as it would give mCRC patients a valuable new treatment option as they fight this devastating disease.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of panitumumab:

Clinical factors:

- In some provinces, bevacizumab plus FOLFIRI is the standard of care for first-line treatment of mCRC
- Alternate treatment option with a different toxicity profile for these patients.

Economic factors:

- Drug wastage
- Testing for RAS mutation would need to be conducted in all patients in the first-line setting

Please see below for more details.

5.1 Factors Related to Comparators

The current standard first-line treatment for patients with metastatic colorectal cancer (mCRC) is bevacizumab plus FOLFOX or bevacizumab plus FOLFIRI. PAG noted that the PRIME trial compared panitumumab plus FOLFOX to FOLFOX alone, which is not current standard of care. The PEAK trial comparing panitumumab plus FOLFOX to bevacizumab plus FOLFOX would be more relevant.

Data on the use of panitumumab plus FOLFIRI would be helpful for implementation in provinces where FOLFIRI is funded for first-line treatment, particularly in comparison to bevacizumab plus FOLFIRI.

5.2 Factors Related to Patient Population

Although the number of patients with mCRC requiring first-line treatment is large, PAG indicated the number of patients with non-mutated wild-type RAS is likely smaller. Panitumumab would be an alternate treatment option with a different toxicity profile for these patients.

PAG noted that bevacizumab plus FOLFOX or FOLFIRI is funded for second-line treatment in some provinces and that panitumumab monotherapy is funded for third-line treatment in some provinces. Information on the use of in bevacizumab second-line after panitumumab in first-line and vice versa would be informative for implementing panitumumab for first-line treatment. In addition,

information on use of panitumumab alone in the third-line setting after its use in the first-line setting would be helpful.

5.3 Factors Related to Dosing

Panitumumab is given in combination with FOLFOX and with the same dosing schedule as FOLFOX. PAG noted this would be convenient for the patients and for scheduling chair time, which are enablers.

PAG has concerns for incremental costs due to drug wastage, specifically in smaller centers where vial sharing may be difficult. As dose is based on weight and the smallest vial size is 100mg, a dose of 420mg (6mg/kg x 70kg) would result in significant wastage of the fifth vial if it cannot be used within 24 hours. This is a barrier.

5.4 Factors Related to Implementation Costs

The cost of panitumumab, the need for RAS testing in first-line setting and the longer infusion time are barriers to implementation of panitumumab in the first-line setting.

The high cost of panitumumab compared to bevacizumab, the higher number of patients in the first-line setting and the undefined number of treatments (i.e. treatment until progression or unacceptable toxicities) could have significant budget impact. In addition, in provinces where FOLFOX is not funded for first-line already, there is the additional cost of also funding FOLFOX.

PAG has indicated that RAS testing is currently done in later lines of therapy and that RAS testing would be conducted in all patients with mCRC to determine. As such, there would be an increase volume for RAS testing to be conducted and PAG has concerns for delay to initiation of treatment while waiting for results. In addition, extended RAS testing is not available in all provinces and PAG would like pERC to address the use of panitumumab without extended RAS testing.

Panitumumab is administered by intravenous infusion over 60 to 90 minutes compared to the 10 minute infusion time for bevacizumab. There would be increased chair time and increased nursing time.

5.5 Factors Related to Health System

Panitumumab, being an intravenous drug, would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of toxicities. Intravenous chemotherapy drugs would be funded fully in all jurisdictions for eligible patients, which is an enabler for patients. As patients would be treated first-line with bevacizumab plus FOLFOX or FOLFIRI already, panitumumab is an alternate to bevacizumab for a subgroup of patients with non-mutated wild-type RAS mCRC. These are enablers.

In provinces that fund panitumumab for third-line treatment of mCRC, there is familiarity with the preparation, administration and monitoring of panitumumab. This would be an enabler.

PAG noted that the monitoring for and treatment of dermatological toxicities related to panitumumab may be an additional burden to the health care system and this would be a

barrier. However, PAG also noted that panitumumab does not have the risk of bleeding that is associated with bevacizumab and this would be an enabler for patients receiving treatment and considering surgery.

5.6 Factors Related to Manufacturer

The high cost of panitumumab compared to bevacizumab.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of panitumumab (Vectibix) in combination with oxaliplatin-based chemotherapy as first-line treatment in patients with wild-type (WT) RAS metastatic colorectal cancer (mCRC).

No Supplemental Questions relevant to the pCODR review or to the Provincial Advisory Group (PAG) were identified.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 2: Selection Criteria				
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published and unpublished RCTs	<p>Previously untreated adult patients (≥18 years) with mCRC and WT RAS tumours</p> <p>Subgroups:</p> <ul style="list-style-type: none"> • ECOG status • RAS (KRAS or NRAS) mutation status • Eligible or ineligible to receive bevacizumab 	<p>Panitumumab in combination with oxaliplatin-based chemotherapy (e.g., FOLFOX)</p> <p><u>Dosage, ROA, and schedule:</u> Panitumumab 6.0 mg/kg, 60-90 min IV infusion q 2 wks until disease progression or intolerability</p>	<ul style="list-style-type: none"> • Bevacizumab plus FOLFOX or FOLFIRI • FOLFOX or FOLFIRI alone 	<ul style="list-style-type: none"> • OS • PFS • HRQoL • ORR • Metastases resection rate • AE • Specific AE: rash • SAE • WDAE
<p>Abbreviations: AE - adverse events; ECOG - Eastern Collaborative Oncology Group; FOLFIRI - irinotecan, leucovorin, and 5-fluorouracil; FOLFOX - oxaliplatin, leucovorin, and 5-fluorouracil; IV - intravenous; KRAS - Kirsten rat sarcoma; mCRC - metastatic colorectal cancer; NRAS - neuroblastoma rat sarcoma; ORR - objective tumour response rate; OS - overall survival; PFS - progression-free survival; q- every; RAS - rat sarcoma; RCT - randomized controlled trial; ROA - route of administration; SAE - serious adverse events; HRQoL - health-related quality of life; WDAE - withdrawal due to adverse events; wks - weeks; WT - wild-type.</p>				
<p>Notes:</p> <p>*Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)</p> <p>§Includes pre-specified retrospective/exploratory analyses from prospective randomized controlled trials.</p>				

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (May 2015) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was panitumumab (Vectibix).

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. The search was also limited to English language documents, but not limited by publication year. The search is considered up to date as of September 2, 2015.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health - clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team independently made the final selection of studies to be included in the review.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

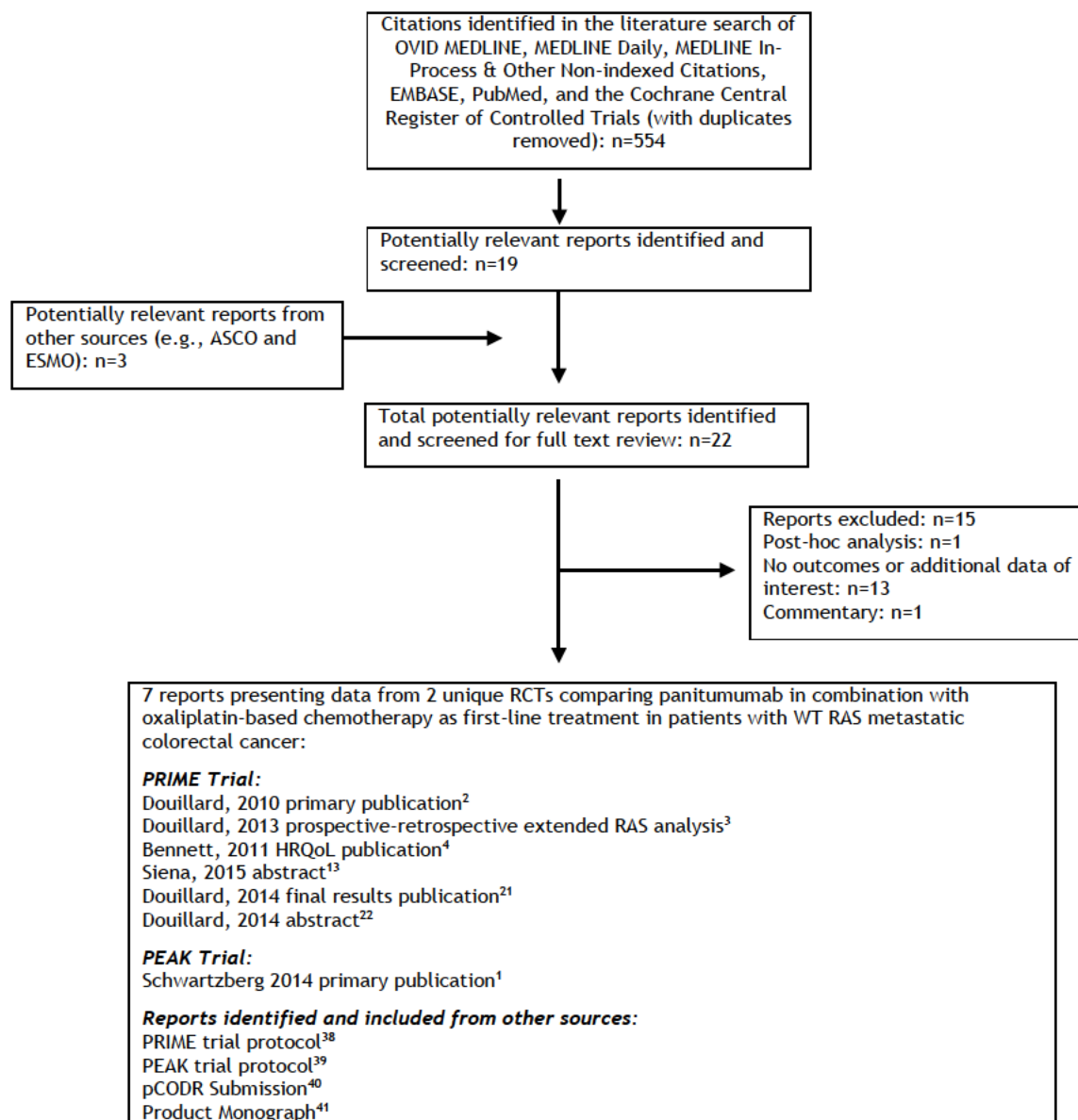
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the potentially relevant reports identified for full text review (n=554), 7 reports were included in the pCODR systematic review^{1-4,13,21,22} and 15 reports were excluded. Studies were excluded because they were post-hoc analyses,²³ reported no outcomes or additional data (i.e., trial abstracts) of interest to this review,²⁴⁻³⁶ or were commentary in nature.³⁷

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of Studies



6.3.2 Summary of Included Studies

Two randomized controlled trials were identified that met the eligibility criteria of this systematic review. Characteristics of the two trials are summarized in Table 3 and specific features of trial quality are summarized in Table 4.

