CADTH | pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Panitumumab (Vectibix) for Left-Sided Metastatic Colorectal Cancer

March 29, 2018

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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.

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1 GUIDANCE IN BRIEF

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 left sided metastatic colorectal cancer. 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 CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding panitumumab (Vectibix) for left sided metastatic colorectal cancer conducted by the Gastrointestinal Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; 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. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on panitumumab (Vectibix) for left sided metastatic colorectal cancer, a summary of submitted Provincial Advisory Group Input on panitumumab (Vectibix) for left sided metastatic colorectal cancer, and a summary of submitted Registered Clinician Input on panitumumab (Vectibix) for left sided metastatic colorectal cancer, and are provided in Sections 2, 3, 4, and 5 respectively.

1.1 Introduction

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

Health Canada issued a Notice of Compliance (NOC) for panitumumab (Vectibix) for the treatment of previously untreated patients with *RAS* wild-type (i.e. non-mutated) mCRC in combination with FOLFOX and as monotherapy for the treatment of patients with non-mutated (wild-type) *RAS* mCRC after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. The funding request under review by pCODR represents a subgroup of patients described in the Health Canada indication.

Panitumumab is a recombinant, fully human IgG2 monoclonal antibody that binds specifically to the human EGFR. Panitumumab is supplied as a solution (20mg/mL) containing 100 or 400 mg of panitumumab in 5 and 20 mL 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 retrospective analyses that used data from two randomized, open-label, trials (i.e. PRIME and PEAK). Briefly, PRIME was an open-label, multi-centre, randomized phase III trial that assessed the efficacy and safety of panitumumab plus FOLFOX4 as compared to FOLFOX4 in 1,183 patients with mCRC.[1-3] PEAK was an open-label, randomized phase II trial that assessed the effect of panitumumab plus FOLFOX6 relative to FOLFOX6 with bevacizumab in 285 patients with previously untreated wild-type K*RAS* exon 2 (codons 12 and 13) mCRC.[4,5]

The first retrospective analysis included in the pCODR systematic review was by Boeckx et al (2017).[6,7] The objective of this analysis was to investigate the association between tumour sidedness and panitumumab efficacy in *RAS* wild-type mCRC patients enrolled in the PRIME and PEAK trials. Patients were considered as *RAS* wild-type carrier status if they did not have a mutation in the K*RAS*/N*RAS* exon 2/3/4 region.[7] Additionally, patients were only included if they had data on a primary tumour location

and those who had missing or unknown information were excluded.[7] Tumours were classified as right-sided if they were located in the cecum to transverse colon while they were classified as left-sided if they were located in the splenic flexure to the rectum.[7] Tumour assessors were blinded to *RAS* and *BRAF* mutation status, treatment allocation and clinical outcomes. The analysis presented in Boeckx et al (2017) represents a descriptive post-hoc analysis of the PRIME and PEAK trials and no formal hypothesis testing was performed. In addition, no power calculation was provided. The authors assessed the effect of tumour sidedness in panitumumab-treated mCRC patients that expressed wild-type *RAS* using the following outcomes: overall response rate (ORR), duration of response (DOR), progression-free survival (PFS) and overall survival (OS).

The other retrospective analysis identified in the pCODR systematic review was conducted by Geissler et al (2017) and it was presented in abstract format.[8,47] This analysis explored the effect of tumour sidedness on panitumumab efficacy using data from the PRIME and PEAK trials. Patients were considered as *RAS* wild-type carrier status if they did not have a mutation in the K*RAS*/N*RAS* exon 2/3/4 region.[8] The authors measured the following outcomes: resection rates, early tumour shrinkage and depth of response rate. In addition, the authors did not report how tumour sidedness was classified and if any formal hypothesis testing or power calculations were performed.

Efficacy

The Boeckx et al (2017) retrospective analysis included *RAS* wild-type patients from the PRIME (N = 505) and PEAK (N =170) trials.[7] Tumour sidedness was determined in 83% of patients from the PRIME (N = 416/505) and the PEAK (N = 143/170) trials (Table 1). The majority of patients in the PRIME and PEAK populations had a left-sided tumour (79% and 75%, respectively)[7]. In the Geissler et al (2017) analysis, tumour sidedness could be determined in 559 patients from both the PRIME and PEAK trials.[8] Here, 78% of patients had a left-sided tumour (N=435). Additionally, patients with left-sided tumours were more likely to have a BRAF wild-type carrier status (94%) as compared to those with a right-sided tumour (68%).[8]

Overall Survival

Using data from PRIME, Boeckx et al (2017) reported that panitumumab plus FOLFOX was associated with a longer OS as compared to FOLFOX in patients with left-sided tumours (adjusted Hazard ratio [HR]: 0.73, 95% Confidence Interval [CI]: 0.57 to 0.93; p–value= 0.0112) (Table 1).[7] There was no difference in OS for patients with a right-sided tumour who were treated with panitumumab plus FOLFOX or FOLFOX (adjusted HR: 0.87, 95% CI: 0.55 to 1.37; p- value = 0.5398).[7] In order to determine whether the treatment effect of panitumumab differs among patients with left or right-sided tumours, a statistical test for interaction is required.[9] A statistical test for interaction tests the hypothesis that the treatment effect of panitumumab does not differ for patients with left or right-sided tumours. If the p-value of the interaction test is greater than 0.05, we fail to reject the null hypothesis that the effect of panitumumab is not different among patients with left or right-sided tumours. However, if the p-value for interaction is less than 0.05, we can assume that there is a statistical difference in the treatment effect of panitumumab among patients with left or right-sided tumours. For instance, a significant p-value for interaction could imply that patients with left-sided tumours who were treated with panitumumab had improved OS as compared to their right-sided counterparts. It should be noted that many retrospective analyses do not have sufficient power to detect treatment effect, and thus, a non-significant test does not necessarily indicate that there is no difference between subgroup groups.[9] The Submitter reported that the p-value of the interaction test that assessed whether the treatment effect of panitumumab differed among patients with left or right-sided tumours for OS was 0.2734.[10] Since the p-value for interaction was greater than 0.05, it is not possible to reject the hypothesis that the effect of panitumumab on OS was the same for patients with left-sided or right-sided tumours.

Boeckx et al (2017) showed that there was no significant treatment difference between panitumumab plus FOLFOX and FOLFOX with bevacizumab on OS in left-sided tumour *RAS* wild-type carriers from the PEAK trial (adjusted HR: 0.77, 95% CI: 0.46 to 1.28; p – value= 0.3125) (Table 1).[7] Similar results were

observed for *RAS* wild-type carriers with right-sided tumours (adjusted HR: 0.67, 95% CI: 0.30 to 1.50; p – value = 0.3239).[7] The p-value for interaction was 0.9503 (Table 1).[10]

Progression-Free Survival

Using data from PRIME, the authors reported that panitumumab plus FOLFOX was associated with a longer PFS as compared to FOLFOX (adjusted HR: 0.72, 95% CI: 0.57 to 0.90; p–value= 0.0048). There was no difference on PFS between *RAS* wild-type patients with a right-sided tumour who were treated with panitumumab plus FOLFOX or FOLFOX (adjusted HR: 0.80, 95% CI: 0.51 to 1.26; p- value = 0.3286) (Table 1). The p-value for interaction was 0.9637, which indicates that the effect of panitumumab on PFS did not differ for patients with left-sided or right-sided tumors (Table 1). [10] There was no treatment difference for PFS in patient with left-sided (HR: 0.68, 95% CI: 0.45 to 1.04; p-value: 0.0732) or right-sided tumours (HR: 1.04, 95% CI: 0.50 to 2.18; p-value: 0.9085) from the PEAK trial (p-value for interaction: 0.2398)] (Table 1).[7,10]

Overall Response Rate

Boeckx et al (2017) demonstrated that *RAS* wild-type carriers from PRIME who had left-sided tumours and received panitumumab plus FOLFOX had a higher ORR (67.9%) as compared to those treated with FOLFOX (52.6%) (Table 1).[7] There was no difference for patients with right-sided tumours (odds ratio (OR): 1.36 [95% CI: 0.51 to 3.62]).[7] There was no treatment difference for ORR in patient with left-sided (OR: 1.33 [95% CI: 0.57 to 3.11]) or right-sided tumours (OR: 1.75 [95% CI: 0.36 to 8.39]) from the PEAK trial (OR: 1.75 [95% CI: 0.36 to 8.39)] (Table 1).[7]

Quality of Life

Health-related quality of life (HRQoL) was assessed using the EuroQoL 5-Dimensions (EQ-5D), such as the EQ-5D Health State Index (HSI) and the EQ-5D Visual Analog Scale (VAS). Patients were assessed at baseline, every month until disease progression, and once at the 4-week safety visit. The Submitter reported that there were no statistically significant differences in changes from baseline for the EQ-5D HSI and EQ-5D VAS between chemotherapy plus panitumumab and chemotherapy for patients with a left or right-sided tumour.[10] Furthermore, the minimally important difference (MID) was not met for the EQ-5D HSI and EQ-5D VAS scales in patients with a left or right-sided tumour.[10] These results should be interpreted with caution due to exploratory analyses and small sample sizes.

Harms

There were 416 patients included in the PRIME safety analysis. Eighty-four percent of patients with a left-sided tumour who were treated with chemotherapy plus panitumumab had a worst grade of 3 and 4 adverse event (AE) as compared to 70.4% of those who were treated with chemotherapy.[10] On the other hand, 89.8% of patients with a right-sided tumour who were treated with chemotherapy plus panitumumab had a worst grade of 3 and 4 AE as compared to 77.5% of patients who were treated with chemotherapy.[10] More patients with a right-sided tumour had any serious AE or an AE that led to a discontinuation as compared to those with a left-sided tumour.[10] Patients with left-sided or right-sided tumours who were treated with chemotherapy plus panitumumab were more likely to experience rash, diarrhoea or hypomagnesemia than their counterparts who were treated with chemotherapy.[10]

There were 143 patients included in the PEAK safety analysis. The majority of patients with a left-sided tumour who were treated with chemotherapy plus panitumumab (90.5%) or with chemotherapy plus bevacizumab (77.8%) had a worst grade of 3 and 4 AE.[10] In contrast, 86.4% of patients with a right-sided tumour who were treated with chemotherapy plus panitumumab had a worst grade of 3 and 4 AE as compared to 64.3% of patients who were treated with chemotherapy plus bevacizumab.[10] Regardless of therapy, more patients with a right-sided tumour had any serious AE or an AE that led to a discontinuation as compared to those with a left-sided tumour (Table 16.[10] Patients with a left-sided or right-sided tumour who were treated with chemotherapy plus panitumumab were more likely to

experience rash or hypomagnesemia than their counterparts who were treated with chemotherapy plus bevacizumab.[10] Almost two-thirds of all patients had diarrhoea.[10]

Limitations

Both the Boeckx et al (2017) and Geissler et al (2017) studies represent post-hoc, retrospective, descriptive analyses. Post-hoc analyses refer to those analyses that are not specified prior to examining RCT data. Post-hoc analyses should be interpreted with caution because they are more subject to multiplicity (i.e. multiple testing), which increases the risk of type 1 error. A type 1 error leads to false-positives, such that a study may report a treatment difference between two groups (p-value ≤ 0.05), when in fact, there is no true difference.[11]

Although subgroup analyses are widely reported in RCTs and meta-analyses, they should be interpreted with caution because they are often considered exploratory in nature and hypothesis generating.[9,12] Oxman and Guyat (1992) developed seven widely used criteria that can be applied to determine the credibility of a subgroup analysis.[13] To assess the credibility of the retrospective subgroup analysis in Boeckx et al (2017)[7], the Methods Lead applied the Oxman and Guyatt criteria.[13,14] It should be noted that the Geissler et al (2017) publication will not be included because it consists of only abstract-level data.[8]

- **Is the difference suggested by comparisons within rather than between studies?**
    - Boeckx et al (2017) used direct evidence from both the PRIME and PEAK trials.[7] Thus, we can conclude that the subgroup is more credible because the results of the subgroup are not influenced by factors other than the treatment itself.
- **Does the interaction test suggest a low probability that chance explains the apparent subgroup?**
    - Boeckx et al (2017) reported that panitumumab plus FOLFOX was associated with a longer OS as compared to FOLFOX in patients with left-sided tumours (p–value= 0.0112) while there was no difference in patients with right-sided tumours who were treated with panitumumab plus FOLFOX or FOLFOX (p- value = 0.5398).[7] Although the authors concluded that panitumumab may be more effective in patients with left-sided tumours as compared to right-sided tumours, the p-value for interaction was non-significant (P for interaction: 0.2734).[10] This means that there is no statistical difference in treatment effect for patients with left or right-sided tumours. However, the lack of statistical difference may be due to small sample size. Indeed, there were substantially more patients with a left-tumour (N = 328) than with a right-tumour (N = 88). Based on this evidence, it is more likely that the reported efficacy estimates in the Boeckx et al (2017)[7] were due to chance or small samples sizes.
- **Was the hypothesis tested a priori?**
    - The subgroup analysis in Boeckx et al (2017) was considered retrospective because it was not specified in the trial protocol.[3,5] Information on tumour sidedness was obtained from free-text surgery descriptions included in the patients' case report forms and from the original pathology reports.[7] In the analysis, primary tumours were classified as right-sided if they were located in the cecum to the transverse colon while left-sided tumours were classified as those tumours located in the splenic flexure to the rectum.[7] Since tumour sidedness was defined according to post-randomization characteristics, the patient population in the Boeckx et al (2017) analysis may be prognostically different from those originally enrolled in the PRIME and PEAK trials.
- **Was the subgroup effect one of a small number of hypothesised effects tested?**
    - Boeckx et al (2017) stated that "As these were retrospective analyses, no formal hypothesis testing was planned." This indicates that the results of the analysis were descriptive and the authors did not attempt to adjust for multiple testing. Thus, these results should be interpreted with caution because there is a high risk of a type 1 error.[15] For instance, the null hypothesis of the Boeckx et al (2017) analysis is that there is no treatment difference between patients with a left and right-sided tumour.[7]

- **Is the magnitude of the subgroup effect large?**
    - Using data from PRIME, Boeckx et al (2017) reported that panitumumab plus FOLFOX was associated with a longer OS as compared to FOLFOX in patients with left-sided tumours than with right-sided tumours (adjusted HR_{left}: 0.73, 95% CI: 0.57 to 0.93; p-value= 0.0112 and adjusted HR_{right}: 0.87, 95% CI: 0.55 to 1.37; p-value= 0.5398).[7] In contrast, there was no treatment difference between panitumumab plus FOLFOX versus bevacizumab plus FOLFOX on OS using data from PEAK (adjusted HR_{left}: 0.77, 95% CI: 0.46 to 1.28; p-value= 0.3125 and adjusted HR_{right}: 0.67, 95% CI: 0.30 to 1.50; p-value= 0.3239). The overall estimates for OS were not reported.[7] The pCODR Clinical Guidance Panel felt that the differences in OS for patients with left or right-sided tumours were clinically meaningful.
- **Is the observed differential effect consistent across studies?**
    - The effect of panitumumab on tumour sidedness was not consistent across the PRIME and PEAK trials.[7] Although the authors state that patients with a left-sided tumour who were treated with panitumumab have better OS as compared to those with a right-sided tumour using data from PRIME, these results did not replicate in the PEAK trial However, the lack of replication using data from PEAK may be due to a small sample size (N = 143).
- **Is there indirect evidence that supports the hypothesised interaction (biological rationale)?**
    - Studies have demonstrated that the sidedness of primary colon tumours is determined at embryological origin and that left or right-sided tumours have different gene expression as well as clinical and molecular characteristics.[16-23] Although there is biological evidence supporting the different pathological features of tumour sidedness, there is a lack of evidence demonstrating the biological mechanism that influences the treatment response to panitumumab in *RAS* wild-type patients with left or right-sided tumours.

Based on the criterion presented in Oxman and Guyatt (1992), there is little evidence to support the credibility of the subgroup analysis reported in Boeckx et al (2017)[7]. Hence, there is uncertainty in whether there is a differential treatment response to panitumumab in *RAS* wild-type patients with left or right-sided tumours. Following review of feedback by the Submitter on the pCODR pERC Initial Recommendation, the Methods Team re-iterated that there is uncertainty on whether there is a differential effect (magnitude and direction) of panitumumab by left or right-sided tumours; based on the current evidence, the Methods Team were unable to conclude that there is a statistically significant difference in benefits or harms with panitumumab for patients with left versus right-sided tumours.

Table 1: Highlights of Key Outcomes

Trial	Event	Tumour Sidedness	Panitumumab Events	Chemotherapy Events	HR (95% CI)	P	P for interaction
PRIME[A]	PFS	Left	146/169	145/159	0.72(0.57, 0.90)	0.0048	
		Right	34/39	46/49	0.80(0.51, 1.26)	0.3286	0.9637
		Total	180/208	191/208			
	OS	Left	126/169	136/159	0.73(0.57, 0.93)	0.0112	
		Right	34/39	44/49	0.87(0.55, 1.37)	0.5398	0.2734
		Total	160/208	180/208			
	ORR	Left	67.9%	52.6%	1.91(1.18,3.07)[A]		
		Right	42.1%	34.8%	1.36(0.51,3.63)[A]		
PEAK[B]	PFS	Left	43/53	47/54	0.68(0.45, 1.04)	0.0732	
		Right	21/22	13/14	1.04(0.50, 2.18)	0.9085	0.2398
		Total	64/75	60/68			
	OS	Left	29/53	33/54	0.77(0.46, 1.28)	0.3125	
		Right	19/22	12/14	0.67(0.30, 1.5)	0.3239	0.9503
		Total	48/75	45/68			
	ORR	Left	64.2%	57.4%	1.33(0.57,3.11) [A]		
		Right	63.6%	50.0%	1.75(0.36,8.39) [A]		

A: The PRIME trial was designed to compare the effect of panitumumab plus FOLFOX4 to FOLFOX4.
B: The PEAK trial was designed to compare the effect of panitumumab plus mFOLFOX6 to bevacizumab plus mFOLFOX6.
Data Sources: Boeckx et al (2017)[7] and Checkpoint Responses[10]

1.2.2 Additional Evidence

See Section 3, Section 4, and Section 5 for a complete summary of patient advocacy group input, Provincial Advisory Group (PAG) Input, and Registered Clinician Input, respectively.

Patient Advocacy Group Input

From a patient's perspective, there are a number of symptoms associated with mCRC that impact quality of life, which include bloody stools, abdominal discomfort, fatigue, constipation and diarrhea, weight loss and bowel obstruction. Respondents identified depression, anxiety, and fear as psychological limitations resulting from mCRC. Caregiver respondents indicated significant impact to their lives in terms of financial, physical, and psychological challenges when caring for their loved ones. With current available therapies, patients noted that some of their needs are not being met and personalized treatment options are needed. Most patients noted fatigue and nausea as commonly experienced side effects from current treatment options with mouth sores as the most difficult to tolerate. Patients desire treatment options that will effectively control their disease with respect to overall survival, progression free survival and quality of life. Patients desire treatment options specific to their cancer's genetic make-up. Of the patients who had experience with panitumumab in combination with chemotherapy for left-sided mCRC, patients noted that the therapy helped shrink patients' disease. The most common reported side effects for panitumumab in combination with chemotherapy were rashes, neuropathy, nausea, fatigue, hair loss, mouth sores, and shortness of breath. Patients rated their quality of life on the treatment on a scale of 1-10, with three patients identifying quality of life as 8/10 and three identifying it as 7/10. One patient noted that on days 5-7 of treatment, quality of life was a 4/10. Patients also noted that panitumumab plus chemotherapy resolved pain/pressure symptoms from metastases.