6.3.2.1 Detailed Trial Characteristics

Table 3: Summary of trial characteristics of included trials of panitumumab in combination with oxaliplatin-based chemotherapy as first-line treatment in patients with wild-type (WT) RAS metastatic colorectal cancer.				
<i>PRIME Trial</i> ^{2,3,38}				
Trial Design	Eligibility Criteria	Intervention	Comparator	Outcomes
<p>Clinical Trial NCT003364013</p> <p>Open label phase 3 RCT</p> <p>Patient enrolment: August 2006 - February 2008</p> <p>Data cut-off date: August 29, 2009</p> <p>N randomized = 1183</p> <p>Multicentre (133 centres from 19 countries)</p> <p>Randomized 1:1 ratio, stratified by:</p> <ul style="list-style-type: none"> • Geographic location (Western Europe, Canada, Australia vs. rest of world) • ECOG PS (0 or 1 vs. 2) <p>EGFR expression and KRAS tumour status not required at trial entry</p> <p>Trial design amended (prior to efficacy analyses) to compare outcomes by KRAS tumour status (WT vs. MT)</p> <p>Blinded central KRAS testing was completed 3 months prior to</p>	<p><u>Key Inclusion Criteria:</u></p> <ul style="list-style-type: none"> • Age ≥ 18 years • Previously untreated histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum • ECOG PS of 0 to 2 • Previous adjuvant FU-based chemotherapy permitted if disease progression occurred >6 months after completion • ≥ 1 measurable lesion (≥ 20 mm) using modified RECIST criteria • Paraffin-embedded tumour tissue for central biomarker analysis • Adequate organ function • Life expectancy ≥ 3 months <p><u>Exclusion Criteria:</u></p> <ul style="list-style-type: none"> • Previous treatment with oxaliplatin or anti-EGFR therapy • Pregnancy • CNS metastases 	<p><u>Panitumumab</u> q 2 weeks: 6.0 mg/kg iv over 1 hour; if tolerated, subsequent infusions could be administered over 30 minutes</p> <p>+</p> <p><u>FOLFOX4</u> q 2 weeks: oxaliplatin 85 mg/m² iv on day 1; leucovorin 200 mg/m² iv + FU 400 mg/m² iv bolus, then 600 mg/m² 22-hour continuous iv on days 1 and 2</p> <p>Given until disease progression or unacceptable toxicity</p>	<p><u>FOLFOX4</u> q 2 weeks (same dose and schedule as intervention arm)</p>	<p><u>Primary:</u></p> <ul style="list-style-type: none"> • Progression-free survival (blinded central review) <p><u>Secondary:</u></p> <ul style="list-style-type: none"> • Overall survival • Objective tumour response (blinded central review) • Metastasis resection rate (complete or partial; status of margins not specifically captured) • Adverse events

primary efficacy analysis				
Funded by AMGEN				
PEAK Trial^{1,39}				
Trial Design	Eligibility Criteria	Intervention	Comparator	Outcomes
<p>Clinical Trial NCT008819780</p> <p>Open label Phase 2 RCT</p> <p>Patient enrolment: April 2009 - December 2011</p> <p>Data cut-off date: May 30, 2012</p> <p>N randomized: 285</p> <p>Multicentre (60 sites)</p> <p>Randomized 1:1 ratio, stratified by:</p> <ul style="list-style-type: none"> • Prior oxaliplatin therapy <p>Extended RAS analysis was performed (blinded, and planned apriori) to compare efficacy outcomes in KRAS tumour subgroups:</p> <ul style="list-style-type: none"> • KRAS exons 2, 3, and 4 • NRAS exons 2, 3, and 4 <p>Funded by AMGEN</p>	<p><u>Key Inclusion Criteria:</u></p> <ul style="list-style-type: none"> • Age \geq 18 years • Previously untreated histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum, with unresectable (M1) metastatic disease • Confirmed WT KRAS exon 2 (codons 12 and 13) tumour status (through validated testing before or during screening for study) • \geq 1 measurable lesion (\geq 20 mm) using modified RECIST criteria • ECOG of 0 or 1 • Adequate organ function <p><u>Exclusion Criteria:</u></p> <ul style="list-style-type: none"> • Any prior chemotherapy, anti-EGFR therapy, or treatment with bevacizumab for mCRC • Radiotherapy \leq 14 days before randomization • Adjuvant chemotherapy (including oxaliplatin) for CRC \leq 52 weeks prior to randomization • Pregnancy • CNS metastases 	<p><u>Panitumumab</u> q 2 weeks: 6.0 mg/kg iv over 1 hour; if tolerated, subsequent infusions could be administered over 30 minutes</p> <p>+</p> <p><u>mFOLFOX6:</u> oxaliplatin 85mg/m² iv on day 1; leucovorin 200 mg/m² iv + FU 400 mg/m² iv bolus, then 2400 mg/m² 46-48-hour continuous iv on days 1 to 3</p> <p>Given until disease progression, unacceptable toxicity, death, withdrawal of consent or investigator decision</p>	<p><u>Bevacizumab</u> q 2 weeks: 5.0 mg/kg iv over 90 minutes; if tolerated, subsequent infusions could be administered over 60 (or 30) minutes</p> <p>+</p> <p><u>mFOLFOX6</u> (same dose and schedule as intervention arm)</p>	<p><u>Primary:</u> Progression-free survival (no independent review)</p> <p><u>Secondary:</u> Overall survival Objective response rate Metastases resection rate Adverse events</p>
<p>Abbreviations: CRC - colorectal cancer; CNS - central nervous system; ECOG - Eastern Cooperative Oncology Group; EGFR - epidermal growth factor receptor; FU - 5-fluorouracil; FOLFOX - oxaliplatin, leucovorin, 5-fluorouracil; iv - intravenous; KRAS - Kirsten Rat Sarcoma oncogene; mCRC - metastatic colorectal cancer; mFOLFOX6 - modified FOLFOX6; MT - mutant; N = number; NRAS - Neuroblastoma RAS oncogene; PS - performance status; RECIST - Response Evaluation Criteria in Solid Tumors; RCT - randomized controlled trial; WT - wild-type.</p>				

a) *Trials*

Two randomized controlled trials, PRIME² and PEAK¹, met the inclusion criteria of this systematic review.

PRIME was a phase III trial and PEAK was a phase II trial. Both trials randomized patients with previously untreated mCRC in a 1:1 ratio to receive treatment with panitumumab and FOLFOX chemotherapy versus, FOLFOX alone (PRIME) or FOLFOX combined with bevacizumab (PEAK).

KRAS wild-type (WT) tumour status was required for trial entry into the PEAK trial but not in the PRIME trial. In PRIME, trial entry required the availability of paraffin-embedded tumour tissue for central biomarker analysis. During the course of patient enrolment the significance of tumour biomarker status on treatment outcomes became apparent. The design of the trial was subsequently amended to prospectively compare treatment outcomes by KRAS (exon 2) tumour status.

PRIME and PEAK were both multi-centred trials. PRIME was conducted at sites primarily in Western Europe, Canada, and Australia (vs. the rest of the world). The locations of study sites in the PEAK trial were not reported in the trial report, but were indicated on the clinical trials.gov website and included sites primarily in the United States, Canada, Belgium, Germany, Italy and Spain.

Patients with previous adjuvant chemotherapy for CRC were permitted entry into either trial as long as the last exposure to treatment was completed within specified time frames prior to randomization. The PRIME trial excluded patients with any previous treatment with oxaliplatin chemotherapy or anti-EGFR therapy. Of note, PRIME included patients with an ECOG performance status of 0 to 2, while PEAK included patients with performance status of 0 to 1.

Central stratified randomization procedures were used in both trials. In the PRIME trial, randomization was stratified by geographic location and ECOG performance status. In PEAK, patients were stratified by previous oxaliplatin chemotherapy using permuted block sizes of 4. Both trials were described as being open label.

The primary outcome in both trials was progression-free survival (PFS) defined as the time from randomization to progression (using RECIST Criteria) or death. Secondary outcomes in each trial included overall survival (OS), objective tumour response rate (ORR), metastasis resection rate, and adverse events. In PRIME, PFS and ORR were evaluated by blinded independent central radiology review. These outcomes were investigator assessed and unblinded in the PEAK trial.

In PRIME, independent data analysts performed interim analyses of safety and PFS data and sponsor data analysts performed the primary and final efficacy analyses. The submitter reported to pCODR that sponsor analysts were blinded to all statistical analyses;⁴⁰ however, the primary analysis of OS was unblinded after the analysis of PFS. Data analysts were not blinded in the PEAK trial.

The estimated sample size requirements for each trial are summarized in Table 4. After the protocol amendment in the PRIME trial, the required sample size was increased from 900 to 1150 patients in order to ensure sufficient power (90%; 380 events) to test for a treatment effect in the WT KRAS stratum of patients. In the PEAK trial, 280 patients were required to provide adequate power (168 events) in the WT KRAS stratum.