Provincial Advisory Group Input

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

Clinical factors:

- Use of panitumumab with FOLFIRI, an alternate combination chemotherapy regimen frequently used for first line metastatic colorectal cancer
- Sequencing of therapies following first line panitumumab + FOLFOX (or other combination chemotherapy) – e.g. bevacizumab second line and the alternate anti-EGFR therapy, cetuximab, third line

Economic factors:

- The number of patients requiring extended RAS testing may be larger as it will be needed for patients with left-sided tumors prior to decision on first line treatment, rather than reserved for those patients who may be candidates for third line treatment.

Registered Clinician Input

Although there are treatments available for mCRC, the clinicians providing input noted that panitumumab plus chemotherapy is superior in survival benefits for the subgroup of patients with *RAS* wild-type left-sided mCRC. They noted that RAS testing is required to determine eligibility for treatment with panitumumab.

Summary of Supplemental Questions

Several reviews have assessed the prognostic effect of tumour sidedness in patients with mCRC. These studies showed that patients with right-sided tumours have worse outcomes as compared to those with left-sided tumours, regardless of treatment.[24] However, the predictive effect of tumour sidedness among *RAS* wild-type mCRC patients treated with an anti-EGFR (i.e. cetuximab and panitumumab) or anti-VEGF (i.e. bevacizumab) is uncertain. Thus, the pCODR Review Team assessed the prognostic and predictive effect of tumour sidedness in wild-type *RAS* mCRC patients treated with anti-EGFR and anti-VEGF therapies. This was achieved by performing a critical appraisal of a meta-analysis[25] and pooled analysis[26] that explored the efficacy of panitumumab plus chemotherapy versus active therapies for the first-line treatment of mCRC patients with left and right-sided primary tumours that express wild-type *RAS*.

See section 7.1 for more information.

The pCODR systematic literature search identified two retrospective analyses that assessed the efficacy of chemotherapy plus panitumumab in patients with wild-type *RAS* mCRC with left-sided tumours.[7,8] Thus, there is a lack of direct evidence comparing chemotherapy with panitumumab to other active anti-cancer agents for the first-line treatment of mCRC patients with left-sided primary tumours that express wild-type *RAS*. Thus, the pCODR Review Team summarized and critically appraised the submitted network meta-analysis (NMA) that provides evidence for the efficacy of chemotherapy with panitumumab in the first-line treatment of *RAS* wild-type mCRC patients with left-sided tumours. Following review of feedback by the Submitter on the pCODR pERC Initial Recommendation, the Methods Team re-iterated that the current review was for panitumumab and the treatment-level NMA was reviewed rather than the class-level NMA (i.e. class-level of anti-EGFR therapies cetuximab and panitumumab). Following review of feedback by the Submitter on the pCODR pERC Initial Recommendation, the Methods Team noted that although several studies and meta-analyses were conducted to support panitumumab in left-sided tumours, all studies used the same sources of trial data of panitumumab (i.e. PEAK and PRIME); therefore, the additional analyses do not constitute new data but additional analyses of the same data. A meta-analysis is a statistical analysis that combines the results of multiple studies and therefore, are limited by the data combined. The results of the NMA indicated that chemotherapy plus panitumumab had a protective effect on OS and PFS relative to chemotherapy (PFS HR: 0.66 [95% CrI: 0.54 to 0.82] and OS HR: 0.73 [95% CrI: 0.58 to 0.91]). There was no difference between chemotherapy plus panitumumab versus chemotherapy plus bevacizumab on PFS and OS. Overall, the NMA was well designed and of high quality since the assumptions of the NMA were met. However, there is limited evidence to support the credibility of the subgroup analysis that assessed the comparative efficacy of chemotherapy plus panitumumab in patients with left and right-sided tumours in Boeckx et al (2017)[7], thus, highlighting concerns with the data incorporated into the NMA. Hence, there is uncertainty in whether there is a differential treatment response to panitumumab in *RAS* wild-type patients with left or right-sided tumours, and therefore, it is difficult to draw conclusions on the estimates from the NMA.

See section 7.2 for more information.

Comparison with Other Literature

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

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

Table 2: Assessment of generalizability of evidence for panitumumab for left-sided mCRC

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(PRIME and PEAK trial and post-hoc Boeckx analysis)</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td rowspan="4">Population</td><td>Stage of disease</td><td><u>PRIME Enrollment Criteria</u>
The trial did not limit eligibility by stage of disease

<u>PEAK Enrollment Criteria</u>
The trial did not limit eligibility by stage of disease</td><td>Does stage limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>Patients with metastatic, stage IV disease should be considered.</td></tr>
<tr><td>Performance Status</td><td><u>PRIME Enrollment Criteria</u>
Patients were eligible if they had an ECOG performance status of 0 to 2
<table>
<tr><td></td><td colspan="2">Panitumumab + Chemotherapy</td><td colspan="2">Chemotherapy</td></tr>
<tr><td></td><td>Left</td><td>Right</td><td>Left</td><td>Right</td></tr>
<tr><td>0</td><td>106 (62.7)</td><td>22 (56.4)</td><td>88 (55.3)</td><td>27 (55.1)</td></tr>
<tr><td>1</td><td>56 (33.1)</td><td>15 (38.5)</td><td>61 (38.4)</td><td>19 (38.8)</td></tr>
<tr><td>2</td><td>7 (4.1)</td><td>2 (5.1)</td><td>9 (5.7)</td><td>3 (6.1)</td></tr>
</table>
<u>PEAK Enrollment Criteria</u>
Patients were eligible if they had an ECOG performance status of 0 to 1
<table>
<tr><td></td><td colspan="2">Panitumumab + Chemotherapy</td><td colspan="2">Bevacizumab + Chemotherapy</td></tr>
<tr><td></td><td>Left</td><td>Right</td><td>Left</td><td>Right</td></tr>
<tr><td>0</td><td>37 (69.8)</td><td>10 (45.5)</td><td>35 (64.8)</td><td>9 (64.3)</td></tr>
<tr><td>1</td><td>16 (30.2)</td><td>12 (54.5)</td><td>19 (35.2)</td><td>5 (35.7)</td></tr>
</table></td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>Patients with an ECOG performance status of 0 to 2 should be considered.</td></tr>
<tr><td>Age</td><td>Both PRIME and PEAK did not limit eligibility by age.

<u>PRIME Baseline Characteristics</u>
<table>
<tr><td></td><td colspan="2">Panitumumab + Chemotherapy</td><td colspan="2">Chemotherapy</td></tr>
<tr><td></td><td>Left</td><td>Right</td><td>Left</td><td>Right</td></tr>
<tr><td>Median (range)</td><td>61 (27, 81)</td><td>62 (42, 80)</td><td>62 (27, 82)</td><td>61 (24, 78)</td></tr>
</table>
<u>PEAK Baseline Characteristics</u>
<table>
<tr><td></td><td colspan="2">Panitumumab + Chemotherapy</td><td colspan="2">Bevacizumab + Chemotherapy</td></tr>
<tr><td></td><td>Left</td><td>Right</td><td>Left</td><td>Right</td></tr>
<tr><td>Median (range)</td><td>60 (23, 77)</td><td>64 (43, 82)</td><td>60 (39, 82)</td><td>66 (50, 78)</td></tr>
</table></td><td>Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population?</td><td>The population was fairly representative of the Canadian population with respect to age.</td></tr>
<tr><td>Organ dysfunction</td><td>Patients were eligible to enroll in the PRIME or PEAK trial if they had adequate organ function</td><td>Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population?</td><td>The exclusion of patients with organ dysfunction does not limit the interpretation of the trial results, it is appropriate to exclude these patients.</td></tr>
</table>

Domain	Factor	Evidence (PRIME and PEAK trial and post-hoc Boeckx analysis)	Generalizability Question	CGP Assessment of Generalizability
	Metastatic Sites	In PRIME and PEAK, patients were eligible if they had previously untreated histologically or cytologically confirmed metastatic adenocarcinoma of the colon or rectum (in PEAK - with unresectable (M1) metastatic disease). In both trials, patients were not eligible if they had CNS metastases.	Did the exclusion of patients with certain sites of metastatic disease limit the interpretation of the trial results with respect to the target population?	No limits based on site of disease.
Intervention	Administration of intervention	**PRIME Intervention** Panitumumab q 2 weeks: 6.0 mg/kg iv over 1 hour; if tolerated, subsequent infusions could be administered over 30 minutes + FOLFOX4 q 2 weeks: oxaliplatin 85 mg/m^2 iv on day 1; leucovorin 200 mg/m^2 iv + FU 400 mg/m^2 iv bolus, then 600 mg/m^2 22- hour continuous iv on days 1 and 2 **PRIME Comparator** FOLFOX4 q 2 weeks (same dose and schedule as intervention arm) **PEAK Interventions** Panitumumab q 2 weeks: 6.0 mg/kg iv over 1 hour; if tolerated, subsequent infusions could be administered over 30 minutes + mFOLFOX6: oxaliplatin 85mg/m^2 iv on day 1; leucovorin 200 mg/m^2 iv + FU 400 mg/m^2 iv bolus, then 2400 mg/m^2 46-48-hour continuous iv on days 1 to 3 **PEAK Comparator** Bevacizumab q 2 weeks: 5.0 mg/kg iv over 90 minutes; if tolerated, subsequent infusions could be administered over 60 (or 30) minutes +mFOLFOX6 (same dose and schedule as intervention arm)	Are the results of the trial generalizable to a different dose or administration schedule?	The trials used fairly standard doses/scheduling of treatment regimens, however, mFOLFOX6 is used in Canada.
	Standard of Care	The interventions and comparators used in the PRIME and PEAK trials are relevant in some Canadian provinces. However, in some provinces, bevacizumab is funded in second line treatment, in combination with FOLFOX or FOLFIRI, for patients who have not received bevacizumab in the first-line setting.	If the comparator is non-standard, are the results of the trial applicable in the Canadian setting?	Bevacizumab is currently funded in first-line, in some provinces, such as British Columbia, bevacizumab use in second-line is permitted if it was not used in first-line.
Setting	Supportive medications, procedures, or care	Data on tumour sidedness was obtained from free-text surgery descriptions included in case report forms and original pathology reports. Tumours were classified as right-sided if they were located in the cecum to transverse colon while they were classified as left-sided if they were located in the splenic flexure to the rectum.	Is determination of tumour sidedness from the trial generalizable to methods to determine tumour sidedness in clinical practice?	Based on clinical (by imaging) or surgical (post-resection), determination of location of primary tumour with left-sided is defined as tumours distal to splenic flexure.

1.2.4 Interpretation

Burden of Illness/Need

The relevant funding population for panitumumab with chemotherapy (FOLFOX or FOLFIRI) is patients with WT *RAS*, left-sided tumours with a preserved performance status (Eastern Cooperative Oncology Group [ECOG] 0-2), suitable to undergo first-line doublet chemotherapy. Left-sidedness is presently defined as primary tumours which are distal to the colonic splenic flexure, representing approximately 70% of colorectal cancers. RAS WT status is observed in 50% of colorectal cancers. Given that an estimated 70% of these patients would be ECOG PS 0-2 and eligible for first-line combination therapy, the resultant treatment-eligible population is then approximately 22% of those with newly diagnosed MCRC or approximately 3,000 Canadians per year.

The CGP notes that a Canadian Expert Consensus statement,[27] recommends that patients with left-sided WT RAS MCRC receive FOLFOX or FOLFIRI chemotherapy plus an anti-EGFR (cetuximab or panitumumab) in the first-line setting. Treatment with bevacizumab plus chemotherapy remains the standard of care for patients with right-sided RAS WT colon cancer, and for patients with mutated RAS disease irrespective of sidedness.

Prognostic and predictive effect of tumour sidedness

The CGP agrees that a right-sided primary tumour location is accepted to be an adverse prognostic factor in MCRC, regardless of therapy, when compared to left-sided tumours, as supported in the analysis by Arnold et al (2017) and Holch et al (2016). This may, in part, be explained by the higher rate of BRAF mutation positivity (a known negative prognostic factor) among right-sided cancers versus left-sided cancers (5% vs 33% in PRIME).

Effectiveness/Safety

Retrospective analysis of PRIME and PEAK stratified by primary tumour sidedness

The use of panitumumab for left-sided MCRC is supported by retrospective subgroup analyses of two randomized first-line trials: PRIME and PEAK. In brief, PRIME was an open-label, multi-centre, randomized phase III trial that assessed the efficacy and safety of first-line panitumumab plus FOLFOX4 as compared to FOLFOX4 in 1183 patients with MCRC. PEAK was an open-label, randomized phase II trial that assessed the effect of panitumumab plus FOLFOX6 relative to FOLFOX6 with bevacizumab in 285 patients with previously untreated wild-type KRAS exon 2 (codons 12 and 13) MCRC.

In the retrospective analysis by Boeckx et al, the treatment effect of panitumumab was assessed in *RAS* wildtype mCRC patients stratified by primary tumour sidedness using data from PRIME (n=416) and PEAK (n=143). The efficacy analysis of PRIME showed a statistically significant OS benefit of panitumumab over chemotherapy in left-sided tumours (HR 0.73, 95% CI: 0.57-0.93, p=0.0112) as compared to patients with right-sided tumours (HR, 0.87, 95%CI: 0.55-1.37, p=0.5398). However, there was no evidence of a statistical difference between treatment effect and tumour sidedness (P for interaction: 0.2734).

The CGP finds the absolute difference in hazard ratios by sidedness (HR 0.73 versus HR 0.87) to be a clinically meaningful difference with an associated median OS difference of 30.3 versus 23.6 months. In PEAK, however, these findings were not reproduced as there was no significant treatment difference observed by sidedness between panitumumab plus FOLFOX

versus bevacizumab plus FOLFOX on OS (HR-left 0.77, p=0.3125, and HR-right p=0.67, p=0.3239; P for interaction: 0.9503).

In PRIME, there was a statistically significant PFS benefit of panitumumab over chemotherapy alone in left-sided tumours (HR 0.72, 95%CI: 0.57-0.90, p=0.0048) however, PFS was not significant in patients with right-sided tumours (HR 0.80, 95%CI: 0.51-1.26, p=0.3286). The clinical significance of this is unclear as right-sided tumours represented only 20% of all PFS events and hence was likely an underpowered comparison. In PEAK, however, there were non-significant differences in PFS for panitumumab plus FOLFOX versus bevacizumab plus FOLFOX for left-sided tumours (HR 0.68, 95%CI: 0.45-1.04, p=0.0732) and right-sided tumours (HR 1.04, 95%CI: 0.50-2.18, p=0.9085). Additional efficacy outcomes included an objective response rate of 67.9% in left-sided tumours for panitumumab versus 52.6% for chemotherapy in PRIME (HR 1.91, 95% CI 1.18, 3.07) and no difference was observed in right-sided tumours (HR 1.35, 95%CI 0.51, 3.62). No significant response rate by sidedness was seen in PEAK.

With respect to toxicity, no notable differences in adverse events stratified by tumour locations status were observed in PRIME and PEAK.

Network Meta-analysis of *panitumumab plus chemotherapy versus active therapies*

The results of the Manufacturer-submitted Network Meta-analysis (NMA) indicated that chemotherapy plus panitumumab has a protective effect on OS and PFS when compared to chemotherapy alone (PFS HR: 0.66 [95% credible intervals [CrI] 0.54, 0.82] and OS HR: 0.73 [95% CrI 0.58, 0.91]). There was no difference between chemotherapy plus panitumumab versus chemotherapy plus bevacizumab for PFS and OS.

Limitations

As highlighted by the Methods Team, the validity of the Boeckx et al subgroup analysis was determined by the criteria of Oxman and Guyat (1992). Limitations of this analysis included: non-significant p-values for interaction test comparing tumour sidedness and treatment effect; the post-hoc nature of the tumour sidedness analysis (i.e. the subgroups of sidedness were not pre-specified in trial protocols); and the lack of adjustment for multiple testing thus increasing the risk of Type 1 error (i.e. false positive error); and the lack of a significant effect in PEAK (which was a smaller study). It should be noted that the Methods Team recognizes that the subgroup analysis may be underpowered since patients with right-sided tumours represent only 21% and 25% of PRIME and PEAK patients, respectively. However, there is important uncertainty in the reported results. With respect to the NMA, the NMA was deemed to be overall well designed and of high quality, but given findings demonstrating uncertainty in the comparative efficacy of chemotherapy plus panitumumab in patients with left-sided tumours, the results of the NMA were difficult to interpret.

Considering the totality of evidence, it was noted that other retrospective pooled analyses and meta-analyses (Arnold et al 2017, Holch et al, 2016) have explored the predictive effect of tumour sidedness on anti-EGFRs and anti-VEGFRs therapy. These reports support the differential treatment effect of anti-EGFRs (i.e. panitumumab and cetuximab) and anti-VEGFRs (i.e. bevacizumab) in left-sided tumours. For instance, Holch et al (2017) reported a significant interaction test between anti-EGFR or anti-VEGF therapies with primary tumour location for OS (P<0.001), PFS (P<0.001) but not for ORR (P=0.41). Although these estimates demonstrate that there appears to be a class effect of anti-EGFR relative to anti-VEGF, it is important to emphasize that the effect of panitumumab and cetuximab cannot be distinguished. While cetuximab and panitumumab are considered equally efficacious when

used as monotherapy in the post-progression setting, the CGP acknowledges there is uncertainty as to whether this interchangeability can be extrapolated to the first-line setting when these anti-EGFR agents are used in combination with chemotherapy (in the absence of a randomized direct head-to-head comparison). It is difficult to apply analyses with pooled anti-EGFR results, to support the efficacy of panitumumab for left-sided cancers as it is unclear if the treatment effect is driven by cetuximab or panitumumab; thus, the CGP's efficacy interpretation comes primarily from analysis of the PRIME and PEAK trials.

1.3 Conclusions

Bevacizumab – Ineligible Patients

In current practice in Canada, the use of panitumumab with chemotherapy in the first-line setting is considered in patients with WT RAS disease (by extended RAS testing) is offered in patients who are deemed ineligible for bevacizumab. The Clinical Guidance Panel concluded that there is still evidence of an overall clinical benefit of panitumumab plus chemotherapy compared to chemotherapy alone in patients with WT RAS disease (by extended RAS testing) who are deemed ineligible for bevacizumab – regardless of tumour-sidedness.

Bevacizumab – Eligible Patients

The relevant population under consideration for this review are patients with WT RAS left-sided colon cancers (defined as colonic tumours distal to the splenic flexure), with a preserved performance status (ECOG 0-2) who would be candidates for doublet chemotherapy (FOLFOX or FOLFIRI) and otherwise also eligible for bevacizumab. The Clinical Guidance Panel concluded that there may be a net overall clinical benefit to panitumumab plus chemotherapy compared to bevacizumab plus chemotherapy in the treatment of left-sided MCRC. The CGP based this conclusion on the published Boeckx et al (2017) analysis of the PRIME and PEAK trials, and notes the limitations identified with this analysis by the Methods Team. They also provide efficacy estimates which support a benefit of anti-EGFR relative to anti-VEGF in this patient population, however, the effect of panitumumab and cetuximab cannot be distinguished in these pooled analyses; while these agents are likely to be similar in this respect, their interchangeability is not confirmed in the first-line setting in combination with chemotherapy.

Following review of feedback on the pERC Initial Recommendation, the CGP acknowledged and previously referenced the Canadian guideline published in Current Oncology supporting use of panitumumab with standard chemotherapy for patients with left-sided RAS wild-type mCRC,[27] however, the CGP noted the fundamental limitations which framed the recommendation were those identified by the pCODR Methods Team. While the CGP agreed with registered clinicians and were of the opinion that anti-EGFR therapy is of net clinical benefit for first-line treatment of left-sided mCRC, most of the data from the meta-analysis supporting this is driven by cetuximab and there are concerns of extrapolating the findings to all anti-EGFR antibodies (i.e. panitumumab). Reviewing panitumumab irrespective of class effect and the retrospective analyses of PRIME and PEAK, panitumumab was unable to convincingly demonstrate a clear net clinical benefit. This leaves some uncertainty on whether the class effect of anti-EGFR therapy for left-sided cancers can be presumed for panitumumab, hence, the CGP concluded that there may be a net overall clinical benefit to panitumumab plus chemotherapy. While the CGP agrees that panitumumab and cetuximab are likely clinically interchangeable, the CGP reiterated that this is limited to the third-line monotherapy setting (i.e., evidence from the randomized ASPECCT trial), the CGP noted

there is currently not the same level of interchangeability of cetuximab and panitumumab in the first-line setting when combined with chemotherapy.

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

- The CGP agreed with the clinician input that this population would not include patients with right-sided cancers, frail performance status (ECOG >2), patients otherwise unable to receive combination chemotherapy and patients with RAS-mutated disease.
- As previously outlined in the Section 2.2, patients with WT RAS disease who receive first-line chemotherapy and bevacizumab are offered subsequent therapy with an anti-EGFR (cetuximab or panitumumab). While the optimal sequencing of biologics in MCRC is not established, if patients with left-sided cancers receive chemotherapy plus panitumumab in the first-line setting, then it is anticipated that these patients may then be offered chemotherapy plus bevacizumab in the second-line setting. However, the CGP notes that second-line chemotherapy and bevacizumab (in patients who have not previously received first-line bevacizumab) is not currently available in all provinces.
- The CGP does not recommend the use of cetuximab in later lines of therapy in patients who previously received panitumumab in the first-line setting.
- The CGP felt extended RAS testing (vs. KRAS) should be used to guide decisions on use of panitumumab in the first-line setting. In most provinces, extended RAS testing is available, the CGP agreed with clinician input that RAS testing must be available at patient diagnosis and be timely within 1 to 2 weeks. Registered clinician feedback on the pERC Initial Recommendation noted that most centres are moving to reflex testing in multiple tumour disease sites, so RAS testing likely should be considered standard of care. The CGP noted that the issue of RAS testing was raised by PAG and that reflex RAS testing is not in place in the majority of centres. While it may happen in the future, the current reality would need to address the wait time for the test results. The CGP noted that subsequent initiation of the biologic (i.e. panitumumab) after RAS testing would be an option.
- The CGP also recognizes that extended RAS testing is not routinely available prior to commencement of first-line chemotherapy. It is anticipated that eligible patients with left-sided tumours may commence first-line chemotherapy while awaiting RAS testing results, and if determined to be RAS WT, would receive the addition of panitumumab (while patients with RAS mutated disease would receive bevacizumab)
- Following review of feedback from registered clinicians on the pERC Initial Recommendation, the CGP agreed with registered clinicians that a larger trial evaluating EGFR therapy in left-sided tumours is not anticipated or expected. The CGP also agreed with feedback that the downstream implications of bevacizumab in second-line, is an important consideration, but funding of bevacizumab is likely a separate discussion.

2 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.

2.1 Description of the Condition

Colorectal cancer is the second leading cause of cancer among men and women, with over 26,800 new cases estimated in 2017, with 9,400 related deaths[28]. An estimated 25% are diagnosed with metastatic (stage IV) disease and, among those with early-stage resectable colorectal cancer, an estimated 40% will relapse within 3-5 years of diagnosis. As such, advanced colorectal cancer represents a significant burden of disease with an estimated 14,750** new diagnosis of mCRC in Canada per year. The 5 year survival for patients with MCRC is less than 10%, with the majority of patients ultimately dying of their disease within 3 years of presentation.

2.2 Accepted Clinical Practice

The goals of therapy for the majority of patients presenting with advanced colorectal cancer are to extend survival, reduce disease-related symptoms and improve quality of life. In this setting, chemotherapy is non-curative. A minority of patients (~10%) may be suitable for upfront resection of oligo-metastatic disease to the liver and lung which may yield a curative outcome. Another 20-25% of patients with MCRC may be determined to have potentially resectable disease – i.e. metastases limited to the liver and lung, which if downsized, may be amenable to a surgical metastatectomy with curative-intent. In this setting, the primary goal of first-line chemotherapy may be to achieve a maximal response rate in the hopes of converting potentially-resectable metastases to resectable metastases.

For patients with unresectable MCRC, the goals of therapy are otherwise palliative and the primary treatment modality is systemic chemotherapy in the hopes of extending survival, and ameliorating or delaying disease-related symptoms. Among these patients, with supportive care alone, the median survival is estimated to be 6-12 months. Recent studies involving treatment with multiple lines of chemotherapy routinely report median survivals of over 24 months.[29]

Chemotherapy

The standard first-line of therapy in Canada is fluoropyrimidine-based chemotherapy combined with bevacizumab.[30] 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 administered as the following commonly used regimens FOLFOX, FOLFIRI, CAPOX, and CAPIRI. Sequencing oxaliplatin and irinotecan in first- versus second-line regimens are considered to be clinically equivalent approaches.[31,32] The anti-EGFR biologics, cetuximab or panitumumab, are currently used in the chemo-refractory setting in patients with *RAS* wild-type disease (50%). With this treatment algorithm, it is likely that 70% of patients would be eligible to receive first-line combination chemotherapy, with 60% then

** Calculation - 26800*0.25+26800*0.75*0.40

proceeding on to receive second-line chemotherapy and 30% then receiving third line anti-EGFR therapy (as dictated by *RAS* status).

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) ligand. The use of bevacizumab in combination with chemotherapy has been supported by several studies (including a 2015? CADTH recommendation) which have demonstrated an increase in progression free survival,[33-35] Bevacizumab is typically well tolerated with notable toxicities including hypertension, proteinuria and a rare increased risk of GI perforation and arterial thrombotic events.

Epidermal Growth Factor Receptor inhibitors (EGFRi)

Cetuximab (chimeric) and panitumumab (humanized) are recombinant monoclonal antibodies to the epidermal growth factor receptor (EGFR) that inhibit its downstream signaling pathways, including the *RAS* pathway. Common toxicities with this class of agents include significant skin rash (papulopustular eruptions), diarrhea, and hypomagnesemia. Infusion reactions can also occur, but are more common with cetuximab due to its murine component.

Initially, the presence of a K*RAS* mutation (in exon 2, codons 12 and 13) was the established negative predictive biomarker for EGFRi treatment selection. Subsequent studies demonstrated the negative predictive value of extended *RAS* mutation testing, including K*RAS* exons 2 and 3, and N*RAS* exons 2, 3 and 4. As a resulted, extended *RAS* testing is now the recommended standard.[36] The presence of a *RAS* mutation is a negative predictor of EGFRi benefit, and hence these drugs are contraindicated in this setting.

Currently in Canada, the use of cetuximab and panitumumab is primarily limited to the third-line setting for patients with non-mutated, 'wild-type' *RAS* tumours based upon the findings of two randomized phase 3 trials. The NCIC.CO.17 trial demonstrated a survival benefit of 5.2 months in K*RAS* WT chemo-refractory disease compared to best supportive care alone.[37] The subsequent phase 3 ASPECCT trial comparing cetuximab and panitumumab in this setting confirmed similar efficacy for both agents.[38]

The survival benefit of combining an EGFRi with earlier-line chemotherapy in WT K*RAS* disease has been demonstrated in the CRYSTAL trial (first-line FOLFIRI +/- cetuximab with median OS 23.5 mos vs 20 mos, p=0.009.[39] The phase 3 PRIME trial of first-line FOLFOX4 +/- panitumumab also demonstrated an OS benefit in WT K*RAS* disease (23.8 mos vs 19.4 mos, p=0.03).[40] In December 2015, pCODR reviewed panitumumab for the treatment of patients with *RAS* WT MCRC in first-line combination with FOLFOX (ref). The final recommendation was for the treatment of patients who have a contraindication or intolerance to bevacizumab and who would otherwise be treated with combination chemotherapy. (conditional upon acceptable cost-effectiveness).[41]

A more recent large North American phase 3 trial, CALGB/SWOG 80405 examined 1074 patients randomized to first-line doublet chemotherapy (73% FOLFOX & 27% FOLFIRI) + bevacizumab versus chemotherapy + cetuximab.[42] The median PFS (10.6 vs 10.5mos) and median OS was similar in both arms (29 mos vs 30 mos, HR 0.95, p=0.45) demonstrating that either bevacizumab or cetuximab were reasonable initial biologic options.[42]

The combination of panitumumab with first-line chemotherapy for left-sided metastatic colorectal cancer is the subject of this submission.

Sidedness as a determinant of prognosis and treatment

Anatomically, the right and the left colon arise from different embryonic origins; the proximal colon arises from the midgut and receives it main blood supply via the superior mesenteric artery, whereas the distal colon arises from the hindgut and is supplied by the inferior mesenteric artery. Left-sidedness is conventionally defined as primary tumours which are distal to the colonic splenic flexure. It is further recognized that right versus left-sided colon cancers exhibit different molecular characteristics with BRAF mutations, mismatch repair deficiency and BRAF mutations observed more commonly in right-sided tumours while *RAS* mutations are observed more commonly in left-sided cancers. Earlier studies have suggested that primary tumour location (PTL) was prognostic - an analysis by sidedness in the CALGB/SWOG 80405 trial demonstrated that right-sided cancers had an inferior OS compared to left sided cancers even when adjusted for age, gender and treatment. There was a significant PTL by biologic interaction with inferiority demonstrated for bevacizumab versus cetuximab among left-sided cancers (HR 1.97, 95% CI 1.56-2.48).[43] In a subsequent meta-analysis which included six randomized trials of *RAS* WT MCRC (CRYSTAL, FIRE-3, CALGB 80405, PRIME, PEAK and 20050181), worse survival was observed for patients with right-sided tumours in both the pooled standard treatment arms (HR 2.03, 95% CI 1.69-2.42) and the pooled experimental arm that included an anti-EGFR (HR1.38, 1.17-1.63) A significant benefit for chemotherapy plus EGFRi was observed in left-sided tumours (HR 0.75, 95%CI 0.67-0.84)[26]

In a recent Canadian Expert Consensus statement,[27] it was recommended that patients with left-sided WT *RAS* MCRC receive FOLFOX or FOLFIRI chemotherapy plus an anti-EGFR (cetuximab or panitumumab) in the first-line setting. Treatment with bevacizumab plus chemotherapy remains the standard of care for patients with right-sided *RAS* WT colon cancer, and for patients with mutated *RAS* disease irrespective of PTL.

2.3 Evidence-Based Considerations for a Funding Population

The relevant funding population for panitumumab with chemotherapy is patients with WT *RAS*, left-sided tumours with a preserved performance status (ECOG 0-2), suitable to undergo first-line doublet chemotherapy (excluding the 10% of patients with upfront resectable metastases). Left-sidedness is conventionally defined as primary tumours which are distal to the colonic splenic flexure, representing approximately 65% of colorectal cancers. *RAS* WT status is observed in 50% of colorectal cancers. As an estimated 70% would be ECOG PS 0-2 and eligible for first-line combination therapy, this would represent a treatment-eligible population of approximately 22% of patients with newly diagnosed MCRC or approximately 3,000* Canadians per year.

The preponderance of combination trial data for panitumumab in the first-line setting is with an oxaliplatin-containing regimen (PRIME, PEAK). The largest study examining the predictive impact of sidedness with an EGFRi is with cetuximab.[42] As a consequence, extrapolations are required for the requested indication. There is data in the second-line setting for FOLFIRI +/- panitumumab from a randomized trial that demonstrated improved response rate (35 vs 10%) and PFS (5.9 vs 3.9 mos) with manageable toxicity[44] and hence, most clinicians will likely be comfortable with a FOLFIRI + panitumumab first-line regimen. With respect to the interchangeability of data for cetuximab and panitumumab, based on their similar monotherapy efficacy as demonstrated in the ASPECCT trial, and their comparable efficacy as demonstrated in the first-line setting

* *Calculation - 14,750*0.9*0.65*0.50*0.7

when comparing across the CRYSTAL and PRIME trials. It would be reasonable to look at the totality of EGFRI evidence in considering this indication.

As previously described, toxicity considerations are important. The use of an EGFRi in the first-line setting is associated with significant but manageable effects including rash, diarrhea and hypomagnesemia. The acneiform skin toxicity is notable and it is anticipated that a small proportion of patients will find the visible cosmetic consequences of this rash to be unacceptable in the first-line setting. In contrast, bevacizumab is associated with relatively less distressing toxicities (namely hypertension, proteinuria, bleeding).

It would be important to also consider the timing of *RAS* testing, now typically conducted during or after first-line therapy. With this proposed treatment indication, tumour RAS testing would need to be performed at the time of diagnosis of metastatic disease.

Additional considerations include the impact of first-line EGFRi therapy on subsequent biologic exposure. It would be recommended that patients with MCRC treated with a first-line chemotherapy and EGFRi combination should, at the time of progression, be permitted to receive bevacizumab in combination with second-line chemotherapy. There is no evidence to support the use of later-line EGFRi in patients who have received and progressed on first-line EGFRi therapy.

2.4 Other Patient Populations in Whom the Drug May Be Used

This indication applies to the unresectable, *RAS* WT, left-sided metastatic colorectal patient population. This may include patients with potentially resectable metastatic disease but is distinct from patients with upfront resectable liver metastases. In this population which is beyond the scope of the current review, chemotherapy may be considered with neoadjuvant or peri-operative intent as EGFRi have been reported to be detrimental based on the new EPOC trial results.[45]

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Colorectal Cancer of Canada (CCC) provided input on panitumumab for the treatment of patients with left-sided metastatic colorectal cancer (mCRC).

To help capture the patient and caregiver experience, Colorectal Cancer Canada (CCC) conducted a national survey from September 1, 2017 to September 14, 2017. Registered colorectal cancer patients and caregivers in Canada provided responses of which 62 were patients and 17 were caregivers. Disease stage distribution from the survey results was as follows:

Stage 0	1%
Stage I	6%
Stage II	9%
Stage III	35%
Stage IV	38%

*Note: five patients whom were able to cite their experience with the therapy under review, three were in the first line setting.

In addition to the national survey, CCC conducted an outreach campaign to online colorectal cancer chat groups/forums throughout Canada and the US to gather information about firsthand experience with panitumumab. CCC was able to conduct seven phone interviews with patients between September 18, 2017 and September 20, 2017. The data for these patients are captured below in section 3.2.2. Thus, inn total, CCC was able to gather information from 69 patients (62 surveyed, 7 interviewed) and 17 caregivers (surveyed), 10 of whom had experience with panitumumab in the first line setting (3 surveyed, 7 interviewed).

From a patient's perspective, there are a number of symptoms associated with mCRC that impact quality of life, which include bloody stools, abdominal discomfort, fatigue, constipation and diarrhea, weight loss and bowel obstruction. Respondents identified depression, anxiety, and fear as psychological limitations resulting from mCRC. Caregiver respondents indicated significant impact to their lives in terms of financial, physical, and psychological challenges when caring for their loved ones. With current available therapies, patients noted that some of their needs are not being met and personalized treatment options are needed. Most patients noted fatigue and nausea as commonly experienced side effects from current treatment options with mouth sores as the most difficult to tolerate. Patients desire treatment options that will effectively control their disease with respect to overall survival, progression free survival and quality of life. Patients desire treatment options specific to their cancer's genetic make-up. Of the patients who had experience with panitumumab in combination with chemotherapy for left-sided mCRC, patients noted that the therapy helped shrink their disease. The most common reported side effects for panitumumab in combination with chemotherapy were rashes, neuropathy, nausea, fatigue, hair loss, mouth sores, and shortness of breath. Patients rated their quality of life on the treatment on a scale of 1-10, with three patients identifying quality of life as 8/10 and three identifying it as 7/10. One patient noted that on days 5-7 of treatment, quality of life was a 4/10. Patients also noted that panitumumab plus chemotherapy resolved pain/pressure symptoms from metastases.

Please see below for a summary of specific input received from CCC. 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.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with Metastatic Colorectal Cancer

Colorectal Cancer Canada (CCC) has reported that colorectal cancer is the second leading cause of cancer death in Canada for men and women combined. CCC has also noted from a study by Boeckx N, et al. (ESMO 2016), that approximately 80% off all colorectal cancers originate on the left side of the colon and 20% originate on the right side. As such, CCC notes that patients with left-sided primary tumours may benefit from the addition of an anti-EGFR therapy such as panitumumab in combination with chemotherapy in the first line treatment of RAS WT mCRC.

CCC noted that mCRC is a fatal disease for which there is no known cure. The intent of treatment is for tumour control/reduction coupled with surgery (in some cases). In addition, CCC noted that approximately 35-50% of the CRC population may present with synchronous metastatic disease or eventually develop metastatic disease after having been diagnosed with early stage disease.

From the online patient survey conducted by CCC, the following CRC symptoms were identified as the most prevalent:

- Bloody Stools
- Abdominal discomfort
- Fatigue
- Constipation/diarrhea
- Weight loss
- Bowel obstruction

Pain and fatigue resulting from the cancer were reported to be the most important and difficult to control with 85% of patients noting that CRC-induced symptoms interfered with their daily activities and they are not able to function "normally" in their family or work setting. Patients noted the following,"cannot/unable to work", "can no longer exercise because of pain/fatigue", and "can no longer perform family obligations".