The PRIME trial was not terminated early. Ascertainment of KRAS tumour status was obtained for 93% of the 1183 patients randomized to the trial. The primary analysis of PFS, dated August 29, 2009, included all randomized patients with evaluable KRAS tumour status (n=1096). The hypothesis of the trial was that the addition of panitumumab to

chemotherapy would increase PFS compared to chemotherapy alone. Progression-free survival curves for each treatment arm were analyzed using the methods of Kaplan Meier and compared using a log-rank test stratified by randomization factors. A Cox proportional hazards model was used to generate the estimate of treatment effect (i.e., hazard ratio and 95% confidence interval). Subgroup analyses were prospectively planned to estimate treatment effects in specific subsets of patients. At the time of the primary analysis of PFS an interim analysis of OS was performed (based on >50% of deaths in the WT KRAS stratum). Objective tumour response rate was estimated using a stratified odds ratio and corresponding 95% confidence interval. Metastasis resection rate was defined as the proportion of patients with a complete or partial resection. The safety analysis included all patients who received at least one dose of study treatment. The final analyses of PFS and OS, dated August 2, 2010, were pre-specified and performed 30 months after the last patient was enrolled in the trial.²¹ An updated exploratory analysis of OS, dated January 24, 2013, was also performed (based on >80% of deaths) and provides the most mature OS data from the PRIME trial to date.³

The PEAK trial was not terminated early and the primary analysis of PFS, dated May 30, 2012, included all randomized patients as assigned. No formal hypothesis was tested. Progression-free survival was analyzed using the same methods as the PRIME trial: Kaplan Meier survival curves were compared using a log-rank test stratified by previous oxaliplatin chemotherapy and Cox proportional hazard modelling was used to estimate treatment hazard ratios and 95% confidence intervals. Overall survival data were deemed immature at the time of the primary analysis (based on 31% of deaths in the WT KRAS stratum). An assessment of OS was performed one year from the date the last patient was enrolled (based on 46% of deaths in the WT KRAS stratum). Objective tumour response rate was defined as the proportion of patients with a complete or partial response. Resection rates were reported as the proportion of patients undergoing resection and the proportion of patients achieving a complete resection. The safety analysis included all randomized patients who received at least one dose of study treatment.

Additional data analyses were performed in both trials to examine treatment effects in patients with and without mutations beyond KRAS exon 2. Referred to as an extended RAS analysis, the following tumour biomarkers were examined in both trials: KRAS exons 3 and 4, and NRAS exons 2, 3, and 4.

In the PRIME trial, the extended RAS analysis was prospectively planned but performed retrospectively using the original PRIME trial data.^{3,42} The statistical plan was pre-specified prior to extended RAS tumour status becoming available, and data analyses were blinded and performed by the sponsor. All analyses were exploratory (i.e., no formal hypothesis testing). A significance level of $p=0.05$ was used to compare treatment effects on PFS and OS in patients with WT RAS. A sequential testing scheme was used to control the overall type I error rate when evaluating efficacy. Cox proportional hazard modelling was used to estimate treatment hazard ratios and 95% confidence intervals, which were compared using a log-rank test stratified by randomization factors.

In the PEAK trial, the extended RAS analysis was evaluated prospectively as a secondary objective of the trial.¹

In both trials extended RAS analyses included all randomized patients with available tumour biomarker information; and assessment of tumour biomarker status was blinded and performed in a central laboratory prior to any efficacy analyses.

Table 4: Select quality characteristics of included randomized controlled trials of panitumumab in combination with oxaliplatin-based chemotherapy as first-line treatment in patients with wild-type (WT) RAS metastatic colorectal cancer.

Trial	Treatment vs. Comparator	Primary Outcome	Required Sample Size	Sample Size	Randomization Method	Allocation Concealment	Blinding	ITT analysis	Final Analysis	Early Termination	Ethics Approval
<i>PRIME</i> ^{2,38}	Panitumumab + FOLFOX4 vs. FOLFOX4	PFS	1150 patients required for 380 events to provide 90% power to detect a HR=0.714 in the WT KRAS stratum, using two-sided overall alpha=0.05 (stratified log-rank test) ^A	546 vs. 550	Central IVRS, stratified ^B	No	Outcome assessment; data analysis ^C	Yes ^D	No	No	Yes
<i>PEAK</i> ^{1,39}	Panitumumab + mFOLFOX6 vs. bevacizumab + mFOLFOX6	PFS	280 patients required for 168 events to detect a HR=0.90 (80% CI) in the WT KRAS stratum, using two-sided overall alpha=0.2 ^E	142 vs. 143	Central IVRS, stratified using permuted blocks (block size of 4) ^F	No	None	Yes	Yes	No	Yes

Abbreviations: CI - confidence interval; HR - hazard ratio; ITT - intent-to-treat analysis; IVRS - Interactive Voice Response System; PFS - progression-free survival; WT KRAS - wild-type KRAS.

Notes:

^A Assumes prevalence of WT KRAS is 55%, and median PFS for WT KRAS subgroup is 14 months with panitumumab-FOLFOX4 and 10 months with FOLFOX4 alone.³⁸

^B Stratified by KRAS tumour status, geographic location, and ECOG performance status.

^C Independent data analysts performed interim analyses of safety and progression-free survival data. Sponsor data analysts performed the primary and final efficacy analyses. The submitter reported to pCODR that sponsor analysts were blinded to all statistical analyses; however, the primary analysis of overall survival was unblinded after the analysis of progression-free survival.⁴⁰

^D ITT analysis includes randomized patients with available KRAS tumour status.

^E No formal hypothesis testing was planned. Assumes prevalence of WT KRAS is 55% and a median PFS for WT KRAS subgroup of 9.6 months with panitumumab-mFOLFOX6 and 10.1 months with bevacizumab-mFOLFOX6.

^F Stratified by previous oxaliplatin chemotherapy (yes/no).

b) Populations

In the PRIME study, a total of 1183 patients were randomized, KRAS status was determined retrospectively, with 1096 patients with known KRAS tumour status (Table 5).² Of those patients, 656 (panitumumab+FOLFOX4, n=325; FOLFOX4, n=331) were evaluated as having WT KRAS tumours and 440 (panitumumab+FOLFOX4, n=221; FOLFOX4, n=219) were evaluated as having mutated (MT) KRAS tumours. In the PEAK trial, 285 patients with WT KRAS were randomly assigned (panitumumab+mFOLFOX6, n=142; bevacizumab+mFOLFOX6, n=143).¹

Both trials reported balance for most patient and disease characteristics at baseline between trial arms (Table 5). Balance of most factors was also reported between treatment arms in each patient stratum of the PRIME trial with the exception of the following: more patients in the MT KRAS stratum of the panitumumab-FOLFOX4 arm (compared to the FOLFOX4 control arm) presented with three or more disease sites and elevated levels of carcinoembryonic antigen and lactate dehydrogenase at baseline. The percentage of patients receiving prior adjuvant chemotherapy ranged from 16-17% among trial arms in the PRIME trial. These data were not reported for PEAK. Data provided by the sponsor indicated that in both trials the majority of patients (PRIME: 75-80%; PEAK: 59-70%) did not present with denovo M1 disease.⁴⁰

The percentage of randomized WT KRAS patients who were evaluable for extended RAS testing was 90% (n=1060) in the PRIME trial³ and 78% (n=221) in the PEAK trial.¹ In PRIME, 17% (n=108) of WT KRAS patients were identified as having other RAS mutations beyond KRAS exon 2. In PEAK, 23% of WT KRAS patients (n=51) had other RAS mutations.

The number of randomized patients with WT RAS tumour status was 512 (panitumumab+FOLFOX4, n=259; FOLFOX4, n=253) in the PRIME trial³ and 170 (panitumumab+mFOLFOX, n=88; bevacizumab+mFOLFOX, n=82) in the PEAK trial.¹ Baseline patient and disease characteristics in the WT RAS subgroups were reported to be similar between trial arms in both trials.

c) Interventions

Details of the dosing and administration of the drug regimens used in the treatment and control arms of each trial can be found in Table 3. In both trials, treatment regimens were given until disease progression, unacceptable toxicity or withdrawal of consent.^{38,39}

Panitumumab was administered at the same dose and schedule in the PRIME and PEAK trials. In PRIME, patients received panitumumab for a median of 11 cycles and median dose intensity was 81%.² In PEAK, panitumumab was administered for a median of 12 cycles with a median dose intensity of 83%. Bevacizumab was administered in the control arm of this trial for 12 cycles with a median dose intensity of 91%.¹

FOLFOX4 was the chemotherapy regimen used in treatment and control arms of the PRIME trial.² The median number of cycles received by patients was similar between arms; oxaliplatin was administered for a median of 11 cycles in each arm, and fluorouracil, bolus and continuous infusion, were each administered for a median of 12 cycles in each arm. The median dose intensity of oxaliplatin was 77% and 79% in treatment and control arms, respectively. The median dose intensity of bolus FU was 77% and 81%; and the median dose intensity of continuous infusion FU was 78% and 81%, respectively.

mFOLFOX6 was the chemotherapy regimen used in treatment and control arms of the PEAK trial.¹ The median number of cycles administered in each arm was not specifically reported but was indicated to be similar. However, it was noted that the mean doses of chemotherapy appeared lower in the panitumumab arm compared to the control arm: oxaliplatin (79% vs. 83%), bolus FU (79% vs. 84%), and infusional FU (79% vs. 84%).

No dose reductions or interruptions were reported in the trial publications for any of the drug regimens used in each trial.

Table 5: Baseline patient characteristics in the included trials of panitumumab in combination with oxaliplatin-based chemotherapy as first-line treatment in patients with wild-type (WT) RAS metastatic colorectal cancer.