In addition, CC notes that rates of depression, anxiety and fear were the most consistently cited by patients as psychological limitations resulting from the cancer. Patients also highlighted the financial hardship or out of pocket expenses incurred by 55% of the patient respondents to help pay for their medications/drugs. The following quote was provided to illustrate this experience:

"No insurance coverage for the rash compounds or for the magic mouthwash. Mouthwash is 440/bottle and lasts 4 days! And lots of costs for OTC meds such as face creams, moisturizers, zinc ointments, etc."

Thirty-eight percent of patients highlighted out of pocket expenditures to help pay for their drug therapies. Examples included, capecitabine and pembrolizumab. One patient noted that they "paid for 30% of all therapies and drugs".

3.1.2 Patients' Experiences with Current Therapy for Metastatic Colorectal Cancer

Colorectal Cancer Canada (CCC) noted that according to the patient survey results, patients accessed combination chemotherapies such as FOLFOX or FOLFIRI with bevacizumab in first line treatment to help reduce the burden of disease. Fifty-seven (57) percent of respondents maintained that these therapies were effective at controlling their cancer-induced symptoms.

Most patients cited fatigue and nausea as being the most difficult to tolerate with current therapies. Patients noted that chemotherapy induced neuropathy and mouth sources were the most difficult to tolerate. When asked if needs were not being met by the current drugs available to treat CRC, 40% responded "yes" and provided the following quotes:

"We need better treatments for KRAS and BRAF mutant patients"

"Pani should be covered plain and simple"

"Desire drug therapy that will eradicate remaining disease"

CCC has noted that there exists an unmet clinical need in the metastatic patient population. In addition, patients who belong to the CC's CRC Information Support Groups have noted that mCRC patients and their caregivers fail to see how their personal disease characteristics form the basis of treatment selection in the first line management of their disease. Patients and caregivers would like to understand how the "personalized" medicine approach was factored into their treatment selection.

3.1.3 Impact of Metastatic Colorectal Cancer on Caregivers

Seventeen caregivers responded to the online survey conducted by Colorectal Cancer Canada (CCC).

CCC noted that the disease significantly impacted the lives of caregivers. Caregivers are fraught with enormous financial, physical, and psychological challenges when caring for their loved ones. The following quotes were provided by caregivers:

"Managing time to attend appts and treatments, feeling helpless when the patient cannot eat or is unable to her regular activities, so I have to take over those activities along with managing my daily chores."

"Had to go part time. Financial challenges. Worry, anxiety, depression."

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for panitumumab (Vectibix)

Colorectal Cancer Canada (CCC) noted that patient's desire to be provided access to therapies that will effectively control their disease with respect to overall survival (OS), progression free survival (PFS), and promote quality of life (QoL). Of the patient respondents, 70% felt that they should be afforded the opportunity to have choice in the selection of the best therapeutic option based on their individual disease characteristics.

CCC noted that a first line anti EGFR therapy such as panitumumab in combination with chemotherapy may represent a preferred therapeutic option in the first line treatment of RAS WT mCRC patients whose primary tumour originated on the left side of the colorectum. CCC noted that every cancer patient's needs are unique and treatments should be based on their cancer's genetic makeup. In addition, CCC has noted that upfront RAS testing for all mCRC patients is recommended as soon as possible to help guide treatment and achieve better outcomes for patients. Patients' hope is to administer the most effective therapy to help shrink their disease upon commencing treatment.

Metastatic patients wish to see significant improvements in their OS and prefer a therapeutic agent that takes the location of their primary tumour into account to achieve maximum therapeutic benefit.

3.2.2 What Experiences Have Patients Had To Date with panitumumab?

From the survey conducted by CCC, the results identified three patients who accessed panitumumab in combination chemotherapy in first line setting. The three patients noted that the therapy was funded "through the government" for them. The patients also noted that the therapy helped shrink patients' disease. The following positive and negative aspects of the therapy were noted:

Positive:

- *"At present, hey say I am cancer free"*
- *"Yes positive"*
- *"Longevity of life"*
- *"CEA in May were 6081, after 8 cycles, CEA down to 83"*

Negative:

- *"Diffuse hepatic metastases with minimal shrinkage"*

The three patients also reported the most common side effects from the therapy. Acceptable side effects were noted as neuropathy, nausea, and fatigued. Unacceptable side effects were noted as hair loss, mouth sores, shortness of breath and neuropathy.

In addition to the above, CCC had conducted extensive telephone interviews with seven patients who had access panitumumab plus FOLFOX in the first line setting and had confirmed RAS WT metastatic left sided CRC. The patient interviews are summarize below in Table 1.

CCC noted that in RAS WT patients with left-sided tumours, panitumumab in combination with chemotherapy may provide better outcomes than comparator treatments and that RAS WT patients with left-sided tumours derive greater benefit from panitumumab containing treatment than chemotherapy alone or combined with bevacizumab. CCC noted that tumour sidedness should be considered when making treatment decisions because distinct molecular differences exist between right and left colorectal cancers. In addition, CCC noted that the mCRC population should be afforded the best therapy for their CRC based on their personal set of disease characteristics, which includes tumour sidedness.

TABLE 1: PATIENT INTERVIEW DEMOGRAPHICS & EXPERIENCE WITH DRUG UNDER REVIEW

PANI + COMBO CHEMO IN 1ST LINE TREATMENT OF RAS WT LEFT SIDED MCRC

	Patient WN	Patient RM	Patient KJ	Patient RR	Patient JD	Patient TH	Patient HC
Interview Date/ Time	Sept 18/17 7:00 - 8:30 p.m.	Sept 19/17 11:00 a.m.- 12:30 p.m.	Sept 19/17 1:30 - 2:30 p.m.	Sept 19/17 2:30 - 3:30 p.m.	Sept 19/17 7:00 - 8:00 p.m.	Sept 19/17 9:00 - 10:00 p.m.	Sept 20/17 11:00 a.m. - 12:00 p.m.
Gender/Age at dx	Male, 48	Female, 55	Female, 45	Male, 51	Female, 31	Female, 37	Female, 44
When Diagnosed	May 2017	June 2017	March 2017	June 2016	January 2017	January 2017	April 2017
City, Country	L.A., California, U.S.	Halifax, NS, CA	Cleveland, Ohio, U.S.	Chicago, Il, U.S.	Minnesota, U.S.	L.A., California, U.S.	Temeculah, California, U.S.

Location of Mets	Rectal sigmoid, liver	peritoneum	Sigmoid Colon, Liver	Sigmoid Colon, Liver, Spine, Lungs	Sigmoid Colon, Liver	Liver	Peritoneum, omentum, ovaries
Confirm RAS WT? (yes/no)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Treatment Centre	City of Hope	NS Cancer Centre	Cleveland Clinic	University of Chicago, North shore Medical Group	Minnesota Oncology	City of Hope	City of Hope
Protocol	Vectibix + Folfox	Vectibix + Folfox	Folfox + Vectibix	Folfox + Vectibix	Vectibix + Folfox	Folfox + Vectibix	Folfox + Vectibix
# of Cycles Received	9 Folfox + 8 Vectibix	4	6	12	8 Folfox + 4 Vectibix (Added vectibix at cycle #2)	12	9 folfox + 8 Vectibix
CEA, Good Indicator?	Yes. May 25/17 CEA= 631. Sept 13/17, CEA= 2.5	Generally, yes.	Yes. March 2017 CEA=102.7. Sept 2017 CEA=6	Yes. Went from 960 to 3	Yes. Went from 453 to 2.5	Yes. Now within normal range my onc tells me.	Yes. Went from 40 to 3.5
Treatment-Induced Side Effects?	Vectibix-induced: Impressive rash on face, chest and back (grade 3). Dry skin. Corners of mouth and cuticles have cracked from time to time. Folfox-induced: Hair loss, fatigue, neuropathy. Meds have helped to relieve the rash and dry skin.	On day 5,6,7: diarrhea & fatigue are quite debilitating. Rash developed after 1st cycle of vectibix. Have been given meds now to help with rash. Antibiotic and topical cream. Imodium for diarrhea as well. Mouth sores as well have developed. Will be dropping 5FU bolus push to help with toxicity.	Slight rash and dry skin but took antibiotic and topical cream to help deal with it from the start. Some diarrhea and fatigue but overall, was very manageable. I used some naturopathic remedies too so that I could lead a normal life.	"Lost 55lbs while on the protocol. Most notable side effects were: neuropathy, skin issues, cold sensitivity. Did not progress on the therapy. Fatigue was at times difficult. Stopped after 12 cycles due to onc's advice but would have happily continued because of its effectiveness."	"I was diagnosed during the winter so the oxaliplatin gave me sensitivity to the cold. The rash came on after I started vectibix and it was brutal but I dealt with it by using antibiotics and topical cream. I lived a pretty normal life considering."	"I had an acne like rash that covered my torso, back, face and scalp. But it was manageable with antibiotics and topical solution. Other side effects included neuropathy, constipation and hair thinning."	"Vectibix induced rash on face and neck, breakout, eczema and red eye lids. Palms peeled, so dermatologist placed me on meds and it all improved."
Rate QoL, 1-10, while on	**7**	On days 5-7 of treatment,	**8**	**6-7**	**7**	**8**	**8**

therapy		rate QoL a **4.** On the rest of the days, QoL is a **7.**					
Cancer Symptoms? Did symptoms resolve on protocol?	Pain/pressure from B.M.s have resolved completely. Salty taste from liver mets resolved	"Pain from tumor in cervix has diminished significantly after 2nd cycle. Qualify for ***CRS.*** "	"I had no cancer symptoms really. I was pretty pain free just some bloating and constipation which led to my diagnosis. The bloating was immediately gone after the first cycle of treatment."	Upon presentation, I had GI symptoms such as diarrhea and abdominal pain. Within 3-4 weeks, the GI issues disappeared. By the end of the 12 cycles, spinal mets disappeared, so did the lung mets and the sigmoid tumor is barely visible through imaging. Just a few liver mets are left. I am now on folfiri.	I had bloody stools when I was diagnosed and I had what they called referred pain from my liver to my shoulder. After treatment #3, I had no more cancer-induced symptoms.	I didn't really have any symptoms from the cancer because I was being monitored after my original surgery from my primary.	Yes. The ascites was immediately relieved by the folfox and vectibix and has not returned since being on it.
CT scan results confirm response to protocol?	July 15/17 CT results showed 80-90% shrinkage of liver mets and primary. Sept.12/17showed continued shrinkage. Am now a ***surgical candidate.***	No CT scan results available to confirm disease regression as of yet.	After the last CT, I qualified for surgery and am **now cancer free!!**	Yes. CT scan showed tremendous regression after 4 cycles.	My tumours shrank by 90% as confirmed by the first and second CT scans! I became a **surgical candidate**.	"Yes. The therapy worked REALLY well for me. My CEA dropped and the mets disappeared completely and I am NED."	Yes. Tumours have shrunk by 80% after the first 3 cycles and by an additional 55% after the first 8 cycles.
Was the protocol worth accessing?	"Absolutely. No doubt about it!"	"Oh God yes! Wanna save my vagina because I have deep love for my husband."	"Yes, yes, yes. It saved my life."	"For sure. The alternative is far worse. It has kept me alive."	"Without a doubt! I would do it again if I had to!"	"Oh yes. I am so happy I got to have it."	"Hell ya. Specially to see that first scan result. I live with gratitude and happiness."

3.3 Additional Information

Colorectal Cancer Canada (CCC) noted that tumour 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 side effects in those who are unlikely to benefit. Additional, CCC noted that patients are aware of the positive impact Primary Tumor Location (PTL) has on mCRC outcomes, specifically with the use of an anti-EGFR therapy such as panitumumab.

CCC also provided information on testing for RAS mutations. They noted that RAS mutation status can provide good quality, actionable information when deciding on a first-line treatment option in mCRC Based on the survey results, one mCRC patient had their RAS mutation status determined prior to starting panitumumab plus combination chemotherapy. Two patients had their testing performed at the treatment centre with no known delay to start of treatment and their health care professional explained the need for testing and both patients understood why RAS testing was required.

Additionally all seven interviewed patients had their RAS mutation status determined prior to the incorporation of panitumumab into their treatment protocol. Once the cancer was diagnosed as RAS WT, there was immediate introduction of the monoclonal antibody into their treatment plan. Of the respondents, one patient experienced delay in accessing panitumumab due to delay in generating test results. Most patients received timely results ensuring timely access to panitumumab. CCC did note however that all patients expressed having experienced feelings of anxiety while waiting for RAS results to be generated and were relieved to learn they were RAS WT and candidates for the therapy.

CCC noted that patients and caregivers have noted that a choice of when those therapies are administered is strongly warranted and that disease characteristics must be taken into account to ensure the most effective response to treatment. Furthermore, CCC noted that patients with tumours that do not harbor any activating RAS mutations stand to benefit from panitumumab plus combination chemotherapy for left sided tumours in the first line setting. CCC noted that taking primary tumour location into account coupled with identifying RAS mutation status will allow clinicians and their patients to jointly develop a personalized approach to optimize treatment in the first line setting.

4 SUMMARY OF PROVINCIAL ADVISORY GROUP 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 provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Use of panitumumab with FOLFIRI, an alternate combination chemotherapy regimen frequently used for first line metastatic colorectal cancer
- Sequencing of therapies following first line panitumumab + FOLFOX (or other combination chemotherapy) – e.g. bevacizumab second line and the alternate anti-EGFR therapy, cetuximab, third line

Economic factors:

- The number of patients requiring extended RAS testing may be larger as it will be needed for patients with left-sided tumors prior to decision on first line treatment, rather than reserved for those patients who may be candidates for third line treatment.

Please see below for more details.

4.1 Factors Related to Comparators

PAG identified that bevacizumab is funded, in combination with FOLFOX or FOLFIRI, for the first-line treatment of mCRC. In some provinces, bevacizumab is funded in second line treatment, in combination with FOLFOX or FOLFIRI, for patients who have not received bevacizumab in the first-line setting.

PAG is seeking information on the use of panitumumab in combination with FOLFIRI as a first line option, given that FOLFIRI is funded in all provinces and FOLFOX is funded in some provinces for first line treatment.

4.2 Factors Related to Patient Population

In the previous review of panitumumab in the first line treatment of *RAS* wild-type mCRC, pERC recommended panitumumab for patients who have contraindications or intolerance to bevacizumab. This review addresses the use of panitumumab first line treatment in a broader subgroup of patients with mCRC whose tumors are *RAS* wild-type and have a left-sided location.

PAG is seeking guidance on the sequencing of panitumumab with bevacizumab and cetuximab. PAG is seeking information on the clinical benefits and cost effectiveness of using bevacizumab second line and cetuximab third line after panitumumab in the first line.

4.3 Factors Related to Dosing

PAG noted that panitumumab would be administered with FOLFOX and patients would be at the chemotherapy clinics already. The standard infusion times (after the first dose) for

panitumumab is 30 minutes and does not significantly differ from bevacizumab (given over 10 to 30 minutes, depending on local policy).

4.4 Factors Related to Implementation Costs

If panitumumab were an option in the first line setting for patients with left-sided colorectal cancer, these patients will require extended *RAS* testing upfront at diagnosis to determine first-line treatment plan.

4.5 Factors Related to Health System

PAG noted that turn-around time for test results would be important for treatment with panitumumab in the first-line setting such that treatment with panitumumab could be started shortly after diagnosis. PAG is seeking guidance on whether patients with left-sided mCRC should start treatment with chemotherapy while waiting for test results or start chemotherapy with bevacizumab while waiting for test results and add or switch to panitumumab if results are *RAS* wild-type.

4.6 Factors Related to Manufacturer

None.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

Two clinician inputs were received: one joint clinician input from Cancer Care Ontario and one joint clinician input from Colorectal Cancer Canada.

Although there are treatments available for metastatic colorectal cancer (mCRC), the clinicians providing input noted that panitumumab plus chemotherapy is superior in survival benefits for the subgroup of patients with RAS wild-type left-sided mCRC. They noted that RAS testing is required to determine eligibility for treatment with panitumumab.

Please see below for details from the clinician input.

5.1 Current Treatment(s) for mCRC

The clinicians providing input indicated that the choice of treatment depends on patients' comorbidities and patient preferences. They identified that the provincially funded options are FOLFIRI +/- bevacizumab, FOLFOX +/- bevacizumab, and capecitabine.

5.2 Eligible Patient Population

The clinicians providing input noted that the proportion of patients with left-sided colorectal cancer is 65-75% of total colorectal cancer cases, and of these, the proportion of patients with RAS wild-type is 40-45%. Thus, 30-40% of overall mCRC population would be eligible for panitumumab. They indicated that panitumumab would be used in first-line treatment of RAS wild-type left-sided colorectal cancer and in first-line treatment of mCRC in patients (regardless of sidedness) who have contraindications to bevacizumab.

They noted that panitumumab should not be used in frail patients who are unable to tolerate combination chemotherapy, first-line right-sided colorectal cancer nor for RAS mutated colorectal cancers.

5.3 Identify Key Benefits and Harms with Panitumumab

The clinicians providing input noted that panitumumab is an improvement over existing first-line treatments for mCRC and is superior for patient survival for the subgroup of patients with left-sided mCRC.

Relative to chemotherapy plus bevacizumab, the clinicians noted that adverse events of chemotherapy plus panitumumab include skin toxicity, diarrhea and fatigue.

5.4 Advantages of Panitumumab Over Current Treatments

As above.

5.5 Sequencing and Priority of Treatments with Panitumumab

The clinicians providing input has indicated that in RAS wild-type left-sided mCRC patients, EGFR inhibitors, such as panitumumab or cetuximab, would replace bevacizumab as first-line treatment. First line treatment for this group of patients would be chemotherapy plus an EGFR inhibitor. Second line treatment for these patients would be chemotherapy plus bevacizumab. Further lines of treatment could include TAS102 or other recently identified targeted therapies but would exclude EGFR inhibitors if given first-line.

They noted that for all other types of mCRC, current standard of care would be maintained.

5.6 Companion Diagnostic Testing

The clinicians providing input stress that RAS testing is mandatory and must be available at presentation of mCRC. They stress that the test results must be timely, within one to two weeks. It is expected that most centers will have access to multiplex/nextgen sequencing techniques which provides comprehensive analysis including that required for RAS.

5.7 Additional Information

The definition of left versus right differs from the various studies, but in discussing this with clinicians around the country, the common cut point is the splenic flexure.

The clinicians providing input noted the need to advocate for bevacizumab for second line treatment of RAS wild-type left sided colorectal cancer in jurisdictions which do not currently fund it and for other EGFR inhibitor, such as cetuximab, plus chemotherapy. However, this is out of scope of the current review.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the efficacy and safety of panitumumab, in combination with chemotherapy, for the first-line treatment of mCRC patients with left-sided primary tumours that express wild-type *RAS*.

Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

- Section 7.1: Critical appraisal of a meta-analysis and pooled analyses that assesses the efficacy of panitumumab plus chemotherapy versus active therapies for the first-line treatment of mCRC patients with left and right-sided primary tumours that express wild-type *RAS*.
- Section 7.2: Critical appraisal of the submitted NMA that assesses the efficacy of panitumumab plus chemotherapy versus active therapies for the first-line treatment of mCRC patients with left-sided primary tumours that express wild-type *RAS*.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP 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. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 3: Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes

Published or unpublished RCTs
 	
In the absence of RCTs, fully published clinical trials investigating the safety and efficacy of panitumumab and chemotherapy should be included.
	Untreated mCRC patients with left-sided primary tumours that express wild-type *RAS*
	
	<u>Subgroups:</u>
	• Age (< 65 years vs. ≥65 years)
	• ECOG status
	• *RAS* (*KRAS* or *NRAS*) genotype status
	• BRAF genotype status
		Chemotherapy + panitumumab
		
		<u>1st line setting</u>
		• FOLFOX + panitumumab
		• FOLFIRI + panitumumab
		• XELOX + panitumumab
			<u>1st line setting</u>
			• Chemotherapy
			  ○ FOLFOX
			  ○ FOLFIRI
			  ○ XELOX
			  ○ FOLFIRINOX
			  ○ Capecitabine
			• Chemotherapy +VEGF
			  ○ FOLFOX + BV
			  ○ FOLFIRI + BV
			  ○ XELOX + BV
				<u>Primary</u>
				• **OS**
				• **PFS**
				• **HRQoL**
				
				<u>Secondary</u>
				• ORR
				• DOR
				• DCR
				• Resection Rate
				• Number of cycles completed
				
				<u>Safety</u>
				• AEs
				• SAEs
				• WDAEs
				• TRAEs
				• AEs of interest (Rash, Diarrhea, Hypomagnesemia)

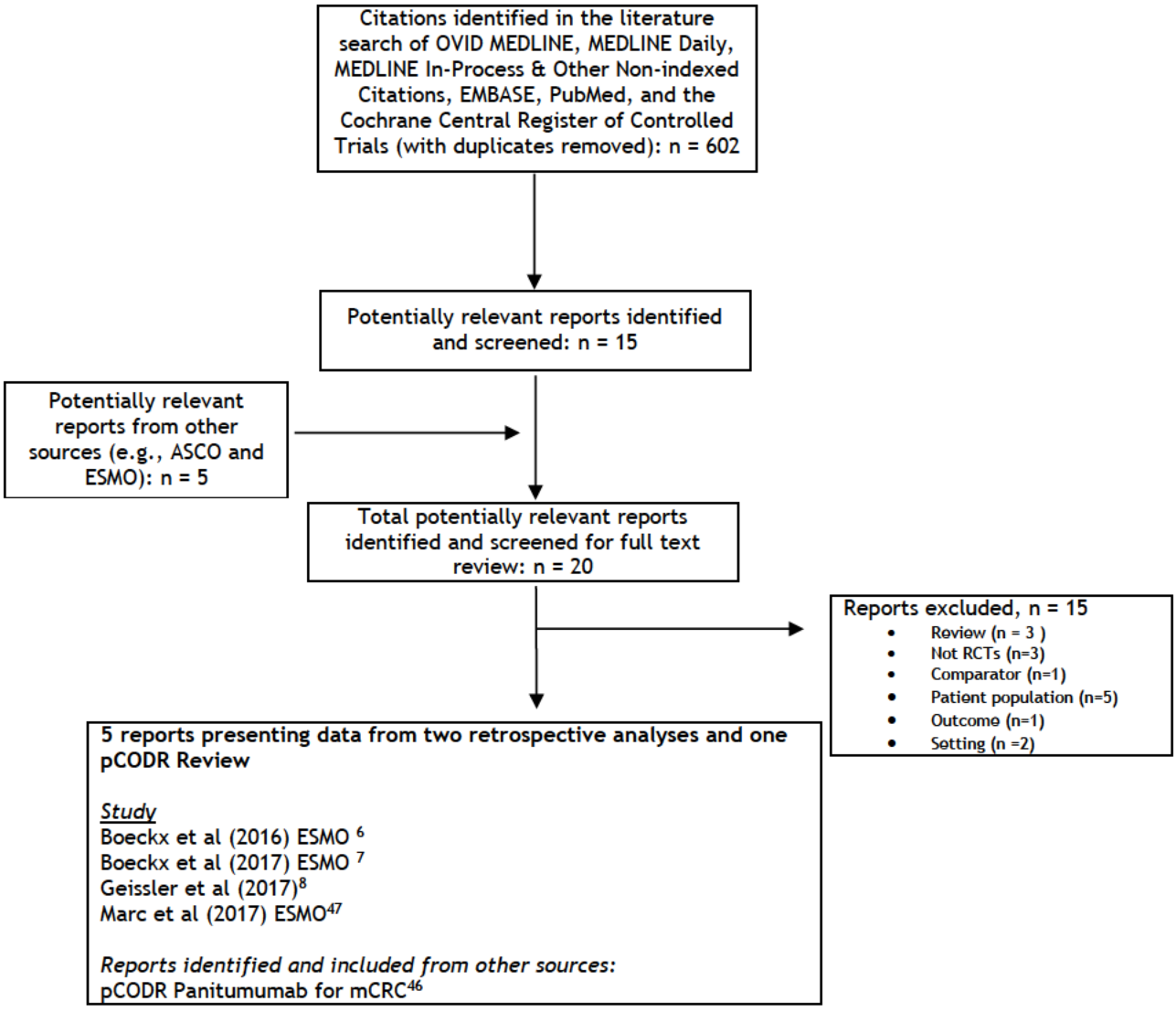
Abbreviations: mCRC=metastatic colorectal cancer; HRQoL=Health related quality of life; SAE=serious adverse events; AE=adverse events; WDAE=withdrawals due to adverse events; DCR=disease control rate; ORR=objective response rate; DOR=duration of response; ORR=overall response rate				
Notes: * Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions).				

6.3 Results

6.3.1 Literature Search Results

Of the 602 potentially relevant reports identified, two trials, PRIME and PEAK, reported in two retrospective analyses, and one pCODR Review, were included in the pCODR systematic review.[6-8,46] Two of the included abstracts[6,47] referred to a published paper[7] or were a duplicate[8]. Fifteen reports were excluded because they were reviews (N = 3); they were not RCTs (N =3); and they did not use a relevant comparator (N =1), outcome (N =1), patient population (N = 5) or trial setting (N = 2). Additional reports related to the submission were obtained from the Submitter.[10,25,26,48]

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



Note: Additional data were also obtained through requests to the Submitter by pCODR [Cornerstone NMA[48], Checkpoint Responses[10], Holch et al (2017)[25] and Arnold et al (2017)[26]]

6.3.2 Summary of Included Studies

The pCODR systematic review included two retrospective analyses[7,8] that assessed the efficacy and safety of panitumumab plus chemotherapy in mCRC patients with left-sided primary tumours that express wild-type *RAS* using data from the PRIME and PEAK trials.[1-5]

6.3.2.1 Detailed Trial Characteristics

a) Trial

The two retrospective analyses explored the association between tumour sidedness and panitumumab efficacy in patients with *RAS* wild-type mCRC undergoing first-line treatment using data from the PRIME and PEAK trials.[1-5] The details and quality assessment of the original PRIME and PEAK trials are presented in Table 4 and Table 5. Further details are located in the pCODR 10060 Panitumumab for mCRC review published in December 2015.[46] Briefly, PRIME was an open-label, multi-centre, randomized phase III trial that assessed the efficacy and safety of panitumumab plus FOLFOX4 as compared to FOLFOX4 in 1,183 patients with mCRC.[1-3] PEAK was an open-label, randomized phase II trial that assessed the effect of panitumumab plus FOLFOX6 relative to FOLFOX6 with bevacizumab in 285 patients with previously untreated wild-type K*RAS* exon 2 (codons 12 and 13) mCRC.[4,5]

Table 4: Summary of trial characteristics of included trials of panitumumab in combination with oxaliplatin-based chemotherapy as first-line treatment in patients with wild-type *RAS* mCRC

PRIME Trial[1-3]				
Trial Design	**Eligibility Criteria**	**Intervention**	**Comparator**	**Outcomes**
Clinical Trial NCT003364013 Open label phase 3 RCT Patient enrolment: August 2006 - February 2008 Data cut-off date: August 29, 2009 N randomized = 1183 Multicentre (133 centres from 19 countries) Randomized 1:1 ratio, stratified by: • Geographic location (Western Europe, Canada, Australia vs. rest of world) • ECOG PS (0 or 1 vs. 2) EGFR expression and K*RAS* tumour status not required at trial entry Trial design amended (prior to efficacy analyses) to compare outcomes by K*RAS* tumour	<u>Key Inclusion Criteria:</u> • 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 <u>Exclusion Criteria:</u> • Previous treatment with oxaliplatin or anti-EGFR therapy • Pregnancy • CNS metastases	<u>Panitumumab</u> q 2 weeks: 6.0 mg/kg iv over 1 hour; if tolerated, subsequent infusions could be administered over 30 minutes + <u>FOLFOX4</u> q 2 weeks: oxaliplatin 85 mg/m^2 iv on day 1; leucovorin 200 mg/m^2 iv + FU 400 mg/m^2 iv bolus, then 600 mg/m^2 22- hour continuous iv on days 1 and 2 Given until disease progression or unacceptable toxicity	<u>FOLFOX4</u> q 2 weeks (same dose and schedule as intervention arm)	<u>Primary</u>: • Progression-free survival (blinded central review) <u>Secondary</u>: • Overall survival • Objective tumour response (blinded central review) • Metastasis resection rate (complete or partial; status of margins not specifically captured) • Adverse events

PRIME Trial[1-3]				
Trial Design	**Eligibility Criteria**	**Intervention**	**Comparator**	**Outcomes**
status (WT vs. MT) Blinded central *KRAS* testing was completed 3 months prior to primary efficacy analysis Funded by AMGEN				
PEAK Trial[4,5]				
Trial Design	**Eligibility Criteria**	**Intervention**	**Comparator**	**Outcomes**
Clinical Trial NCT008819780 Open label Phase 2 RCT Patient enrolment: April 2009 - December 2011 Data cut-off date: May 30, 2012 N randomized: 285 Multicentre (60 sites) Randomized 1:1 ratio, stratified by: • Prior oxaliplatin therapy Extended *RAS* analysis was performed (blinded, and planned a priori) to compare efficacy outcomes in *KRAS* tumour subgroups: • *KRAS* exons 2, 3, and 4 • *NRAS* exons 2, 3, and 4 Funded by AMGEN	<u>Key Inclusion Criteria:</u> • Age ≥ 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) • ≥ 1 measurable lesion (≥ 20 mm) using modified RECIST criteria • ECOG of 0 or 1 • Adequate organ function <u>Exclusion Criteria:</u> • Any prior chemotherapy, anti-EGFR therapy, or treatment with bevacizumab for mCRC • Radiotherapy ≤ 14 days before randomization • Adjuvant chemotherapy (including oxaliplatin) for CRC ≤ 52 weeks prior to randomization • Pregnancy • CNS metastases	<u>Panitumumab</u> q 2 weeks: 6.0 mg/kg iv over 1 hour; if tolerated, subsequent infusions could be administered over 30 minutes + <u>mFOLFOX6:</u> oxaliplatin 85mg/m^2 iv on day 1; leucovorin 200 mg/m^2 iv + FU 400 mg/m^2 iv bolus, then 2400 mg/m^2 46-48-hour continuous iv on days 1 to 3 Given until disease progression, unacceptable toxicity, death, withdrawal of consent or investigator decision	<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 + <u>mFOLFOX6</u> (same dose and schedule as intervention arm)	<u>Primary</u>: Progression-free survival (no independent review) <u>Secondary</u>: Overall survival Objective response rate Metastases resection rate Adverse events

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.

Table 5: 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 *RAS* mCRC[1-5]

Trial	Treatment vs. Comparator	Primary Outcome	Required Sample Size	Sample Size	Randomization Method	Allocation Concealment	Blinding	ITT analysis	Final Analysis	Early Termination	Ethics Approval
PRIME	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]	Yes	No	Yes
PEAK	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 [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.[3]
[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.[49]
[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) using permuted blocks (block size of 4)

The first retrospective analysis included in the pCODR systematic review was by Boeckx et al (2017).[6,7] The objective of this analysis was to investigate the association between tumour sidedness and panitumumab efficacy in *RAS* wild-type mCRC patients enrolled in the PRIME and PEAK trials. Patients were considered as *RAS* wild-type carriers if they did not have a mutation in the *KRAS*/*NRAS* exon 2/3/4 region.[7] Patients were only included in the analysis if there was available information on primary tumour location and those who had missing or unknown data were excluded.[7] Data on tumour sidedness was obtained from free-text surgery descriptions included in case report forms and original pathology reports.[7] Tumours were classified as right-sided if they were located in the cecum to transverse colon while they were classified as left-sided if they were located in the splenic flexure to the rectum.[7] Tumour assessors were blinded to *RAS* and *BRAF* mutation status, treatment allocation and clinical outcomes. The analysis presented in Boeckx et al (2017) represents a descriptive post-hoc analysis of the PRIME and PEAK trials and no formal hypothesis testing or power calculations were performed. The

authors assessed the effect of tumour sidedness in panitumumab-treated mCRC patients that expressed wild-type *RAS* using the following outcomes: ORR, DOR, PFS and OS.

The other retrospective analysis identified in the pCODR systematic review was conducted by Geissler et al (2017) and it was presented in abstract format. Similar to Boeckx et al (2017), this analysis explored the effect of tumour sidedness on panitumumab efficacy using data from the PRIME and PEAK trials. Patients were considered as *RAS* wild-type carrier status if they did not have a mutation in the K*RAS*/N*RAS* exon 2/3/4 region.[8] The authors measured the following outcomes: resection rates, early tumour shrinkage and depth of response rate. In addition, the authors did not report on how tumour sidedness was classified and if any formal hypothesis testing or power calculations were performed.

b) Populations

The baseline characteristics of the PRIME and PEAK trials have been reported previously. [1-5,46] Briefly, in the PRIME trial, 1,183 patients were randomly assigned to treatment with panitumumab plus FOLFOX4 or FOLFOX4. Among these patients, 512 were retrospectively identified as *RAS* wild-type carriers (panitumumab+FOLFOX4, n=259; FOLFOX4, n=253). [1-3] In the PEAK trial, 170 patients with wild-type *RAS* were randomly assigned to either panitumumab plus mFOLFOX6 (n=88) or bevacizumab plus mFOLFOX6 (n=82).[4,5]

The Boeckx et al (2017) retrospective analysis included *RAS* wild-type patients from the PRIME (N = 505) and PEAK (N =170) trials.[7] Tumour sidedness was determined in 83% of patients from the PRIME (N = 416/505) and the PEAK (N = 143/170) trials (Table 6). The majority of patients in the PRIME and PEAK populations had a left-sided tumour (79% and 75%, respectively).[7] There appeared to be differences in *BRAF* carrier status and site of metastasis across tumour sidedness and treatment group; however, these results are difficult to determine given the small sample size.

Table 6: Baseline characteristics of mCRC patients that express wild-type *RAS* from the PRIME and PEAK trials stratified by tumour sidedness and treatment group

Table 1. Baseline demographics and disease characteristics of the *RAS* WT population

Baseline characteristic		PRIME				PEAK			
		Pmab arm		Comparator arm		Pmab arm		Comparator arm	
		Left	Right	Left	Right	Left	Right	Left	Right
	Patient number	169	39	159	49	53	22	54	14
Baseline ECOG, *n* (%)	Missing	–	–	1 (0.6)	–	–	–	–	–
	0	106 (62.7)	22 (56.4)	88 (55.3)	27 (55.1)	37 (69.8)	10 (45.5)	35 (64.8)	9 (64.3)
	1	56 (33.1)	15 (38.5)	61 (38.4)	19 (38.8)	16 (30.2)	12 (54.5)	19 (35.2)	5 (35.7)
	2	7 (4.1)	2 (5.1)	9 (5.7)	3 (6.1)	–	–	–	–
Prior adjuvant chemotherapy, *n* (%)	No	140 (82.8)	29 (74.4)	133 (83.6)	39 (79.6)	45 (84.9)	18 (81.8)	41 (75.9)	10 (71.4)
	Yes	29 (17.2)	10 (25.6)	26 (16.4)	10 (20.4)	8 (15.1)	4 (18.2)	13 (24.1)	4 (28.6)
Sex, *n* (%)	Female	49 (29.0)	18 (46.2)	56 (35.2)	24 (49.0)	19 (35.8)	7 (31.8)	16 (29.6)	4 (28.6)
	Male	120 (71.0)	21 (53.8)	103 (64.8)	25 (51.0)	34 (64.2)	15 (68.2)	38 (70.4)	10 (71.4)
BRAF status, *n* (%)	Test failure	6 (3.6)	0 (0.0)	3 (1.9)	1 (2.0)	–	–	–	–
	Mutant	7 (4.1)	13 (33.3)	8 (5.0)	16 (32.7)	1 (1.9)	9 (40.9)	1 (1.9)	1 (7.1)
	Wild-type	156 (92.3)	26 (66.7)	148 (93.1)	32 (65.3)	52 (98.1)	13 (59.1)	53 (98.1)	13 (92.9)
Sites of metastasis, *n* (%)	Liver+other	119 (70.4)	21 (53.8)	108 (67.9)	35 (71.4)	21 (39.6)	13 (59.1)	21 (38.9)	9 (64.3)
	Liver only	33 (19.5)	6 (15.4)	31 (19.5)	5 (10.2)	18 (34.0)	4 (18.2)	15 (27.8)	4 (28.6)
	Other only	17 (10.1)	12 (30.8)	20 (12.6)	9 (18.4)	14 (26.4)	5 (22.7)	18 (33.3)	1 (7.1)
Age, years (range)	Median	61 (27, 81)	62 (42, 80)	62 (27, 82)	61 (24, 78)	60 (23, 77)	64 (43, 82)	60 (39, 82)	66 (50, 78)

ECOG, Eastern Cooperative Oncology Group; *n*, number; Pmab, panitumumab.