Patient Characteristics	PRIME Trial ²				PEAK Trial ¹			
	Panitumumab + FOLFOX4		FOLFOX4		Panitumumab + mFOLFOX6		Bevacizumab + mFOLFOX6	
N randomized	593		590					
N randomized with KRAS (exon 2) status	546		550		142		143	
KRAS Subgroup	WT KRAS ^A	MT KRAS ^B	WT KRAS	MT KRAS	WT KRAS	WT KRAS		
N	325 (59)	221 (40)	331 (60)	219 (40)	142	143		
Age (years)								
Median	62	63	61	61	63	61		
Range	27-85	33-83	24-82	27-82	23-82	28-82		
Male, n (%)	217 (67)	145 (66)	204 (62)	128 (58)	86 (61)	96 (67)		
White race, n (%)	296 (91)	196 (89)	307 (93)	196 (89)	131 (92)	127 (89)		
ECOG PS								
0 - 1	305 (94)	213 (96)	312 (94)	209 (95)	142 (100)	142(99)		
≥ 2	20 (6)	8 (4)	18 (5)	10 (5)	-	-		
Primary tumour, n (%)								
Colon	214 (66)	151 (68)	216 (65)	160 (73)	96 (68)	92 (64)		
Rectum	111 (34)	70 (32)	115 (35)	59 (27)	46 (32)	51 (36)		
No. of metastatic sites, n (%)								
1	68 (21)	39 (18)	67 (20)	43 (20)	53 (37)	56 (39)		
2	112 (34)	70 (32)	116 (35)	80 (37)	50 (35)	49 (34)		
>3	143 (44)	110 (50)	147 (44)	95 (43)	39 (27)	37 (26)		
Liver only metastases, n (%)	60 (18)	32 (14)	56 (17)	36 (16)	37 (26)	39 (27)		
Denovo M1 disease, n (%) [*]	66 (20)		82 (25)		58 (41)	42 (30)		
Prior adjuvant chemotherapy, n (%)	53 (16)	35 (16)	55 (17)	26 (12)	NR	NR		
<i>Prospective-Retrospective Extended RAS Analysis^{3,42}</i>					<i>Prospective Extended RAS Analysis¹</i>			
N randomized and evaluable for RAS status ^C	1060 ^D				227 (221) ^E			
Other RAS mutation status in patients with WT KRAS in exon 2:					Other RAS mutation status in patients with WT KRAS in exon 2:			
N	320		321		115		112	
	WT	MT	WT	MT	WT	MT	WT	MT
KRAS								
Exon 3	308 (96)	10 (3)	306 (95)	14 (4)	112 (97)	2 (2)	104 (93)	7 (6)
Exon 4	288 (90)	21 (7)	296 (92)	15 (5)	103 (90)	10 (9)	103 (92)	7 (6)
NRAS								
Exon 2	308 (96)	8 (2)	307 (96)	14 (4)	108 (94)	6 (5)	104 (93)	6 (5)
Exon 3	305 (95)	12 (4)	305 (95)	14 (4)	108 (94)	6 (5)	104 (93)	7 (6)
Exon 4	316 (99)	0	313 (98)	0	113 (98)	0	110 (98)	0

Other RAS mutation totals, n (%)		51(16)		57 (18)		24 (21)		27(24)
Extended RAS Subgroups	WT RAS ^F	MT RAS ^G	WT RAS	MT RAS	WT RAS	MT RAS	WT RAS	MT RAS
N	259	272	253	276	88	24	82	27
Abbreviations: WT - wild-type; WT KRAS - wild-type KRAS; WT RAS - wild-type RAS; MT - mutant; MT KRAS - mutant KRAS.								
Notes:								
A WT KRAS subgroup includes patients with non-mutated KRAS in exon 2.								
B MT KRAS subgroup includes patients with mutated KRAS in exon 2.								
C Number of randomized patients evaluable for RAS (KRAS and NRAS) mutation status.								
D 641 of the 656 WT KRAS patients were tested for additional mutations (15 patients could not be tested because of consent issues or unavailability of samples (21 of these patients failed RAS testing). ⁴⁰ The 440 patients with KRAS mutations in exon 2 were not retested for other RAS mutation status.								
E Tumour samples from 250 patients were available for extended RAS testing; 23 samples were excluded from analysis because they were deemed an inadequate sample or mutant by a Sanger/Wave test. The remaining 227 patients with WT KRAS in exon 2 were tested for other RAS mutations; 221 yielded a RAS result (6 patients failed testing).								
F WT RAS subgroup includes patients with non-mutated KRAS and NRAS in exons 2, 3, and 4.								
G MT RAS subgroup includes patients with non-mutated KRAS in exon 2, and any mutation in KRAS exons 3 or 4 NRAS exons 2, 3 or 4.								
*Data obtained through a request to the submitter. ⁴⁰								

d) Patient Disposition

The reporting of patient disposition was incomplete in PRIME trial reports. The submitter provided pCODR with information on patient disposition for the original randomized patient population (n=1183). In the PEAK trial, patient disposition was reported for all randomized (WT KRAS) patients (n=285). A request for information on the disposition of the WT RAS patient population in each trial was made to the submitter,⁴⁰ and is summarized as follows:

In the PRIME trial, all randomized patients who were evaluable and yielded a valid result for RAS testing (n=512) were included in efficacy analyses by assigned treatment. Of the 259 patients randomized to the panitumumab+FOLFOX4 treatment arm, 211 discontinued panitumumab and 49 were still in treatment at the primary analysis data cut-off date. The main reasons for ending treatment with panitumumab were disease progression (n=102), adverse events (n=39), and subject request (n=33). No patients in the panitumumab arm were lost to follow-up. Of the 253 patients randomized to the FOLFOX4 control arm, 228 patients discontinued FOLFOX4 and 22 patients were still in treatment at the data cut-off date. The main reasons for ending treatment were disease progression (n=125), subject request (n=33), and adverse events (n=26). One patient in the control arm was lost to follow-up. Following disease progression, patients could receive subsequent anti-cancer therapy. Table 6 summarizes subsequent anti-cancer therapy following study treatment for all randomized WT KRAS patients in the PRIME trial. Compared to the panitumumab arm, a greater percentage of patients (10%) in the control arm received subsequent anti-EGFR therapy and chemotherapy. Median time-to subsequent therapy was also shorter in the control arm. The final number of deaths reported in the trial was 239 (79%) in the panitumumab arm and 218 (86%) in the FOLFOX4 control arm.

In the PEAK trial, all randomized patients who were evaluable and yielded a valid result for RAS testing (n=170) were included in efficacy analyses by assigned treatment. Of the 88 patients randomized to panitumumab+mFOLFOX6, 68 patients discontinued panitumumab and 18 patients were still in treatment at the primary analysis data cut-off date. The main reasons for discontinuing panitumumab treatment were disease progression (n=28) and adverse events (n=17). Of the 82 patients randomized to the

bevacizumab-mFOLFOX6 control arm, 73 patients discontinued treatment and 7 patients were still in treatment at the data cut-off date. The main reasons for discontinuing bevacizumab treatment were disease progression (n=27) and adverse events (n=20). No patients were lost to follow-up in the PEAK trial. Following disease progression, patients could receive subsequent anti-cancer therapy. Anti-cancer therapy following discontinuation of study treatment in all randomized patients (WT KRAS and WT RAS) in the PEAK trial is summarized in Table 6. A higher percentage of patients in the bevacizumab control arm subsequently received anti-EGFR therapy (15%), while more patients in the panitumumab arm received anti-VEGF therapy post-progression (7%). The number of patients receiving subsequent chemotherapy and median time-to start of subsequent therapy appeared similar between trial arms. The final number of deaths reported in the trial was 57 (65%) in the panitumumab arm and 66 (80%) in the bevacizumab control arm.

e) Limitations/Sources of Bias

Refer to Table 4 for a summary of quality-related features of both trials.

Overall, the PRIME trial² was well conducted; the methods used for randomization (central IVRS and stratified) were appropriate, and the trial sample size was amended to ensure sufficient power to test for superiority over the control arm. All efficacy analyses were performed according to assigned treatment. However, the following biases and limitations should be noted:

- The trial was open label, and as such, is at risk for a number of different biases that can affect the internal validity of a trial (e.g., patient selection for eligibility, performance bias due to knowledge of assigned treatment). Investigators, study personnel, treating physicians and patients in the PRIME trial were not blinded to treatment assignment, which can introduce the potential to bias results in favour of whichever treatment arm the assessor (investigator or patient) believes is likely to provide benefit. Assessments of PFS and tumour response were conducted via a blinded independent central review, which reduces the potential for biased results of these outcomes.
- Due to the protocol amendment, tumour status data were not available for all patients originally randomized to the trial. 87 patients (7%) were excluded from analyses, which could have introduced selection bias (i.e., patients analyzed may not be representative of the original population of randomized patients). Sensitivity analyses were performed with the subgroup of patients with unevaluable tumour status and the results were reported to be consistent with the primary analysis.
- The extended RAS analysis³ is also prone to bias. Extended RAS tumour status was unevaluable in 123 patients (10%) and these patients were excluded from analyses (and therefore prone to the same biases mentioned above). The extended RAS analysis was conducted retrospectively and thus suffers from the biases and limitations inherent to this type of design. However, appropriate measures were carried out to minimize the potential for bias and these include: specifying the statistical plan a priori (in advance of obtaining extended RAS tumour status and performing efficacy analyses), blinding the assessors of tumour status to treatment assignment and patient outcome, confirming patient tumour status using two different validated tests, performing statistical tests for interaction to compare treatment effects, and adjusting for multiple comparisons to the control type I error rate. However, it is extremely important to emphasize that the extended analyses were exploratory in nature and included no formal hypothesis testing, and

therefore the results should be interpreted with caution and considered as hypothesis generating requiring further validation in prospective trials.

- The sponsor Amgen funded the trial and the extended RAS analysis, and sponsor employees/stock-holders were involved in all aspects of conducting the trial including performing data analyses. The submitter reported to pCODR that sponsor analysts were blinded to all statistical analyses;⁴⁰ however, the primary analysis of OS was unblinded after the analysis of PFS. The extent to which the use of independent investigators and data analysts may have influenced the results and the reporting of the trial is uncertain.
- The comparator arm in the PRIME trial was FOLFOX chemotherapy. This regimen is not the current standard of care in Canada, and therefore the generalizability of the trial results should be interpreted within this context.
- The percentage of patients receiving prior adjuvant chemotherapy in the PRIME trial was low (ranging from 16-17%), suggestive that a majority of patients presented with mCRC; however, data provided by the sponsor indicated that only 20-25% of patients in the trial presented with denovo M1 disease at baseline.⁴⁰ As higher rates of prior adjuvant chemotherapy would be expected in this patient population with mCRC, the findings of this trial may not be generalizable to patients with previous exposure to adjuvant chemotherapy for their CRC disease.
- Approximately 91% of patients in the PRIME trial were Caucasian. If this population has a disease course or treatment response that is different from other populations, it may be inappropriate to generalize the findings of this trial to non-Caucasian populations.
- While not a limitation, the trial included patients with an ECOG performance status of 2. This aspect of the trial should be considered when comparing results to the PEAK trial, which included patients with better ECOG performance status of 0 or 1.
- The use of subsequent (post-progression) anti-cancer therapy differed between trial arms. The degree to which these treatments influenced OS outcomes at the different assessment periods (i.e., primary, final, and updated analyses) is unknown.