Data Source: Reproduced from Boeckx N, Koukakis R, Op De BK, Rolfo C, Van CG, Siena S, et al. Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer. Ann Oncol. 2017 Aug 1;28(8):p.1864. Creative Commons CC-BY-NC 4.0[7]

In the Geissler et al (2017) analysis, tumour sidedness could be determined in 559 patients from both the PRIME and PEAK trials.[8] Here, 78% of patients had a left-sided tumour (N=435). Additionally, patients with left-sided tumours were more likely to have a BRAF wild-type carrier status (94%) as compared to those with a right-sided tumour (68%).[8]

c) *Interventions*

Details of the dosing and administration of the drug regimens used in the treatment and control arms of PRIME and PEAK are presented in Table 4 and further details are located in the pCODR 10060 Panitumumab for mCRC review.[46] In both trials, treatment regimens were given until disease progression, unacceptable toxicity or withdrawal of consent. [1-5,46] No dose reductions or interruptions were reported in the trial publications for any of the drug regimens used in each trial.

d) *Patient Disposition*

Details on the patient disposition for PRIME and PEAK are reported in the pCODR 10060 Panitumumab for mCRC review.[1-5,46]

The number of patients included in the Boeckx et al (2017) analysis using data from PRIME and PEAK are presented in Table 7 and 8[50]. Six hundred and seventy-five patients were included in the analysis (N_{PRIME} = 505 and N_{PEAK} = 170). Patients were excluded in the trial if they had a *RAS* mutation, which included codons 12, 13, 59, 61, 117 and 146.[10] Codon 59 was included as a sensitivity analysis because its impacts on anti-EGFR efficacy was not known at the time of the analysis.[10] Seven patients were excluded because they had a codon 59 mutation.[10] Furthermore, 89 patients were excluded from PRIME (N=89/505) and 27 patients were excluded from PEAK (N=27) because of missing or unknown information on tumour sidedness.[10]

Table 7: Patient disposition for the retrospective analysis in Boeckx et al (2017) using data from the PRIME trial

PRIME Publication					
Treatment group	Panitumumab + chemotherapy		Chemotherapy		Total
N	253		252		505
Boeckx publication					
Treatment group	208		208		416
N					
	Left- side	Right-side	Left-side	Right-Side	
Subgroup N	169	39	159	49	
Missing N* (based on PRIME publication)	45		44		89

Data Source: PRIME trial[1-3], Boeckx et al (2017)[7] and Checkpoint Responses[10]

Table 8: Patient disposition for the retrospective analysis in Boeckx et al (2017) using data from the PEAK trial

PEAK Publication					
Treatment group	Panitumumab + chemotherapy		Chemotherapy + bev		Total
N	88		82		170
Boeckx publication					
Treatment group	Panitumumab + chemotherapy		Chemotherapy + bev		Total
N	75		68		143
	Left- side	Right-side	Left-side	Right-Side	
Subgroup N	53	22	54	14	
Missing N* (based on PEAK publication)	13		14		27

Data Source: PEAK trial[4,5], Boeckx et al (2017)[7] and Checkpoint Response[10]

e) Limitations/Sources of Bias

The objective of this pCODR review is to evaluate the efficacy and safety of panitumumab, in combination with chemotherapy, for the first-line treatment of mCRC patients with left-sided primary tumours that express wild-type *RAS*. The pCODR systematic literature search identified two retrospective, subgroup analyses that sought to determine if the effect of panitumumab varies among *RAS* wild-type mCRC patients who have a left-sided or a right-sided tumour, using data from the PRIME and PEAK trials.[7,8]

Both the Boeckx et al (2017) and Geissler et al (2017) studies represent post-hoc, retrospective, descriptive analyses. Post-hoc analyses refer to those analyses that are not specified prior to examining RCT data. Post-hoc analyses should be interpreted with caution because they are more subject to multiplicity (i.e. multiple testing), which increases the risk of type 1 error. A type 1 error leads to false-positives, such that a study may report a treatment difference between two groups (p-value ≤ 0.05), when in fact, there is no true difference.[11] Several statistical techniques have to developed to control for type 1 error because as the number of statistical tests increases so does the risk of type 1 error.[51] However, it was stated in Boeckx et al (2017) that the authors did not adjust for multiplicity, and therefore, the observed effect estimates of OS and PFS in this analysis are more prone to type 1 error. In contrast, Geissler et al (2017) did not state whether they adjusted for type 1 error.

Although subgroup analyses are widely reported in RCTs and meta-analyses, they should be interpreted with caution because they are often considered exploratory in nature and hypothesis generating.[9,12] Oxman and Guyat (1992) developed seven widely used criteria that can be applied to determine the credibility of a subgroup analysis.[13] Strong inferences can be made about a subgroup analysis when 1) valid comparisons are made within rather than between studies, 2) the test for interaction suggests that chance is unlikely explanation for the apparent differences, 3) the subgroup was specified *a priori*, 4) there is a small number of hypothesis tested, 5) the difference between subgroup categories is large, 6) there is consistency across studies, and 7) there is indirect evidence to support the apparent differences.[13]

To assess the credibility of the retrospective subgroup analysis in Boeckx et al (2017)[7], the Methods Lead applied the Oxman and Guyatt criteria.[13,14] It should be noted that the Geissler et al (2017) publication will not be included because it consists of only abstract-level data.[8] More specifically:

- **Is the difference suggested by comparisons within rather than between studies?**
    - A subgroup is more credible when the evidence supporting the analysis is made from a within-trial comparison rather than a between-trial comparison.[13] Here, a within-trial comparison uses direct evidence from one trial while a between-trial comparison uses indirect evidence from multiple trials.[13] Between-study comparisons weaken the credibility of a subgroup analysis because the observed treatment effect may be explained by factors other than the treatment itself. These factors may include differences in the patient populations, the schedule and administration of the intervention or control and outcome measurements. Thus within-study differences are preferred because potential confounders are controlled for within a single trial.
    - Boeckx et al (2017) used direct evidence from both the PRIME and PEAK trials.[7] Thus, we can conclude that the subgroup is more credible because the results of the subgroup are not influenced by factors other than the treatment itself.
- **Does the interaction test suggest a low probability that chance explains the apparent subgroup?**
    - A subgroup is more credible when there is presence of a significant statistical test for interaction rather than using the p-values from the subgroup themselves.[13] Here, a test for interaction is a formal statistical procedure that assesses whether the treatment effect differs across subgroup categories and that these apparent differences are not due to chance alone.[12] Using the p-values from the subgroup analysis weakens

credibility because some subgroups will be significant, regardless of the overall effect estimate, due to chance or sample size.[52] Furthermore, relying solely on subgroup p-values does not address whether the effect estimates observed across subgroups categories are truly different.[53] On the other hand, a non-significant interaction p-value does not imply that there are no true differences across subgroup categories because the analysis could be underpowered to detect an effect.[53] Thus, it is important to consider the interaction p-value as well as other criterion when assessing the credibility of the subgroup.

- Boeckx et al (2017) reported that panitumumab plus FOLFOX was associated with a longer OS as compared to FOLFOX in patients with left-sided tumours (p–value= 0.0112) while there was no difference in patients with right-sided tumours who were treated with panitumumab plus FOLFOX or FOLFOX (p- value = 0.5398).[7] Although the authors concluded that panitumumab may be more effective in patients with left-sided tumours as compared to right-sided tumours, the p-value for interaction was non-significant (P for interaction: 0.2734).[10] This means that there is no statistical difference in treatment effect for patients with left or right-sided tumours. However, the lack of statistical difference may be due to small sample size. Indeed, there were substantially more patients with a left-tumour (N = 328) than with a right-tumour (N = 88). Based on this evidence, it is more likely that the reported efficacy estimates in the Boeckx et al (2017)[7] were due to chance or small samples sizes.

- **Was the hypothesis tested a priori?**
  - A subgroup is more credible when the analysis is specified prior to conducting the trial rather than after the data has been collected (i.e. post-hoc).[13] Post-hoc analyses weaken the credibility of a subgroup analysis because they are more susceptible to bias and spurious results.[12] Unlike a priori hypotheses, post hoc subgroup analysis are more exploratory in nature and should be considered "hypothesis-generating rather than hypothesis-testing".[13] Furthermore, it is also important that the subgroup variable is measured at baseline rather than defined according to post-randomization characteristics.[9,54] Creating subgroups based on clinical characteristics that emerge after randomization will violate the principles of randomization because the observed effect may only reflect a difference in the patients themselves and not a difference in the treatment.[12]
  - The subgroup analysis in Boeckx et al (2017) was considered retrospective because it was not specified in the trial protocol.[3,5] Information on tumour sidedness was obtained from free-text surgery descriptions included in the patients' case report forms and from the original pathology reports.[7] In the analysis, primary tumors were classified as right-sided if they were located in the cecum to the transverse colon while left-sided tumours were classified as those tumours located in the splenic flexure to the rectum.[7] Since tumour sidedness was defined according to post-randomization characteristics, the patient population in the Boeckx et al (2017) analysis may be prognostically different from those originally enrolled in the PRIME and PEAK trials.
- **Was the subgroup effect one of a small number of hypothesised effects tested?**
  - A subgroup is more credible when fewer hypotheses are tested. Multiple hypothesis tests weaken the credibility of a subgroup analysis because they will increase the risk of type I error. Type 1 error leads to false positives, where the null hypothesis is rejected when it should not be rejected.[55] In other words, the reported results suggest that there is a treatment difference when there is no true treatment effect.
  - Boeckx et al (2017) stated that "As these were retrospective analyses, no formal hypothesis testing was planned." This indicates that the results of the analysis were descriptive and the authors did not attempt to adjust for multiple testing. Thus, these results should be interpreted with caution because there is a high risk of a type 1 error.[15] For instance, the null hypothesis of the Boeckx et al (2017) analysis is that there is no treatment difference between patients with a left and right-sided tumour.[7]

- **Is the magnitude of the subgroup effect large?**
    - A subgroup analysis is more credible when there are large effect sizes across subgroups rather than smaller effect sizes.[13] Small effect sizes weaken the credibility of a subgroup analysis because modest differences may be more likely due to chance.[52] Therefore, it is more likely that a true difference exists if there are larger effect sizes between subgroups.[13]
    - Using data from PRIME, Boeckx et al (2017) reported that panitumumab plus FOLFOX was associated with a longer OS as compared to FOLFOX in patients with left-sided tumours than with right-sided tumours (adjusted HR_{left}: 0.73, 95% CI: 0.57 to 0.93; p-value= 0.0112 and adjusted HR_{right}: 0.87, 95% CI: 0.55 to 1.37; p-value= 0.5398).[7] In contrast, there was no treatment difference between panitumumab plus FOLFOX versus bevacizumab plus FOLFOX on OS using data from PEAK (adjusted HR_{left}: 0.77, 95% CI: 0.46 to 1.28; p-value= 0.3125 and adjusted HR_{right}: 0.67, 95% CI: 0.30 to 1.50; p-value= 0.3239). The overall estimates for OS were not reported.[7] The pCODR Clinical Guidance Panel felt that the differences in OS for patients with left or right-sided tumours were clinically meaningful.
- **Is the observed differential effect consistent across studies?**
    - A subgroup is more credible when it is consistent across studies rather than within one study.[53] Single study estimates weaken the credibility of a subgroup analysis because replication improves the reliability of the results.[53] However, it should be noted that failure to replicate across studies may be a result of small sample sizes or differences in study design and patient characteristics.[13]
    - The effect of panitumumab on tumor sidedness was not consistent across the PRIME and PEAK trials.[7] Although the authors state that patients with a left-sided tumour who were treated with panitumumab have better OS as compared to those with a right-sided tumour using data from PRIME, these results did not replicate in the PEAK trial However, the lack of replication using data from PEAK may be due to a small sample size (N = 143).
- **Is there indirect evidence that supports the hypothesised interaction (biological rationale)?**
    - A subgroup is more credible if there is an existing biological rationale that supports the biological mechanism of disease.[13] A lack of a biological rationale weakens the credibility of a subgroup analysis because the results of the analysis may not align with the pathology of disease or current understanding.[12] However, several authors have cautioned that a biological rationale can be tailored to the specific example, and therefore, it has been suggested that the clinical or biological rationale for a subgroup should be published and clearly stated within the protocol.[12]
    - Studies have demonstrated that the sidedness of primary colon tumours is determined at embryological origin and that left or right-sided tumours have different gene expression as well as clinical and molecular characteristics.[16-23] Although there is biological evidence supporting the different pathological features of tumour sidedness, there is a lack of evidence demonstrating the biological mechanism that influences the treatment response to panitumumab in *RAS* wild-type patients with left or right-sided tumours.

Based on the criterion presented in Oxman and Guyatt (1992), there is little evidence to support the credibility of the subgroup analysis reported in Boeckx et al (2017)[7]. Hence, there is uncertainty in whether there is a differential treatment response to panitumumab in *RAS* wild-type patients with left or right-sided tumours.

It has been stated that mCRC patients with right versus left-sided exhibit different molecular characteristics, such as differences in *RAS* and *BRAF* mutations. For instance, *BRAF* mutations are observed more frequently in patients with right-sided tumours while *RAS* mutations are observed more commonly in left-sided cancers. However, it has been argued that the apparent differences in patients with left and right-sided tumours may, in part, be explained by the higher rate of *BRAF* mutation positivity (a known negative prognostic factor) among right-sided cancers versus left-sided cancers (5%

vs 33% in PRIME). Thus, subgrouping patients by tumour sidedness using data from PRIME and PEAK may introduce imbalances in the *BRAF* carrier status, and therefore, bias the reported effect estimates in favour of those with left-sided tumours. Furthermore, there is also the potential that the effect estimates reported in the Boeckx et al (2017)[7] may be confounded by an unmeasurable variable. For instance, the authors stated that only *RAS* and *BRAF* genotype carrier status was available at the time of the analysis and they did have any information on microsatellite instability, mismatch repair deficiency or methylation, which have also been shown to influence clinical outcomes among mCRC patients.[56]

f) Efficacy Outcomes

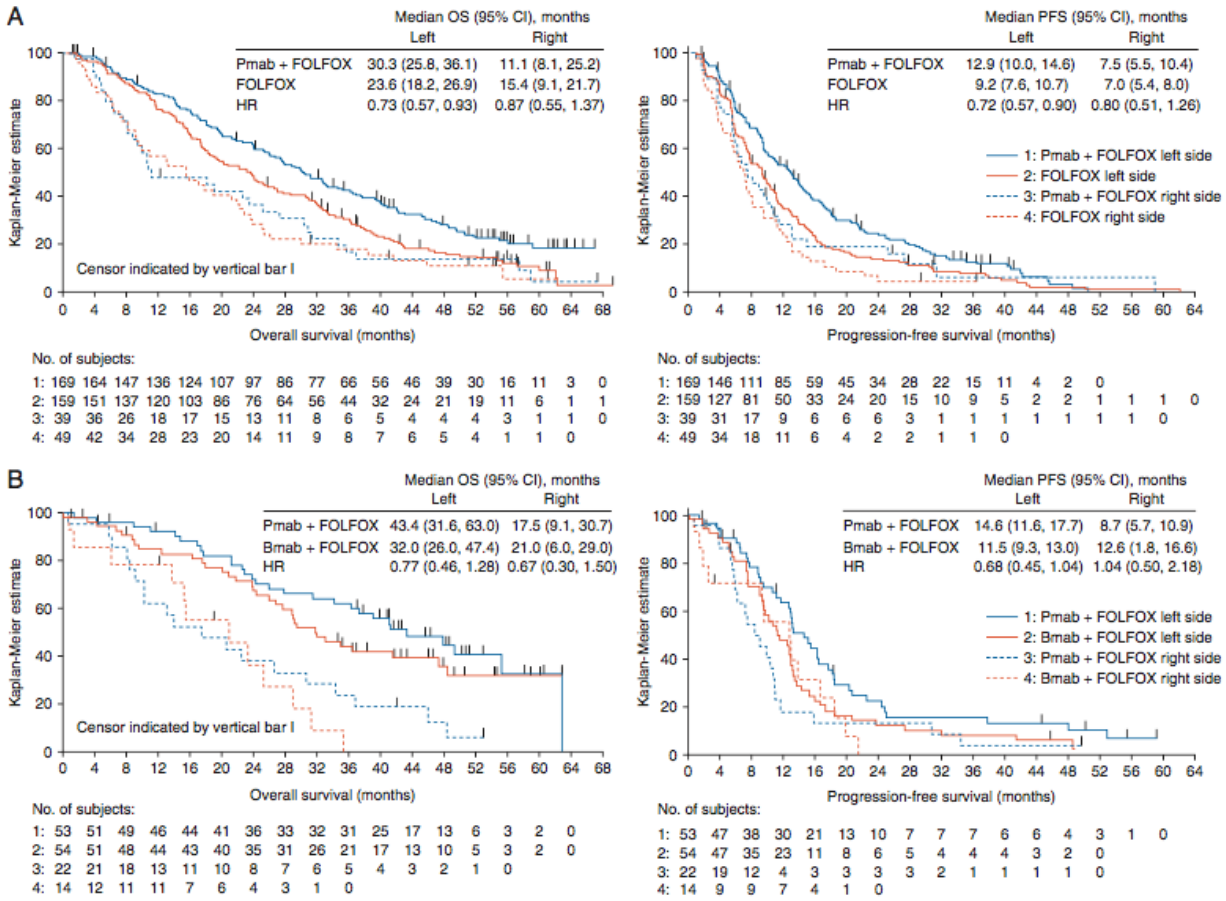
The objective of the Boeckx et al (2017) and Geissler et al (2017) analyses were to explore the efficacy of panitumumab in *RAS* wildtype mCRC patients with left-sided primary tumours using data from PRIME and PEAK. Patients in the Boeckx et al (2017) analyses were considered as *RAS* wild-type carrier status if they did not have a mutation in the K*RAS*/N*RAS* exon 2/3/4 region.[7] Tumours were classified as right-sided if they were located in the cecum to transverse colon while they were classified as left-sided if they were located in the splenic flexure to the rectum.[7] The data cut-off for PRIME was 24-Jan-2013 and the data cut-off for PEAK was 11-Feb-2015.[10] The other retrospective analysis identified in the pCODR systematic review was conducted by Geissler et al (2017) and it was presented in abstract format. Patients were considered as *RAS* wild-type carrier status if they did not have a mutation in the K*RAS*/N*RAS* exon 2/3/4 region.[8]

The analysis presented in Boeckx et al (2017) represents a descriptive post-hoc analysis of the PRIME and PEAK trials and no formal hypothesis testing or power calculations were performed. Post-hoc analyses should be interpreted with caution because they are more subject to multiplicity (i.e. multiple testing), which increases the risk of type 1 error. A type 1 error leads to false-positives, such that a study may report a treatment difference between two groups (p-value ≤ 0.05), when in fact, there is no true difference.[11]

Overall Survival

Boeckx et al (2017) assessed the effect tumour sidedness on OS in panitumumab-treated mCRC patients that express wild-type *RAS* using data from the PRIME and PEAK trials.[7] OS was defined as the time from randomization to death.[7] OS effect estimates for the primary analysis were obtained using stratified Cox proportional hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) and Wald tests to generate p-values. The Cox model was adjusted for *BRAF* status, prior adjuvant therapy and ECOG status. The data cut-off for PRIME was 24-Jan-2013 and the data cut-off for PEAK was 11-Feb-2015.[10] These results should be interpreted with caution because this analysis was descriptive and there was no adjustment for multiplicity.