In the PEAK trial,¹ the methods used for randomization (central IVRS and stratified) were appropriate, and the trial sample size was calculated to ensure sufficient power to estimate the treatment effect of panitumumab on PFS relative to bevacizumab in combination with chemotherapy. All efficacy analyses were performed according to assigned treatment. The following limitations should be noted:

- The trial was open label, and as such, is at high-risk for a number of different biases that can affect the internal validity of a trial (e.g., patient selection for eligibility, performance bias due to knowledge of assigned treatment). Investigators, study personnel, treating physicians and patients in the PEAK trial were not blinded to treatment assignment introducing the potential to bias results in favour of whichever treatment arm the assessor (investigator or patient) believes is likely to provide benefit. This is of great concern considering no central independent review of the primary outcome (or tumour response) was performed, and the investigators assessing these outcomes and data analysts were not blinded to treatment assignment.
- The extended RAS analysis,¹ although conducted prospectively in this trial, included a small number of WT RAS patients (n=170). The efficacy results associated with this small subgroup should be interpreted in consideration of its small sample size. The same applies to the results of subgroup analyses in this

trial. As well, the methods associated with the analysis of subgroups were not reported.

- The sponsor Amgen funded the trial. Sponsor employees/stock-holders were involved in all aspects of conducting the trial, including data analyses, which were not blinded. The extent to which the use of blinded independent investigators and data analysts may have influenced the results and reporting of the trial is uncertain.
- Approximately 91% of patients in the PEAK trial were Caucasian. If this population has a disease course or treatment response that is different from other populations, it may be inappropriate to generalize the findings of this trial to non-Caucasian populations.
- The use of subsequent (post-progression) anti-cancer therapy differed between trial arms. The degree to which these treatments influenced OS outcomes at the different assessment periods (i.e., primary, final, and updated analyses) is unknown.

Table 6: Subsequent anti-cancer therapy after discontinuation of study treatment (post-progression) in included trials of panitumumab in combination with oxaliplatin-based chemotherapy as first-line treatment in patients with wild-type (WT) RAS metastatic colorectal cancer.

Trial	PRIME ²		PEAK ¹		WT RAS ^A	
	WT KRAS Panitumumab + FOLFOX4 (n=325)	FOLFOX4 (n=331)	WT KRAS ^A Panitumumab + mFOLFOX6 (n=142)	Bevacizumab + mFOLFOX6 (n=143)	Panitumumab + mFOLFOX6 (n=88)	Bevacizumab + mFOLFOX6 (n=82)
Number of patients discontinuing study treatment (at data cut-off date)*	268	293	114	122	68	73
Subsequent Therapy:						
Anti-EGFR mAB, n (%)	26 (8)	59 (18)	30 (21)	54 (38)	19 (22)	30 (37)
Median time-to-therapy (mos) ^B	18	11	14.1	12	14.7	15.4
Anti-VEGF, n (%)	NR	NR	57 (40)	35 (24)	35 (40)	27(33)
Median time-to-therapy (mos) ^B	NR	NR	12.5	10.6	13	10.6
Any Chemotherapy, n (%) (oxaliplatin, irinotecan, and/or fluoropyrimidine)	173 (53)	205 (62)	90 (63)	85 (59)	53 (60)	50 (61)
Median time-to-therapy (mos) ^{B,5}	10.5	9.7	9.3	9.1	10.5	9.7
Oxaliplatin-based chemotherapy	NR	NR	22 (15)	28 (20)	11 (13)	19 (23)
Median time-to-therapy (mos) ^B	NR	NR	8.6	6.9	8.6	9
Irinotecan-based chemotherapy	NR	NR	73 (51)	72 (50)	44 (50)	42 (51)
Median time-to-therapy (mos) ^B	NR	NR	10.7	11.1	12.6	11.6
Abbreviations: EGFR - epidermal growth factor receptor; mAB - monoclonal antibody; mos - months; n - number; NR - not reported; VEGF -vascular endothelial growth factor.						
Notes:						
^A Data cut-off date of January 3, 2013.						
^B Subsequent therapy is the time interval from random assignment date to start of subsequent therapy.						
*Data obtained through a request to the submitter. ⁴⁰						
⁵ Data obtained from Vectibix product monograph. ⁴¹						

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

A summary of efficacy results can be found in Table 7.

Progression-free Survival

Both trials reported statistically significant improvements in PFS in favour of the panitumumab-containing arm among patients with extended WT RAS tumour status.

PRIME

In PRIME, analyses of PFS were conducted for the primary analysis² and the final analysis²¹ (performed at 30 months after the first patient was enrolled).

The primary analysis of the PRIME trial (WT KRAS stratum) showed a statistically significant improvement in PFS of 1.6 months with panitumumab-FOLFOX4 compared to control after a median follow-up of 13.6 months (median: 9.6 vs. 8 months; HR=0.80, 95% CI, 0.66-0.97; p=0.02). An improvement in PFS was observed in all planned subgroups of patients (i.e., either statistically significant or a trend toward the panitumumab arm with treatment HRs <1 but confidence limits including 1), with the exception of patients greater than 65 years old (n=261; HR=1.02, 95% CI, 0.75-1.38), women (n=235; HR=1.00, 95% CI, 0.73-1.39) and patients with an ECOG performance status of 2 (n=38; HR=1.99, 95% CI, 0.96-4.15).²

In the extended RAS analysis (WT RAS), PFS was prolonged by 2.2 months with panitumumab-FOLFOX4; median PFS times were 10.1 months with panitumumab and 7.9 months with FOLFOX4 (HR=0.72, 95% CI, 0.58-0.90; p=0.004). An improvement was observed (statistically significant or a trend toward the panitumumab arm) in all patient subgroups with the exception of patients with an ECOG performance status of 2 (n=32; HR=1.69, 95% CI, 0.75-3.82).³

In the subgroup of patients with MT KRAS (n=440) or MT RAS (n=548),^{2,3} PFS was significantly shorter in the panitumumab-FOLFOX4 arm compared to the FOLFOX4 control arm (MT KRAS: median of 7.3 months vs. 8.8 months; HR=1.29, 95% CI, 1.04-1.62, p=0.02; MT RAS: median of 7.3 months vs. 8.7 months; HR=1.31, 95% CI, 1.07-1.60, p=0.008).

The final analysis of PFS (reported for the WT KRAS and MT KRAS strata) confirmed the primary analysis results.²¹

PEAK

In the PEAK trial (WT KRAS), no difference in PFS was observed between trial arms (HR=0.87, 95% CI, 0.65 to 1.17, p=0.353). Similar treatment effects (i.e., all treatment HR confidence limits included the value of 1) were observed in all planned subgroups of patients with the exception of patients with greater than 3 metastatic sites (n=76; HR=0.52, 95% CI, 0.29-0.95).¹

In the extended RAS analysis (WT RAS), panitumumab-mFOLFOX6 significantly improved PFS by 3.5 months; median PFS times were 13 months with panitumumab and 9.5 with bevacizumab-mFOLFOX6 (HR=0.65, 95% CI, 0.44-0.96, p=0.029). An improvement was observed (either statistically significant or a trend towards the panitumumab arm with treatment HRs <1 but confidence limits including 1) in all patient subgroups with the exception of patients in the "other race" category (n=18; HR=1.24, 95% CI, 0.39-3.92).¹

In the subgroup of patients with MT RAS (n=51), no statistically significant difference in PFS was observed between panitumumab-mFOLFOX6 and bevacizumab-mFOLFOX6 treatment arms (median of 7.8 months vs. 8.9 months, respectively; HR=1.39, 95% CI, 0.73-2.64, p=0.318).¹

Overall Survival

Both trials reported improvements in OS in favour of the panitumumab-containing arm among patients with extended WT RAS tumour status; however, the improvement observed in the PEAK trial did not reach statistical significance.

PRIME

In PRIME, analyses of OS were conducted for the primary analysis (interim analysis, 54% of patients had died),² the final analysis (performed at 30 months after the first patient was enrolled; 68% of patients had died),²¹ and for an updated analysis (82% of patients had died).³

The primary (interim) analysis of OS (WT KRAS stratum) showed no difference between the panitumumab-FOLFOX4 and FOLFOX4 trial arms.² In the extended RAS analysis (WT RAS), however, a survival benefit of 5.8 months was observed with panitumumab-FOLFOX4 (median: 26 vs. 20.2 months; HR=0.78, 95% CI, 0.62-0.99, p=0.04) (Table 7).³

For patients in the MT KRAS subgroup (n=440), no statistically significant difference in OS was observed between trial arms at the interim analysis.² In the MT RAS subgroup (extended RAS analysis, n=548), patients in the panitumumab arm had statistically significant shorter survival compared to those in the FOLFOX4 control arm (median: 15.6 vs. 19.2 months, respectively; HR=1.21, 95% CI, 1.01-1.45, P=0.04).³

The final analysis of OS confirmed the primary interim results for both WT KRAS and MT KRAS patients.²¹

The updated analysis of OS demonstrated statistically significant differences between the panitumumab-FOLFOX4 and FOLFOX4 treatment arms in each WT patient stratum.

In the WT KRAS stratum, median survival was improved by approximately 4.4 months in the panitumumab-FOLFOX4 arm compared to the FOLFOX4 control arm (median: 23.8 vs. 19.4 months; HR=0.83, 95% CI, 0.70-0.98, p=0.03).³

In the extended group of WT RAS patients, median survival was improved by 5.6 months with panitumumab-FOLFOX4 over control (median: 25.8 vs. 20.2 months; HR=0.77, 95% CI 0.64-0.94, p=0.009). The survival benefit was observed consistently (either statistically significant or a trend towards the panitumumab arm with treatment HRs <1 but confidence limits including 1) in all patient subgroups with the exception of patients with an ECOG performance status of 2 (n=32; HR=1.34, 95% CI, 0.63-2.89).³

For patients with MT KRAS and MT RAS, the updated analysis of OS showed shortened OS with panitumumab-FOLFOX4 compared with FOLFOX4 alone, which was statistically significant in the MT RAS subgroup of patients (median of 15.5 months vs. 18.7 months; HR=1.21, 95% CI, 1.01-1.45, p=0.04) but not in the MT KRAS subgroup.³

PEAK

In the PEAK trial, OS was deemed immature at the time of the primary analysis (31% of deaths had occurred). Overall survival was analyzed one year from the date the last patient was enrolled (when 46% of deaths had occurred). After a median follow-up of approximately 16 months in each arm (WT KRAS), a statistically significant difference in median survival of approximately 10 months in favour of the panitumumab-mFOLFOX6 arm was observed (median: 34.2 vs. 24.3 months; HR=0.62, 95% CI, 0.44-0.89, p=0.009). In the extended WT RAS group, the difference in OS between the panitumumab (30 deaths, median survival = 41.3 months) and bevacizumab (40 deaths, median survival=28.9 months) trial arms did not reach statistical significance (HR=0.63, 95% CI, 0.39-1.02, p=0.058).¹

In the group of patients with MT RAS (n=51), OS was significantly longer for patients treated with panitumumab-mFOLFOX6 compared to bevacizumab-mFOLFOX6; median survival times were 27 months and 16.6 months, respectively (HR=0.41, 95% CI, 0.19-0.87, p=0.02).¹

Table 7: Summary of efficacy outcomes in included trials of panitumumab in combination with oxaliplatin-based chemotherapy as first-line treatment in patients with wild-type (WT) RAS metastatic colorectal cancer.

Treatment Arms (n)	Median Follow-up (mos)	PFS		OS		OS Updated Analysis		Objective Response Rate		Complete Metastases Resection Rate (%)
		Median (mos)	HR (95% CI)	Median (mos)	HR (95% CI)	Median (mos)	HR (95% CI)	%	OR (95% CI)	
PRIME Trial Primary Analysis in WT KRAS Subgroup^{2,3}										
Panitumumab + FOLFOX4 (n=325)	13.2	9.6	0.80 ^A (0.66-0.97) p=0.02	23.9	0.83 ^B (0.67-1.02) p=0.072	23.8	0.83 ^C (0.70-0.98) p=0.03	55	OR=1.35 (NR) p=0.068	8.3
FOLFOX4 (n=331)	12.5	8.0		19.7		19.4		48		7
PRIME Trial Extended RAS Analysis in WT RAS Subgroup³										
Panitumumab + FOLFOX4 (n=259)	14.5	10.1	0.72 ^D (0.58-0.90) p=0.004	26.0	0.78 ^E (0.62-0.99) p=0.04	25.8	0.77 ^F (0.64-0.94) p=0.009	59	1.63 (1.13-2.38) p=0.009	NR
FOLFOX4 (n=253)	13.5	7.9		20.2		20.2		46		
PEAK Primary Analysis in WT KRAS Subgroup¹										
Panitumumab + mFOLFOX6 (n=142)	NR	10.9	0.87 ^G (0.65-1.17) p=0.353	NR ^H		34.2	0.62 ^I (0.44-0.89) p=0.009	57.8	NR	10
Bevacizumab + mFOLFOX6 (n=143)	NR	10.1				24.3		53.5		8
PEAK Extended Analysis in WT RAS Subgroup¹										
Panitumumab + mFOLFOX6 (n=88)	16.3 ^S	13	0.65 ^J (0.44-0.96) p=0.029	NR ^H		41.3	0.63 ^K (0.39-1.02) p=0.058	63.6	NR	NR
Bevacizumab + mFOLFOX6 (n=82)	16.2 ^S	9.5				28.9		60.5		
Abbreviations:										
CI - confidence interval; HR - hazard ratio; mos - months; n = number; NR - not reported; OR - odds ratio; ORR - objective response rate; OS - overall survival; p = p-value; PFS - progression-free survival; WT KRAS - wild-type KRAS; WT RAS = wild-RAS.										

Notes:

- ^A Data cut-off date was August 29, 2009. Based on 199 (61%) events in the panitumumab-FOLFOX4 arm and 215 (65%) events in the FOLFOX4 arm.
- ^B Data cut-off date was August 29, 2009. Based on 165 (51%) deaths in the panitumumab-FOLFOX4 arm and 190 (57%) deaths in the FOLFOX4 arm.
- ^C Data cut-off date was January 24, 2013. Based on 82% of patient deaths.
- ^D Data cut-off date was August 29, 2009. Based on 156 (60%) events in the panitumumab-FOLFOX4 arm and 170 (67%) events in the FOLFOX4 arm.
- ^E Data cut-off date was August 29, 2009. Based on 128 (49%) deaths in the panitumumab-FOLFOX4 arm and 148 (58%) deaths in the FOLFOX4 arm.
- ^F Data cut-off date was January 24, 2013. Based on 204 deaths (79%) in the panitumumab-FOLFOX4 arm and 218 (86%) deaths in the FOLFOX4 arm.
- ^G Data cut-off date was May 30, 2012. Based on 90 events (63%) deaths in the panitumumab-mFOLFOX6 arm and 94 events (66%) in the bevacizumab-mFOLFOX6 arm.
- ^H OS outcomes were immature at the time of primary analysis with 87 (31%) deaths reported (data cut-off March 30, 2013).
- ^I Data cut-off date was January 3, 2013. Based on 52 (37%) deaths in the panitumumab-mFOLFOX6 arm and 78 (55%) deaths in the bevacizumab-mFOLFOX6 arm.
- ^J Data cut-off date was May 30, 2012. Based on 50 (57%) events in panitumumab-mFOLFOX6 arm and 60 (73%) events in the bevacizumab-mFOLFOX6 arm.
- ^K Data cut-off date was January 3, 2013. Based on 30 (34%) deaths in the panitumumab-mFOLFOX6 arm and 40 (49%) deaths in the bevacizumab-mFOLFOX6 arm.
- * Data obtained from Vectibix product monograph.⁴¹
- § Data obtained from pCODR submission.⁴⁰

Health-related Quality of Life

Health-related quality of life (HRQoL) was assessed in the PRIME trial⁴ as a tertiary outcome of interest and was not assessed in the PEAK trial.

The EuroQoL 5-Dimensions (EQ-5D), a standardized and validated tool, was used to measure patient-reported HRQoL between trial arms. The EQ-5D Health State Index (HSI) assesses health across five dimensions that include mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has three possible outcomes: no problems, moderate problems, and extreme problems. Possible scores on the EQ-5D HSI range from -0.594 to 1. A change in score ≥ 0.08 has been established as the minimal clinically important difference (MCID) for the EQ-5D HSI. The EQ-5D Visual Analogue Scale (VAS) provides an assessment of current overall health using a vertical scale ranging from 0 to 100, with 0 representing worst imaginable health and 100 representing best imaginable health. The MCID for the EQ-5D VAS has been established as a change in score of ≥ 7 . In PRIME, these tools were completed by patients to measure and estimate the average difference in the effect of panitumumab-FOLFOX4 compared to FOLFOX4 alone in the WT KRAS patient group.

Patients were assessed at baseline, every month until disease progression, and once at the 4-week safety visit. Patients discontinuing treatment due to adverse events or unacceptable toxicity were encouraged to complete monthly assessments until disease progression and at the safety visit. Changes in HSI and VAS scores from baseline for treatment effects were analyzed using a linear mixed model regression for repeated measures. Backward selection was used to eliminate variables and interaction terms if not significant ($p \leq 0.05$). The least squares mean (LSM) (and corresponding 95% confidence interval) was used to estimate treatment-specific average change from baseline for each outcome. Sensitivity analyses were performed (using pattern mixture models) to estimate the impact of missing data (patterns of early vs. late drop-outs) on the results.

Of the 656 WT KRAS patients randomized in the PRIME trial, 88% of these patients (n=576) were included in the primary analysis of HRQoL. In the panitumumab-FOLFOX4 arm, 279 and 278 patients were included in the EQ-5D HSI and VAS analyses, respectively. In the FOLFOX4 arm, 289 and 285 patients were included in these analyses.

Baseline EQ-5D HSI scores were 0.778 and 0.756 for the panitumumab and control arms; the EQ-5D VAS scores at baseline were 74.1 and 70.1, respectively. Baseline patient and disease characteristics were generally balanced between treatment groups and comparable to the original randomized WT KRAS patient population. In the HSI analysis, the difference between treatment arms (in the estimated LSM in change from baseline) was -0.005 (95% CI, -0.378-2.834); a difference considered neither statistically or clinically significant. The LSM (change from baseline) was 0.022 (95% CI, 0.003-0.041) in the panitumumab arm and 0.027 (95% CI, 0.008-0.046) in the FOLFOX4 control arm. Similar non-significant results were obtained in the analysis of the VAS overall health rating; the difference in the LSM between treatment arms was -0.653 (95% CI, -2.925-1.618). The LSM was 1.228 (95% CI, 0.378-2.834) with panitumumab and 1.881 (95% CI, 0.275-3.487) with FOLFOX4 alone. These results suggest no apparent differences in HRQoL, as measured by the EQ-5D, between patients treated with panitumumab-FOLFOX4 and FOLFOX4 alone. Sensitivity analyses showed no meaningful differences between treatment groups by pattern of patient dropout. Updated HRQoL has been reported for this patient group (WT KRAS)²¹ as well as for patients in the extended WT RAS subgroup¹³ and shows results similar to the primary analysis.

Objective Tumour Response

Both trials reported on ORR; however, statistical comparisons of these data were generally not reported.

In the PRIME trial, the ORR for the WT KRAS patient stratum was 55% in the panitumumab-FOLFOX4 arm and 48% in the FOLFOX4 control arm ($p=0.068$).² In the final results paper, updated response rates of 57% and 48% were reported.²¹ One patient (1%) in the panitumumab arm and 2 (<1%) patients in the control arm had complete responses.

In the extended RAS analysis (WT RAS), objective tumour response rates were 59% and 46% for the panitumumab and control arms, respectively.³

In the PEAK trial, the ORRs for WT KRAS patients were 57.8% in the panitumumab-mFOLFOX6 arm and 53.5% in the bevacizumab-mFOLFOX6 arm. Three patients (2%) in the panitumumab arm and two patients (<1%) in the bevacizumab arm had complete responses.¹

In the extended RAS analysis (WT RAS), ORRs of 63.6% and 60.5% were reported for the panitumumab and bevacizumab trial arms; complete responses were observed in 2 patients (2%) and 1 patient (1%), respectively.¹

Metastases Resection Rate

Metastasis resection rates, of any site, were reported in both trials. Neither trial reported statistical comparisons for the differences in rates between trial arms.