Figure 2: Subgroup analysis of OS and PFS stratified by treatment group and tumour sidedness in mCRC patients that express wild-type *RAS* using data from the (A) PRIME and (B) PEAK trials



Data Source: Reproduced from Boeckx N, Koukakis R, Op De BK, Rolfo C, Van CG, Siena S, et al. Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer. Ann Oncol. 2017 Aug 1;28(8):p.1866. Creative Commons CC-BY-NC 4.0[7]

Using data from PRIME, the authors reported that patients with a left-sided tumour who were treated with panitumumab plus FOLFOX had a longer median OS than those treated with FOLFOX alone (30.3 months [95% CI: 25.8 to 36.1] vs. 23.6 months [95% CI: 18.2 to 26.9]) (Figure 2).[7] Panitumumab plus FOLFOX was associated with a longer OS as compared to FOLFOX in patients with left-sided tumours (adjusted HR: 0.73, 95% CI: 0.57 to 0.93; p-value= 0.0112).[7] There was no difference between patients with a right-sided tumour who were treated with panitumumab plus FOLFOX or FOLFOX (adjusted HR: 0.87, 95% CI: 0.55 to 1.37; p- value = 0.5398) (Figure 2).[7] In order to determine whether the treatment effect of panitumumab differs among patients with left or right-sided tumours, a statistical test for interaction is required.[9] A statistical test for interaction tests the hypothesis that the treatment effect of panitumumab does not differ for patients with left or right-sided tumours. If the p-value of the interaction test is greater than 0.05, we fail to reject the null hypothesis that the effect of panitumumab is not different among patients with left or right-sided tumours. However, if the p-value for interaction is less than 0.05, we can assume that there is a statistical difference in the treatment effect of panitumumab among patients with left or right-sided tumours. For instance, a significant p-value for interaction could imply that patients with left-sided tumours who were treated with panitumumab had improved OS as compared to their right-sided counterparts. It should be noted that many retrospective analyses do not have sufficient power to detect treatment effect, and thus , a non-significant test does not indicate that there is no difference between subgroup groups.[9] The Submitted

reported that the p-value of the interaction test that assessed whether the treatment effect of panitumumab differed among patients with left or right-sided tumours for OS was 0.2734.[10] Since the p-value for interaction was greater than 0.05, this indicates that the effect of panitumumab on OS did not differ between patients with left-sided or right-sided tumours.

Boeckx et al (2017) showed that there was no significant treatment difference between panitumumab plus FOLFOX and FOLFOX with bevacizumab on OS in left-sided tumour *RAS* wild-type carriers from data from PEAK (adjusted HR: 0.77, 95% CI: 0.46 to 1.28; p – value= 0.3125) (Figure 2).[7] Similar results were observed for *RAS* wild-type carriers with right-sided tumours (adjusted HR: 0.67, 95% CI: 0.30 to 1.50; p – value= 0.3239).[7] The p-value for interaction was 0.9503 (Table 9).[10]

Table 9: Subgroup analysis of overall survival stratified by treatment group and tumour sidedness in mCRC patients that express wild-type *RAS* using data from the PRIME and PEAK trials

Trial	Tumour Sidedness	Panitumumab Events	Chemotherapy Events	HR (95% CI)	P	P for interaction
PRIME[A]	Left	126/169	136/159	0.73(0.57, 0.93)	0.0112	0.2734
	Right	34/39	44/49	0.87(0.55, 1.37)	0.5398	
	Total	160/208	180/208			
PEAK[B]	Left	29/53	33/54	0.77(0.46, 1.28)	0.3125	0.9503
	Right	19/22	12/14	0.67(0.30, 1.5)	0.3239	
	Total	48/75	45/68			

A: The PRIME trial was designed to compare the effect of panitumumab plus FOLFOX4 to FOLFOX4.
B: The PEAK trial was designed to compare the effect of panitumumab plus mFOLFOX6 to bevacizumab plus mFOLFOX6.
Data Sources: Boeckx et al (2017)[7] and Checkpoint Responses[10]

Table 10 represents a secondary analysis, where the PRIME and PEAK patient populations were subset to only include those with a *RAS*/*BRAF* wild-type carrier status (PRIME, N = 362 and PEAK, N = 131). The secondary analysis explored the prognostic impact of tumour sidedness in a subset of *BRAF* and *RAS* (*BRAF*/*RAS*) wild-type carriers. For this analysis, the Cox model using PRIME data was adjusted for region and ECOG status while the Cox model using PEAK data was adjusted for prior adjuvant oxaliplatin therapy. Using data from PRIME, patients with a left-sided tumour who were treated with panitumumab plus FOLFOX had a longer OS relative to those treated with FOLFOX alone (adjusted HR: 0.68, 95% CI: 0.52 to 0.87; p-value: 0.0027). The results for OS were not significant for patients with a right-sided tumour (p=0.9295). There was no difference in treatment effect for patients in PEAK with left-sided (p=0.2945) or right-sided tumours (p=0.3326) (Table 10). However, it is difficult to determine if there is a true difference between those with left or right-sided tumours since there is a limited sample size, the retrospective nature of the analyses and there is no interaction p-value.

Table 10: Subgroup analysis of overall survival and PFS stratified by treatment group and tumour sidedness in mCRC patients that express wild-type *RAS*/*BRAF* using data from the PRIME and PEAK trials

Table 3. Efficacy outcomes in the *RAS/BRAF* WT population

Study	Treatment	*n* Patients		OS (m)		PFS (m)	
		Left	Right	Left	Right	Left	Right
PRIME	Pmab+FOLFOX	156	26	32.5 (27.5, 37.6)	22.5 (8.1, 30.8)	12.9 (10.0, 14.9)	8.9 (5.5, 11.3)
	FOLFOX	148	32	23.6 (18.2, 27.7)	21.5 (10.8, 26.0)	9.3 (7.7, 10.8)	7.3 (4.2, 11.1)
	Adjusted HR[a]			0.68 (0.52, 0.87)	0.97 (0.55, 1.74)	0.69 (0.54, 0.88)	0.75 (0.42, 1.33)
	P-value			0.0027	0.9295	0.0028	0.3260
PEAK	Pmab+FOLFOX	52	13	43.4 (34.2, 63.0)	22.5 (8.4, 36.9)	14.6 (11.6, 18.1)	10.3 (6.1, 11.6)
	Bmab+FOLFOX	53	13	32.0 (26.9, 48.5)	23.3 (6.0, 29.0)	11.5 (9.3, 13.0)	12.6 (1.8, 18.4)
	Adjusted HR[b]			0.76 (0.45, 1.27)	0.64 (0.26, 1.58)	0.65 (0.43, 1.00)	0.90 (0.39, 2.07)
	P-value			0.2945	0.3326	0.0514	0.8092

[a]Adjusted treatment HR calculated from model with factors for region and baseline ECOG. HR below 1 favors the pmab arm (PRIME).
[b]Adjusted treatment HR calculated from model with factors for prior adjuvant oxaliplatin therapy. HR below 1 favors the pmab arm (PEAK).
Bmab, bevacizumab; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; *n*, number; OS (m), overall survival in months; PFS (m), progression-free survival in months; Pmab, panitumumab.

Data Source: Reproduced from Boeckx N, Koukakis R, Op De BK, Rolfo C, Van CG, Siena S, et al. Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer. Ann Oncol. 2017 Aug 1;28(8):p.1865.Creative Commons CC-BY-NC 4.0[7]

Progression Free Survival

Boeckx et al (2017) assessed the effect tumour sidedness on PFS in panitumumab-treated mCRC patients that express wild-type *RAS* using data from the PRIME and PEAK trials.[7] PFS was defined as the time from randomization to disease progression as assessed by modified RECIST or death (whichever occurred first).[7] PFS effect estimates for the primary analysis were obtained using stratified Cox proportional HRs with corresponding 95% CIs and Wald tests to generate p-values. The Cox model was adjusted for *BRAF* status, prior adjuvant therapy and ECOG status. The data cut-off for PRIME was 24-Jan-2013 and the data cut-off for PEAK was 11-Feb-2015.[10] These results should be interpreted with caution because this analysis was descriptive and there was no adjustment for multiplicity.

Using data from PRIME, the authors reported that patients with a left-sided tumour who were treated with panitumumab plus FOLFOX had a longer PFS than those treated with FOLFOX alone (12.9 months [95% CI: 10.0 to 14.6] vs. 9.2 months [95% CI: 7.6 to 10.7]) (Figure 2).[7] Panitumumab plus FOLFOX was associated with a longer PFS as compared to FOLFOX (adjusted HR: 0.72, 95% CI: 0.57 to 0.90; p-value= 0.0048). There was no difference on PFS between *RAS* wild-type patients with a right-sided tumour who were treated with panitumumab plus FOLFOX or FOLFOX (adjusted HR: 0.80, 95% CI: 0.51 to 1.26; p-value = 0.3286) (Figure 2). The p-value for interaction was 0.9637, which indicates that there was no difference in treatment effect for patients with left-sided or right-sided tumors (Table 11). [10]

There was no significant treatment difference between panitumumab plus FOLFOX and FOLFOX with bevacizumab on PFS in left-sided tumour *RAS* wild-type carriers from data from PEAK (adjusted HR: 0.68, 95% CI: 0.45 to 1.04; p – value= 0.0732) (Figure 2). Similar results were observed for PFS in *RAS* wild-type carriers with right-sided tumours (adjusted HR: 1.04, 95% CI: 0.50 to 2.18; p – value= 0.9085). The p-value for interaction was 0.2398, which indicates that there was no difference in treatment effect for patients with left-sided or right-sided tumors (Table 11). [10]

Table 11: Subgroup analysis of PFS stratified by treatment group and tumour sidedness in mCRC patients that express wild-type *RAS* using data from the PRIME and PEAK trials

Trial	Tumour Sidedness	Panitumumab Events	Chemotherapy Events	HR (95% CI)	P	P for interaction
PRIME[A]	Left	146/169	145/159	0.72(0.57, 0.90)	0.0048	0.9637
	Right	34/39	46/49	0.80(0.51, 1.26)	0.3286	
	Total	180/208	191/208			
PEAK[B]	Left	43/53	47/54	0.68(0.45, 1.04)	0.0732	0.2398
	Right	21/22	13/14	1.04(0.50, 2.18)	0.9085	
	Total	64/75	60/68			

A: The PRIME trial was designed to compare the effect of panitumumab plus FOLFOX4 to FOLFOX4.
B: The PEAK trial was designed to compare the effect of panitumumab plus mFOLFOX6 to bevacizumab plus mFOLFOX6.
Data Sources: Boeckx et al (2017)[7] and Checkpoint Responses[10]

The authors also subset the patient population of PRIME and PEAK to only include those who were *RAS*/*BRAF* wild-type carriers (PRIME, N = 362 and PEAK, N = 121) (Table 10). Carriers of the *RAS*/*BRAF* wild-type with a left-sided tumour who were treated with panitumumab plus FOLFOX had a longer PFS as compared relative to those treated with FOLFOX alone using PRIME data (adjusted HR: 0.69, 95% CI: 0.54 to 0.88; p-value: 0.0028). In contrast, there was no treatment difference on PFS for *RAS*/*BRAF* wild-type carriers with right-sided tumours (p-value=0.3260). Furthermore, Boeckx et al (2017) did not observe any treatment differences on PFS for *RAS*/*BRAF* wild-type carriers with left-sided tumours (p-value: 0.0732) or right-sided tumours (p-value: 0.9085) using data from PEAK. As previously mentioned, these results should be interpreted with caution because there is no adjustment for multiplicity and there are small sample sizes.

Objective Response Rate
Boeckx et al (2017) also assessed the effect tumour sidedness on ORR in panitumumab-treated mCRC patients that express wild-type *RAS* using data from the PRIME and PEAK trials.[7] ORR was defined as the incidence of either a confirmed CR or PR while on the first-line treatment. [10] All patients that did not meet the criteria for objective response by the analysis cut-off date were considered non-responders. [10] The data cut-off for PRIME was 24-Jan-2013 and the data cut-off for PEAK was 11-Feb-2015.[10] The treatment effect estimates for ORR were estimated using odds ratios (ORs) with corresponding 95% CIs and Wald tests to generate p-values. It should be noted that these results should be interpreted with caution because this analysis was descriptive and there was no adjustment for multiplicity.

Boeckx et al (2017) demonstrated that *RAS* wild-type carriers with left-sided tumours from PRIME who received panitumumab plus FOLFOX had a higher RR (67.9%) as compared to those treated with FOLFOX (52.6%) (Table 12).[7] There was no difference for patients with right-sided tumours from the PRIME trial (OR: 1.36 [95% CI: 0.51 to 3.62]).[7] The authors also showed that there was no treatment difference for patient with left-sided (OR: 1.33 [95% CI: 0.57 to 3.11]) or right-sided tumours (OR: 1.75 [95% CI: 0.36 to 8.39]) from the PEAK trial (OR: 1.75 [95% CI: 0.36 to 8.39)] (Table 12).[7]

Table 12: Subgroup analysis of efficacy outcomes stratified by treatment group and tumour sidedness in mCRC patients that express wild-type *RAS* using data from the PRIME and PEAK trials

Table 2. Efficacy outcomes in the *RAS* WT population

Study	Treatment	*n* patients		OS (m)		PFS (m)		RR (%)		DoR (m)	
		Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
PRIME	Pmab+	169/168[a]	39/	30.3	11.1	12.9	7.5	67.9	42.1	11.8	9.7
	FOLFOX		38[a]	(25.8, 36.1)	(8.1, 25.2)	(10.0, 14.6)	(5.5, 10.4)			(9.6, 14.8)	(3.9, 13.3)
	FOLFOX	159/156[a]	49/46[a]	23.6	15.4	9.2	7.0	52.6	34.8	9.3	7.6
				(18.2, 26.9)	(9.1, 21.7)	(7.6, 10.7)	(5.4, 8.0)			(7.7, 11.0)	(4.2, 9.4)
	Adjusted HR[b]			0.73	0.87	0.72	0.80	1.91[c]	1.36[c]		
				(0.57, 0.93)	(0.55, 1.37)	(0.57, 0.90)	(0.51, 1.26)	(1.18, 3.07)	(0.51, 3.62)		
	P-value			0.0112	0.5398	0.0048	0.3286	–	–		
PEAK	Pmab+	53/	22/	43.4	17.5	14.6	8.7	64.2	63.6	16.1	8.7
	FOLFOX	53[a]	22[a]	(31.6, 63.0)	(9.1, 30.7)	(11.6, 17.7)	(5.7, 10.9)			(11.1, 20.9)	(3.7, 14.2)
	Bmab+	54/	14/	32.0	21.0	11.5	12.6	57.4	50.0	9.5	9.2
	FOLFOX	54[a]	14[a]	(26.0, 47.4)	(6.0, 29.0)	(9.3, 13.0)	(1.8, 16.6)			(7.9, 13.8)	(5.9, 16.6)
	Adjusted HR[b]			0.77	0.67	0.68	1.04	1.33[c]	1.75[c]		
				(0.46, 1.28)	(0.30, 1.50)	(0.45, 1.04)	(0.50, 2.18)	(0.57, 3.11)	(0.36, 8.39)		
	P-value			0.3125	0.3239	0.0732	0.9085	–	–		

[a]Number of patients assessable for response.
[b]Adjusted treatment HR calculated from model with factors for *BRAF* status, prior adjuvant therapy and baseline ECOG. HR below 1 favors pmab arm (PRIME, PEAK).
[c]Odds ratio for treatment difference in RR presented. An odds ratio >1 favors the pmab arm (PRIME, PEAK).
Bmab, bevacizumab; DoR (m), duration of response in months; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; *n*, number; OS (m), overall survival in months; PFS (m), progression-free survival in months; Pmab, panitumumab; RR, response rate.

Data Source: Reproduced from Boeckx N, Koukakis R, Op De BK, Rolfo C, Van CG, Siena S, et al. Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer. Ann Oncol. 2017 Aug 1;28(8):p.1865.Creative Commons CC-BY-NC 4.0[7]

Duration of Response

Boeckx et al (2017) assessed the effect tumour sidedness on DOR in panitumumab-treated mCRC patients that express wild-type *RAS* using data from the PRIME and PEAK trials. DOR was calculated only for those patients with a confirmed objective response as time from first confirmed objective response to radiologic disease progression per modified RECIST 1.0 criteria or death.[10] For patients who responded and had not progressed or died, DOR was censored at their last evaluable disease assessment date.[10] The authors presented Kaplain-Meier curves stratified by treatment group and side with corresponding 95% CIs.[10] These results should be interpreted with caution because there are no statistical tests to determine if there is a difference between DOR for each treatment group and tumour sidedness.

The DOR appears to be longer in PRIME for *RAS* wild-type carriers with left-sided tumours ($DOR_{panitumumab\ plus\ FOLFOX}$: 11.8 months [95%: 9.6 to 14.8] vs. DOR_{FOLFOX}: 9.3 months [95%: 7.7 to 11.0]) and right-sided tumours ($DOR_{panitumumab\ plus\ FOLFOX}$: 9.7 months [95%: 3.9 to 13.3] vs. DOR_{FOLFOX}: 7.6 months [95%: 4.2 to 9.4]) (Table 12). Using data from PEAK, panitumumab plus FOLFOX treated *RAS* wild-type carriers with left-sided tumours had a longer DOR as compared to those treated with FOLFOX (DOR: 16.1 months [95%: 11.1 to 20.9] vs. DOR: 9.5 months [95%: 7.9 to 13.8]). However, *RAS* wild-type carriers with right-sided tumours treated with FOLFOX plus bevacizumab had a longer DOR than those treated with panitumumab plus FOLFOX (DOR: 9.2 months [95%: 5.9 to 16.6] vs. DOR: 8.7 months [95%: 3.7 to 14.2]) (Table 12).

Disease Control Rate

The pCODR systematic literature search did not locate any information on DCR for mCRC patients with left-sided primary tumours that express wild-type *RAS*.

Resection Rate

Geissler et al (2017) reported the treatment effect of primary tumour location on resection rates using data from PRIME and PEAK.[8] The definition of resection rates were not provided in the abstract.[8] More left-sided patients underwent resection as compared to those with right-sided tumours (Table 13).

Table 13: Subgroup analysis of resection rates, ETS and depth of response stratified by treatment group and tumour sidedness in mCRC patients that express wild-type *RAS*/*BRAF* using data from the PRIME and PEAK trials[8]

	PRIME				PEAK			
	Pmab + FOLFOX		FOLFOX		Pmab + FOLFOX		Bev + FOLFOX	
	Left (n=169)	Right (n=39)	Left (n=159)	Right (n=49)	Left (n=53)	Right (n=22)	Left (n=54)	Right (n=14)
ETS[a] ≥30%, %	62	31	36	31	58	55	41	21
Median PFS, months	14.8	14.9	11.1	7.3	16.2	10.8	12.9	18.4
Median OS, months	35.0	27.2	31.7	23.6	55.4	24.6	48.5	26.2
ETS[a] <30%, %	29	56	55	55	38	32	52	64
Median PFS, months	9.4	6.5	6.9	6.9	11.6	5.8	12.4	12.6
Median OS, months	19.9	10.6	17.2	13.1	34.2	15.3	27.7	23.3
Median DpR, %	59	37	49	50	70	50	48	45
Any resection, %	15	10	13	12	17	9	19	7
R0 resection, %	11	5	10	2	13	4	11	7

Bev, bevacizumab; DpR, depth of response; ETS, early tumour shrinkage; OS, overall survival; PFS, progression-free survival; Pmab, panitumumab; R0, complete resection; [a]ETS status was unknown for some patients

Data Source: Reproduced with a permission of S. Karger AG, Medical and Sientific Publishers, from Geissler M, Peeters M, Price T, Taieb J, Rivera F, Canon JL, et al. Impact of primary tumour location (PTL) on response and resection outcomes in metastatic colorectal cancer (mCRC) patients (pts) receiving first-line panitumumab (Pmab) treatment [abstract]. Oncology Research and Treatment. 2017;40 Suppl 3:164.[8]

Number of Cycles Completed

The pCODR systematic literature search did not locate any information on number of cycles completed for mCRC patients with left-sided primary tumours that express wild-type *RAS*.