In PRIME, metastectomy was attempted in 10.5% of WT KRAS patients in the panitumumab-FOLFOX4 arm and in 9.4% of patients in the FOLFOX4 control arm; 8.3% and 7% of patients achieved complete resections, respectively.² In the final results paper, resections rates for patients with liver-only metastases were reported; complete resection were achieved in 17 patients (28%) treated with panitumumab-FOLFOX4 ($n=61$) and 10 patients (18%) treated with FOLFOX4 alone.²¹

Resection rates (of any metastases) were not reported for the extended WT RAS analysis.

In the PEAK trial, metastectomy was attempted in 18 patients (13%) in the panitumumab-mFOLFOX6 arm and 16 patients (11%) in the bevacizumab-mFOLFOX6 arm; complete resections were achieved in 14 (10%) and 12 (8%) patients, respectively.¹

Harms Outcomes

Both trials provided data on the harm outcomes of interest. Harms data are summarized in Table 8. No statistical comparisons of the rates of adverse events between trial arms were reported in either trial.

In both trials, all patients who received at least one dose of study treatment were included in analyses of safety^{38,39} (PRIME: $n=649$ in the WT KRAS stratum; $n=506$ in the WT RAS stratum; PEAK: $n=278$ in patients with WT KRAS; $n=174$ in WT RAS subgroup).^{1,2}

Since the event rates among WT patient groups were similar between trial arms, the data presented below is for WT KRAS patients unless otherwise specified. For specific event rates in the WT RAS patient subgroup refer to Table 8.

Grade 3 or 4 Adverse Events

In the PRIME trial, the incidence of any grade 3 or 4 adverse events was 85% in the panitumumab-FOLFOX4 arm and 69% in the FOLFOX4 control arm. The incidence of the following adverse events was higher in patients treated with panitumumab compared with control: skin toxicity/skin disorders (36% vs. 2%), diarrhea (18% vs. 9%), hypokalemia (10%

vs. 5%), fatigue (9% vs. 3%), mucositis/mucosal inflammation (6% vs. <1%) and hypomagnesemia (6% vs. <1%).²

In the PEAK trial, the incidence of any grade 3 or 4 adverse events was 90% in the panitumumab-mFOLFOX6 arm and 83% in the bevacizumab-mFOLFOX6 arm. The incidence of the following adverse events was higher in patients treated with panitumumab compared with control: skin toxicity/skin disorders (32% vs. 1%), hypokalemia (11% vs. 5%), mucositis/mucosal inflammation (7% vs. 1%), stomatitis (5% vs. <1%), and hypomagnesemia (7% vs. 0). Treatment with bevacizumab was associated with a higher incidence of hypertension (7%) compared to treatment with panitumumab (0%).¹

Bevacizumab is associated with other adverse events including pulmonary embolism, deep vein thrombosis (DVT) and proteinuria. These adverse events were not reported in the PEAK trial publication. A request to the submitter obtained the following incidence rates for these events in the bevacizumab arm: pulmonary embolism (9%), DVT (10%), and proteinuria (8%).⁴⁰ The incidence of these events appeared lower in the WT RAS subgroup (refer to Table 8).

Grade 3 or 4 infusion-related reactions were reported in both trials. In PRIME, 2 patients (<1%) treated with panitumumab had grade 3 infusion reactions.² In PEAK, 3 patients (2%) treated with panitumumab and 7 patients (5%) treated with bevacizumab had grade 3 infusion reactions. No grade 4 reactions were reported in either trial.¹

Rash

The incidence of rash was not specifically reported in either trial. Rash, along with other skin disorders, comprised a composite measure of skin toxicity.^{38,39}

The incidence of rash was reported in the panitumumab product monograph provided to pCODR as part of this submission. In the WT RAS subgroup of patients, the incidence of rash was reported to be 17% with panitumumab-FOLFOX4 (n=256) compared to <1% in patients treated with FOLFOX4 alone (n=250).⁴¹

Serious and Fatal Adverse Events

The incidence of serious adverse events and fatal adverse events can be found in Table 8.

In the PRIME trial,² grade 3 or 4 serious adverse events occurred in 40% of patients in the panitumumab-FOLFOX4 arm and 36% of patients in the FOLFOX4 arm.

The incidence of fatal adverse events was similar between trial arms; 5% of patients treated in the panitumumab arm and 6% of patients in the FOLFOX4 control arm experienced fatal events.

Grade 3 or 4 treatment-related adverse events occurred in 82% of patients in the panitumumab-FOLFOX4 arm and 63% of patients in the FOLFOX4 control arm. Four patients (1%) in the panitumumab arm had a fatal treatment-related adverse event. Two of these were attributed to panitumumab; information on the type of events that occurred was not provided in the trial report. The two other fatal treatment-related events included pneumonitis and pneumonia. Four patients (1%) in the FOLFOX4 control arm were reported to have fatal adverse events related to treatment.

In the PEAK trial,¹ the incidence of fatal adverse events was similar between trial arms; 5% of patients in the panitumumab-mFOLFOX6 arm and 6% of patients in the bevacizumab-mFOLFOX6 arm experienced fatal events.

Three patients (2%) in the panitumumab arm had a treatment-related fatal adverse event. These events included a rectal perforation related to panitumumab, one case of sepsis

related to chemotherapy, and one case of respiratory failure related to panitumumab and chemotherapy.

Two patients (1%) in the bevacizumab arm experienced a treatment-related fatal adverse event. These events included an intestinal perforation and a small intestinal perforation, both attributed to bevacizumab and chemotherapy.

Adverse Events Leading to Withdrawals (Treatment Discontinuation)

In the PRIME trial, the proportion of patients in each trial arm with adverse events leading to treatment discontinuation was not reported. In the final results publication, the number of patients in the panitumumab arm (n=322) discontinuing treatment due to an adverse event was reported to be 19% (n=61);²¹ these data were not reported for the control arm.

In the PEAK trial, 34 patients (24%) in the panitumumab arm and 37 patients (27%) in the bevacizumab arm discontinued therapy due to an adverse event.¹

Table 8: Number of patients with Grade 3 - 5 adverse events in included trials of panitumumab in combination with oxaliplatin-based chemotherapy as first-line treatment in patients with wild-type (WT) RAS metastatic colorectal cancer.

Trial	PRIME ²		PRIME Extended RAS Analysis ^{41^}		PEAK ¹		PEAK Extended RAS Analysis ¹	
Patient Subgroup	WT KRAS		WT RAS		WT KRAS		WT RAS	
Treatment Arm	Panitumumab + FOLFOX4	FOLFOX4	Panitumumab + FOLFOX4	FOLFOX4	Panitumumab + mFOLFOX6	Bevacizumab + mFOLFOX6	Panitumumab + mFOLFOX6	Bevacizumab + mFOLFOX6
N	322	327	256	250	139	139	86	80
Grade 3 or Higher Adverse Events								
Any adverse event, n (%)	270 (84)	227 (69)	217 (85)	175 (70)	126 (90)	115 (83)	81 (94)	65 (81)
Skin toxicity/skin disorders	116 (36)	7 (2)	NR	NR	44 (32)	2 (1)	29 (34)	1(1)
Rash	NR	NR	44 (17)	1 (<1)	NR	NR	NR	NR
Neutropenia	136 (42)	134 (41)	NR	NR	NR	NR	NR	NR
Diarrhea	59 (18)	29 (9)	48 (19)	22 (9)	NR	NR	NR	NR
Neurologic toxicities	52 (16)	51 (16)	NR	NR	NR	NR	NR	NR
Paraesthesia	NR	NR	23 (9)	15 (6)	NR	NR	NR	NR
Hypokalemia	32 (10)	15 (5)	NR	NR	15 (11)	7 (5)	7 (8)	6 (8)
Fatigue	30 (9)	10 (3)	26 (10)	7 (3)	15 (11)	12 (9)	10 (12)	8 (10)
Mucositis/mucosal inflammation	28 (9)	2 (<1)	13 (5)	1 (<1)	10 (7)	2 (1)	6(7)	2 (1)
Stomatitis	NR	NR	14 (5)	1(<1)	7 (5)	1 (<1)	NR	NR
Hypomagnesemia	20 (6)	1 (<1)	19 (7)	0	10 (7)	0	7(8)	0
Paronychia	11 (3)	0	10 (4)	0	2 (1)	0	2 (2)	0
Pulmonary embolism	9 (3)	5 (2)	NR	NR	NR	13 (9) ⁵	NR	2 (3) ⁵
DVT	NR	NR	NR	NR	NR	14 (10) ⁵	NR	3 (4) ⁵
Febrile neutropenia	8 (2)	7 (2)	NR	NR	NR	NR	NR	NR
Nausea	NR	NR	NR	NR	2 (1)	1 (<1)	1(1)	0
Decreased appetite	NR	NR	NR	NR	7 (5)	2 (1)	5 (6)	0
Dehydration	NR	NR	6 (2)	4 (2)	6 (4)	1 (<1)	5 (6)	1 (1)
Weight loss	NR	NR	3 (1)	0	2(1)	1 (<1)	2 (2)	1 (1)
Dysesthesia	NR	NR	NR	NR	0	2 (1)	0	2 (3)
Hypertension	NR	NR	NR	NR	0	10 (7)	0	6 (8)
Hypocalcemia	NR	NR	3 (1)	1 (<1)	2 (1)	0	1 (1)	0
Proteinuria	NR	NR	NR	NR	NR	11 (8) ⁵	NR	5 (6) ⁵
Pyrexia	NR	NR	2 (<1)	7 (3)	1 (<1)	1 (<1)	0	0
Thrombocytopenia	NR	NR	NR	NR	2 (1)	0	1 (1)	0
Infusion-related reaction	2 (<1)	NA	NR	NR	3 (2)	7 (5)	NR	NR
Serious adverse event, n (%)	129 (40) ⁴	118 (36) ⁴	110 (43)	92 (37)	61 (44)	53 (38)	37 (43)	31 (39)
Any fatal adverse event, n (%)	16 (5)	20 (6)	14 (5) ^{B,5}	16 (6) ^{C,5}	7 (5)	9 (6)	0	0

Fatal treatment-related adverse events, n (%)	4 (1) ^A	4 (1) ^A	NR	NR	3 (2) ^D	2 (1) ^E	3 (3) ^{F,5}	4 (5) ^{G,5}
Adverse event leading to discontinuation of treatment, n (%)	61 (19) [¶]	NR	65 (25)	40 (16)	34 (24)	37 (27)	21 (24)	23 (29)

Abbreviations: DVT - deep vein thrombosis; N- number; NA - not applicable; NR -not reported; WT KRAS - wild-type KRAS; WT RAS - wild-type RAS.

Notes:

[^] Includes information from the primary (data cut off of August 2009) and final analysis (data cut off of August 2010)

^{*} Number of patients estimated based on reported percentage of patients.

^A Includes “two cases that were panitumumab related, pneumonitis (no infectious etiology identified) and pneumonia”.

^B Includes the following fatal adverse events: metastatic colorectal cancer (n=5), cardio respiratory arrest (n=2), hepatic failure (n=2), intestinal obstruction (n=1), cardiogenic shock (n=1), hypokalemia (n=1), interstitial lung disease (n=1), and pneumonitis (n=1).

^C Includes the following fatal adverse events: metastatic colorectal cancer (n=4), pneumonia (n=2), intestinal obstruction (n=1), sudden death (n=1), bronchopneumonia (n=1), dyspnea (n=1), general physical health deterioration (n=1), multi-organ failure (n=1), performance status decreases (n=1), pulmonary fibrosis (n=1), renal failure (n=1), and tumour local invasion (n=1).

^D Includes one case of rectal perforation related to panitumumab, one case of sepsis related to chemotherapy, and one case of respiratory failure related to panitumumab and chemotherapy.

^E Includes one case of intestinal perforation and one case of small intestinal perforation both related to bevacizumab and chemotherapy.

^F Two of these events occurred in the same patient. Includes two cases of respiratory failure, one related to panitumumab and one to chemotherapy, and one case of sepsis related to chemotherapy.

^G Four events occurred in the same two patients. Includes two cases of intestinal perforation and two cases of small intestinal perforation, to both bevacizumab and chemotherapy.

[¶] Information reported in Douillard et al.²¹

⁵ Data obtained through a request made to the submitter.⁴⁰

6.4 Ongoing Trials

Two ongoing randomized trials investigating the efficacy of panitumumab combined with oxaliplatin-based chemotherapy in patients with previously untreated mCRC with WT RAS tumour status met the eligibility criteria of this review. The primary objective of the phase II VOLFI trial (NCT01328171)⁴³ is to investigate the efficacy of panitumumab in optimizing response rates and rates of metastases resection in patients with initially unresectable WT RAS mCRC. The primary objective of the PARADIGM trial (NCT02394795)⁴⁴ is to confirm the efficacy of panitumumab combined with mFOLFOX6 chemotherapy compared to bevacizumab-mFOLFOX6 chemotherapy as first-line treatment in patients with WT RAS mCRC. A summary of the two trials is provided in Table 9 below.

Table 9: Ongoing trials of panitumumab in combination with oxaliplatin-based chemotherapy as first-line treatment in patients with wild-type (WT) RAS metastatic colorectal cancer.			
Trial Design	Key Inclusion Criteria	Interventions and Comparators	Outcomes
<p>Trial NCT01328171 (VOLFI) Multicentre (all sites in Germany), open-label, randomized phase II trial.</p> <p>Start date: April 2011 Expected completion date: June 2017</p> <p>Status: Last verified July 2015, currently recruiting patients</p> <p>Estimated enrolment: 93</p> <p>Sponsor: AIO-Studien-gGmbH</p> <p>Collaborators: Amgen Pharmaceuticals ClinAssess GmbH</p>	<ul style="list-style-type: none"> • Patients with histologically confirmed and definitively inoperable or unresectable mCRC (cohort 1) <u>or</u> patients with chance of secondary resection with curative intent defined and reviewed by an expert panel (cohort 2) • WT RAS tumour status (KRAS exons 2, 3, 4 and NRAS exons 2, 3, and 4) • At least one measureable lesion according to RECIST • No previous chemotherapy for mCRC • ECOG performance of 0 or 1 	<p><u>Panitumumab</u> iv 6 mg/kg q 2 wks on day 1 of each 2 week cycle + <u>FOLFOXIRI</u> Irinotecan 150 mg/m² + oxaliplatin 85 mg/m² + leucovorin 200 mg/m² + 5-FU 3000 mg/m² continuous iv infusion</p> <p>vs.</p> <p><u>FOLFOXIRI</u> Irinotecan 165 mg/m² + oxaliplatin 85 mg/m² + leucovorin 200 mg/m² + 5-FU 3200 mg/m² continuous infusion all on day 1 of each 2 week cycle</p> <p>Treatment given until disease progression or resectability or to a maximum of 12 cycles</p>	<p><u>Primary:</u></p> <ul style="list-style-type: none"> • Overall response rate <p><u>Secondary:</u></p> <ul style="list-style-type: none"> • Secondary resection rate (cohort 2) • Pathological response (complete and partial) • Disease control rate • Progression-free survival • Duration of response • Time-to-response • Overall survival • Time-to-recurrence • Toxicity • QoL

<p>Trial NCT02394795 (PARADIGM) Multicentre (all sites in Japan), open label, randomized phase III trial.</p> <p>Start date: May 2015 Expected completion date: February 2020</p> <p>Status: Last verified June 2015, currently recruiting patients</p> <p>Estimated enrolment: 800</p> <p>Sponsor: Takeda Pharmaceuticals</p>	<ul style="list-style-type: none"> • Patients with unresectable adenocarcinoma originating in the large intestine • Measurable lesions • Previous chemotherapy for mCRC • WT KRAS tumour status (KRAS exons 2, 3, 4, and NRAS exons 2, 3 and 4. 	<p><u>Panitumumab</u> iv 6 mg/kg q 2 wks (day 1 of each 2 week cycle) + <u>mFOLFOX6</u> oxaliplatin 85 mg/m² on day 1 + leucovorin 200 mg/m² on day 1 + 5-FU iv bolus 400 mg/m² on day 1, and 2400 mg/m² continuous iv infusion days 1-3</p> <p>vs.</p> <p><u>Bevacizumab</u> iv 5 mg/kg q 2wks (on day 1 of each 2 week cycle) + <u>mFOLFOX6</u> oxaliplatin 85 mg/m² on day 1 + leucovorin 200 mg/m² on day 1 + 5-FU iv bolus 400 mg/m² on day 1, and 2400 mg/m² continuous iv infusion</p>	<p><u>Primary:</u></p> <ul style="list-style-type: none"> • Overall survival <p><u>Secondary:</u></p> <ul style="list-style-type: none"> • Progression-free survival • Best response (complete and partial) • Duration of response • Resection rate • Adverse events
<p>Abbreviations: ECOG - Eastern Cooperative Oncology Group; FU - 5-fluorouracil; FOLFOXIRI - oxaliplatin, leucovorin, 5-fluorouracil, and irinotecan; KRAS - Kirsten Rat Sarcoma oncogene; mCRC - metastatic colorectal cancer; mFOLFOX6 - modified FOLFOX6; NRAS - Neuroblastoma RAS oncogene; q - every; QoL - quality of life; RECIST - Response Evaluation Criteria in Solid Tumors; RCT - randomized controlled trial; WT - wild-type.</p>			

in patients with initially unresectable WT RAS mCRC. The primary objective of the PARADIGM trial (NCT02394795)⁴⁴ is to confirm the efficacy of panitumumab combined with mFOLFOX6 chemotherapy compared to bevacizumab-mFOLFOX6 chemotherapy as first-line treatment in patients with WT RAS mCRC. A summary of the two trials is provided in Table 9 below.

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Gastrointestinal Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on panitumumab (Vectibix) for metastatic colorectal cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic 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 Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

The Gastrointestinal Clinical Guidance Panel is comprised of three oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s):

EBM Reviews - Cochrane Central Register of Controlled Trials May 2015,
Embase 1974 to 2015 June 10,
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations,
Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches
1	(Vectibix* or Vectibex* or panitumumab* or ABX-EGF or Abenix*).ti,ot,kw,ab,sh,rn,hw,nm.
2	(339177-26-3 or 6A901E312A).rn,nm.
3	or/1-2
4	3 use cctr
5	3 use pmez
6	*panitumumab/
7	(Vectibix* or Vectibex* or panitumumab* or ABX-EGF or Abenix*).ti,ab.
8	or/6-7
9	8 use oomezd
10	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
11	Randomized Controlled Trial/
12	Randomized Controlled Trials as Topic/
13	"Randomized Controlled Trial (topic)"/
14	Controlled Clinical Trial/
15	Controlled Clinical Trials as Topic/
16	"Controlled Clinical Trial (topic)"/
17	Randomization/
18	Random Allocation/
19	Double-Blind Method/
20	Double Blind Procedure/
21	Double-Blind Studies/
22	Single-Blind Method/
23	Single Blind Procedure/
24	Single-Blind Studies/
25	Placebos/
26	Placebo/
27	Control Groups/
28	Control Group/
29	(random* or sham or placebo*).ti,ab,hw.
30	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.

31	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
32	(control* adj3 (study or studies or trial*)).ti,ab.
33	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
34	allocated.ti,ab,hw.
35	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
36	or/10-35
37	5 or 9
38	36 and 37
39	4 or 38
40	remove duplicates from 39

2. Literature search via PubMed

Search	Add to builder	Query
#7	Add	Search (#4 AND #5 AND #6)
#6	Add	Search publisher[sb] OR 2015/06[mhda]
#5	Add	Search (randomized controlled trial[pt] OR randomized controlled trials as topic[mh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR random*[tw] OR "Placebos"[Mesh] OR placebo[tiab] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw] OR dumm*[tw])))
#4	Add	Search ((panitumumab[nm] OR Vectibix*[tiab] OR Vectibex*[tiab] OR panitumumab*[tiab] OR ABX-EGF[tiab] OR Abenix*[tiab]))

3. Cochrane Central Register of Controlled Trials (Central) Searched via Ovid

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
<http://www.clinicaltrials.gov/>

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
<http://www.canadiancancertrials.ca/>

Search terms: Vectibix/panitumumab

Select international agencies including:

Food and Drug Administration (FDA):
<http://www.fda.gov/>

European Medicines Agency (EMA):
<http://www.ema.europa.eu/>

Search terms: Vectibix/panitumumab

Conference abstracts:

American Society of Clinical Oncology (ASCO)
<http://www.asco.org/>

European Society for Medical Oncology (ESMO)
<http://www.esmo.org/>

Search terms: Vectibix/panitumumab / last 5 years

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