Quality of Life

Briefly, HRQoL was assessed in the PRIME trial[57] as a tertiary outcome of interest and was not assessed in the PEAK trial.[4,5] In the PRIME trial, HRQoL was measured using the EQ-5D HSI and EQ-5D VAS.[57] The EQ-5D HSI assesses health across five dimensions that include mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Possible scores on the EQ-5D HSI range from -0.594 to 1. A change in score ≥ 0.08 has been established as the MID for the EQ-5D HSI. The EQ-5D 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 MID for the EQ-5D VAS has been established as a change in score of ≥7.

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 CIs) 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.

Although the HRQoL of the PRIME trial had been previously reported[46], the pCODR systematic literature search did not locate any published data specifically for *RAS* wild-type mCRC patients with left-sided tumours. Upon the request of the pCODR Methods Team, the Submitter provided estimates using the EQ-5D HSI and VAS scales stratified by tumour sidedness for *RAS* wild-type patients with mCRC using data from PRIME.[10]

Of the 328 *RAS* wild-type patients with a left-sided tumour from the PRIME trial[7], 90.9% of these patients (n=298) were included in the HRQoL analysis.[10] There were 155 patients in the chemotherapy plus panitumumab arm and 143 patients in the chemotherapy arm.[10]

Compliance rates for the EQ-5D HSI and the EQ-5D VAS scales were calculated using the number of evaluable assessments relative to expected assessments.[10] For patients with a left-sided tumour, the compliance rates for the EQ-5D HSI and the EQ-5D VAS scales were 57.3% and 57.2%, respectively.[10] Similar estimates were observed for *RAS* wild-type patients with a right-sided tumour (56.8% and 56.2%, respectively).[10]

The change from baseline for the EQ-5D HSI and the EQ-5D VAS scales are presented in Table 14. The Submitter reported that there were no statistically significant differences in changes from baseline for the EQ-5D HSI and EQ-5D VAS between chemotherapy plus panitumumab and chemotherapy for patients with a left or righted sided tumour (Table 14).[10] Furthermore, the MID was not met for the EQ-5D HSI and EQ-5D VAS scales in patients with a left or righted sided tumour.[10] These results should be interpreted with caution because of small sample sizes and there was no adjustment for type 1 error.

Table 14: LSM difference in changes from baseline in EQ-5D Health State Index and EQ-5D Overall Heath Rating scores (visual analogue scale) between FOLFOX4 only and Panitumumab and FOLFOX4 using linear mixed models

	PRIME			
	Left-sided Tumour		Right-sided Tumour	
	FOLFOX4	Panitumumab + FOLFOX4	FOLFOX4	Panitumumab + FOLFOX4
Health State Index				
Adjusted LS mean	-0.05254	-0.07797	-0.01011	-0.04436
95% CIs	(-0.09975, -0.005533)	(-0.1249, -0.03105)	(-0.1035, 0.08324)	(-0.1424, 0.05367)
Difference	0.02543 (-0.01683, 0.06769)		0.03426 (-0.04487, 0.1134)	
P-value	0.2364		0.3877	
Overall Health Rating (VAS)				
Adjusted LS mean	-1.7233	-3.3216	0.9372	-4.0678
95% CIs	(-5.6102, 2.1636)	(-7.1727, 0.5296)	(-6.8781, 8.7526)	(-12.3848, 4.2491)
Difference	1.5982 (-1.8737, 5.0701)		5.0051 (-1.9061, 11.9163)	
P-value	0.3652		0.1522	

Data Source: Checkpoint responses from Amgen[10]

Harms Outcomes

The pCODR systematic literature search did not locate any information on safety outcomes specifically for mCRC patients with left-sided primary tumours that express wild-type *RAS*. However, upon the request of the pCODR Methods Team, the Submitter provided safety outcomes stratified by tumour sidedness for *RAS* wild-type patients with mCRC (Table 15 and Table 16).[10] There were 416 patients and 143 patients included in the PRIME and PEAK safety analyses, respectively.

Among patients with a left-sided tumour in the PRIME trial, 100% in the chemotherapy plus panitumumab arm and 99.4% in the chemotherapy arm had any adverse event (AE) (Table 15).[10] Similar results were observed for patients with a right-sided tumour (chemotherapy plus panitumumab: 100% and chemotherapy: 100%) (Table 15). Eighty-four percent of patients with a left-sided tumour who were treated with chemotherapy plus panitumumab had a worst grade of 3 and 4 AE as compared to 70.4% of those who were treated with chemotherapy (Table 15).[10] On the other hand, 89.8% of patients with a right-sided tumour who were treated with chemotherapy plus panitumumab had a worst grade of 3 and 4 AE as compared to 77.5% of patients who were treated with chemotherapy (Table 15).[10] Regardless of therapy, more patients with a right-sided tumour had any serious AE or an AE that led to a discontinuation as compared to those with a left-sided tumour (Table 15). [10] Patients with left-sided or right-sided tumours who were treated with chemotherapy plus panitumumab were more likely to experience rash, diarrhoea or hypomagnesemia than their counterparts who were treated with chemotherapy (Table 15).[10] Following review of feedback by the Submitter and registered clinicians on the pCODR pERC Initial Recommendation, the Methods Team acknowledged that the Submitter indicated that the recommendation only looks at the issues from the viewpoint of benefit and not the potential harm from panitumumab in patients with the wrong clinical characteristic (i.e., right-sided tumour). Although there appears to be differences across tumour and treatment groups, these results should be interpreted with caution because of small sample sizes and number of events in patients with right-sided tumours. Furthermore, the focus of the current review is patients with left-sided tumours, which represents the majority of patients in the PEAK and PRIME trials.

Table 15: Summary of Adverse Events stratified by tumour location status using data from the PRIME trial

PRIME				
	Left-sided Tumours		Right-sided Tumours	
AEs	Panitumumab-FOLFOX4 (N = 169)	FOLFOX4 Alone (N = 159)	Panitumumab-FOLFOX4 (N = 39)	FOLFOX4 Alone (N = 49)
Any AE	169 (100)	158 (99.4)	39 (100)	49 (100)
Worst grade of 3	95 (56.2)	83 (52.2)	23 (59)	25 (51)
Worst grade of 4	47 (27.8)	29 (18.2)	12 (30.8)	13 (26.5)
Worst grade of 5	7 (4.1)	9 (5.7)	3 (7.7)	4 (8.2)
Any serious AE	64 (37.9)	55 (34.6)	20 (51.3)	24 (49)
AE leading to discontinuation	52 (30.8)	26 (16.4)	8 (20.5)	7 (14.3)
AEs of special interest				
Rash	102 (60.4)	13 (8.2)	18 (46.2)	2 (4.1)
Diarrhoea	112 (66.3)	76 (47.8)	29 (74.4)	31 (63.3)
Hypomagnesemia	54 (32)	8 (5)	11 (28.2)	6 (12.2)

Data Source: Checkpoint responses from Amgen[10]

Among patients with a left-sided tumour in the PEAK trial, 100% in the chemotherapy plus panitumumab arm and 100% in the chemotherapy plus bevacizumab arm had any AE (Table 16).[10] Similar results were observed for patients with a right-sided tumour (chemotherapy plus panitumumab: 100% and chemotherapy plus bevacizumab: 100%) (Table 16). The majority of patients with a left-sided tumour who were treated with chemotherapy plus panitumumab (90.5%) or with chemotherapy plus bevacizumab (77.8%) had a worst grade of 3 and 4 AE (Table 16).[10] In contrast, 86.4% of patients with a right-sided tumour who were treated with chemotherapy plus panitumumab had a worst grade of 3 and 4 AE as compared to 64.3% of patients who were treated with chemotherapy plus bevacizumab (Table 16).[10] Regardless of therapy, more patients with a right-sided tumour had any serious AE or an AE that led to a discontinuation as compared to those with a left-sided tumour (Table 16). [10] Patients with a left-sided or right-sided tumour who were treated with chemotherapy plus panitumumab were more likely to experience rash or hypomagnesemia than their counterparts who were treated with chemotherapy plus bevacizumab (Table 16).[10] Almost two-thirds of all patients had diarrhoea in the PEAK trial (Table 16).[10] Although there appear to be differences across tumour and treatment groups, these results are difficult to interpret because of small sample sizes.

Table 16: Summary of AEs stratified by tumour location status using data from the PEAK trial

PEAK				
	Left-sided Tumours		Right-sided Tumours	
AEs	**Panitumumab + mFOLFOX6 (N = 53)**	**Bevacizumab + mFOLFOX6 (N = 54)**	**Panitumumab + mFOLFOX6 (N = 22)**	**Bevacizumab + mFOLFOX6 (N = 14)**
Any AE	53 (100)	54 (100)	22 (100)	14 (100)
Worst grade of 3	35 (66)	32 (59.3)	17 (77.3)	6 (42.9)
Worst grade of 4	13 (24.5)	10 (18.5)	2 (9.1)	3 (21.4)
Worst grade of 5	2 (3.8)	3 (5.6)	3 (13.6)	2 (14.3)
Any serious AE	20 (37.7)	19 (35.2)	12 (54.5)	6 (42.9)
AE leading to discontinuation	14 (26.4)	12 (22.2)	9 (40.9)	4 (28.6)
AEs of special interest				
Rash	33 (62.3)	4 (7.4)	15 (68.2)	2 (14.3)
Diarrhoea	32 (60.4)	33 (61.1)	15 (68.2)	8 (57.1)
Hypomagnesemia	24 (45.3)	5 (9.3)	9 (40.9)	1 (7.1)

Data Source: Checkpoint responses from Amgen[10]

6.4 Ongoing Trials

No ongoing trials were identified.

7 SUPPLEMENTAL QUESTIONS

7.1 Critical appraisal of a meta-analysis and pooled analyses that assesses the efficacy of panitumumab plus chemotherapy versus active therapies for the first-line treatment of mCRC patients with left and right-sided primary tumours that express wild-type *RAS*.

Background

Several reviews have assessed the prognostic effect of tumour sidedness in patients with mCRC. These studies showed that patients with right-sided tumours have worse outcomes as compared to those with left-sided tumours, regardless of treatment.[24,58-63]

Other studies have explored the predictive effect of tumour sidedness in patients with *RAS* wild-type mCRC.[61,64] For instance, Tejpar et la (2017) performed a retrospective analysis that assessed the predictive effect of tumour sidedness among patients treated with chemotherapy (FOLFIRI) plus cetuximab versus chemotherapy alone or chemotherapy plus bevacizumab using data from the CRYSTAL (N = 364) and FIRE-3 (N = 394) trials, respectively.[64] The authors reported that there was a treatment effect in patients with left and right-sided tumours who were treated with chemotherapy plus cetuximab versus chemotherapy plus bevacizumab using data from the FIRE-3 trial (p-value for interaction: 0.009).[64] Indeed, patients who had left-sided tumours had improved OS (HR: 0.63, 95% CI: 0.48 to 0.85) while there was no difference in patients with a right-sided tumour (HR: 1.31 [95% CI: 0.81 to 2.11]).[64] On the other hand, Boeckx et al (2017) did not demonstrate a treatment effect of panitumumab in patients with left or right-sided tumours using data from the PRIME and PEAK trials.[7] However, it is likely that some of these retrospective analyses were underpowered, and therefore, the predictive effect of tumour sidedness among *RAS* wild-type mCRC patients treated with an anti-EGFR (i.e. cetuximab and panitumumab) or anti-VEGF (i.e. bevacizumab) is unknown.

Given the lack of evidence supporting the effect of panitumumab in left and right-sided tumour sidedness, the pCODR Review Team assessed the prognostic and predictive effect of tumour sidedness in wild-type *RAS* mCRC patients treated with anti-EGFR and anti-VEGF therapies.

Methods

In order to assess the prognostic and predictive effect of tumour sidedness, the pCODR Review Team assessed two reviews that were provided by the Submitter as supplemental material to inform the submitted NMA. The reviews include one systematic review by Holch et al (2017)[25] and one pooled analysis by Arnold et al (2017)[26]. It should be noted that the pCODR Review Team did not perform a formal systematic review to assess the prognostic and predictive effect of tumour sidedness in wild-type *RAS* mCRC patients.

Holch et al (2017) conducted a systematic review and meta-analysis using prospective clinical trials (13 RCTs including PRIME and PEAK as well as one prospective trial) to evaluate the prognostic and predictive effect of tumour sidedness in patients with *RAS* wild-type mCRC who received anti-EGFR and/or anti-VEGF therapy.[25] Trials were included in the systematic review if they evaluated the relevance of tumour sidedness in mCRC patients and there was no date restrictions reported. Data on primary tumour location were obtained from each trial. To locate relevant articles, the authors searched the database PubMed, major oncological conferences (American Society of Clinical Oncology, European Society for Medical Oncology and World Gastrointestinal Cancer Conferences), and hand-searching of reference lists of relevant report identified. The authors did not provide details on data extraction or whether the risk of bias was assessed for individual studies; however they did assess publication bias.

Holch et al (2017) reported OS and PFS using HRs, corresponding 95% CIs and p-values while ORR was reported using medians, odds ratios (ORs) with corresponding 95% CIs and p-values.[25] The authors used

fixed and random effects models to calculate the weighted overall effect estimates for OS, PFS and ORR. Heterogeneity was assessed using Cochran's Q-test and the I^2 statistics and it was explored by comparing the fixed and random effects models. The authors tested the predictive effect of tumour sidedness in patients treated with anti-EGFRs or anti-VEGF therapies using a meta-regression. Follow-up times and time of recruitment were also incorporated into the meta-regression to identify potential bias.

Arnold et al (2017) performed a retrospective pooled analysis to assess the prognostic and predictive effects of tumour sidedness in patients with *RAS* wild-type mCRC who had received first or second-line chemotherapy with or without anti-EGFR therapy in six RCTs, including PRIME and PEAK.[26] Patients were included in the analysis if they were *RAS* wild-type carriers (i.e. K*RAS* exon 2-4; N*RAS* exon 2-4). Primary tumours were classified as left-sided if they were located in the splenic flexure, descending colon, sigmoid colon and rectum while tumours were classified as right-sided if they were located in the appendix, caecum, ascending colon, hepatic flexure and transverse colon. However, the CALGB 80405 trial excluded patients who had a primary tumour in the transverse colon. Data on primary tumour location were obtained from the patients' case report forms from each trial.

All of the analyses conducted in Arnold et al (2017) were retrospective.[26] OS and PFS were reported using HRs, corresponding 95% CIs and p-values while ORR was reported using ORs with corresponding 95% CIs and p-values. The authors assessed the prognostic effect of tumour sidedness on OS, PFS and ORR by comparing the experimental arms and control arms separately. On the other hand, the authors tested the predictive effect of tumour sidedness in patients treated with anti-EGFRs using an interaction test using likelihood ratio test within Cox proportional hazards and logistic regression models. The effect estimates of interaction for OS, PFS and ORR were pooled using a fixed effects model. The effect estimates of OS and PFS for both analyses were adjusted according to covariates that accounted for the difference between studies but the effect estimates of ORR were not adjusted. Estimates were pooled based on a two-step analysis. Heterogeneity was evaluated with a Cochrane test ($P < 0.10$) and I^2 statistics. The authors used fixed effects models to calculate the weighted overall effect estimates for OS, PFS and ORR if there was no evidence of heterogeneity. The authors conducted sensitivity analysis to account for differences in patient characteristics (i.e. study phase and treatment line). In addition, the authors also explored the predictive effect of tumour sidedness in patients treated with anti-EGFRs for each individual study included in the analysis.

Results

The study characteristics of the Holch et al (2017)[25] and Arnold et al (2017)[26] analyses are presented in Table 1 and Table 2. Holch et al (2017) conducted a systematic review and a meta-analysis using 13 RCTs and one prospective trial[25] while Arnold et al (2017) conducted a retrospective pooled analysis using six RCTs[26]. All of the studies identified in Holch et al (2017)[25] and five of the trials in Arnold et al (2017)[26] were conducted in the first-line setting. The length of follow-up for all of the trials included in Holch et al (2017) ranged from 18.4 to 150 months,[25] this information was not reported in Arnold et al (2017)[26]. The sample size of the trials included in Holch et al (2017)[25] ranged from 110 to 1,390 while it ranged from 143 to 474 in Arnold et al (2017)[26].

Table 1: Summary of the trials included in the Holch et al (2017) systematic review[25]

Study	Biomarker population	Treatment arms	Number of patients	Percentage of patients with RC	Demarcation line of PTL	Year of initial publication	Recruitment	Follow-up (months)
NO16966 [16]	(K)RAS/BRAF unselected	CapOx/FOLFOX CapOx/FOLFOX + bev	1268	26.3	Splenic flexure	2008	2004–2005	57
FIRE-1 [12]	(K)RAS/BRAF unselected	FuFIRI mIrOx	423	19.4	Splenic flexure	2011	2000–2004	60
FOCUS [15]	(K)RAS/BRAF unselected	FU IrFu OxFu	1390	n.r.	n.r.	2009	2000–2003	150
AVF2107g [16]	(K)RAS/BRAF unselected	IFL IFL + bev	559	36.9	Splenic flexure	2004	2000–2002	33
AGITG MAX [14]	(K)RAS/BRAF unselected	Cap Cap + bev Cap + Mito + bev	440	28.2	Transverse colon (excluded)	2010	2005–2007	42
PROVETTA [16]	(K)RAS/BRAF unselected	FOLFIRI + bev	200	28.0	Splenic flexure	n.r.	n.r.	54
MAVERICC [30]	KRAS WT/ BRAF unselected	FOLFOX + bev FOLFIRI + bev	376	41.0	n.r.	n.r.	n.r.	18.4
FIRE-2 [13]	KRAS WT/ BRAF unselected	CapOx + cet CapIri + cet	146	31.5	Splenic flexure	2011	2004–2006	60
JACCRO-CC 05/06 [18]	KRAS WT/ BRAF unselected	FOLFOX/SOX + cet	110	18.2	Splenic flexure	2016	2010–2013	48
CRYSTAL [21]	RAS WT/ BRAF unselected	FOLFIRI FOLFIRI + cet	364	23.1	Splenic flexure	2009	2004–2005	60
PRIME [29]	RAS WT/ BRAF unselected	FOLFOX FOLFOX + pani	416	21.2	Splenic flexure	2010	2006–2008	68
CALGB/SWOG 80405 [19]	RAS WT/ BRAF unselected	FOLFOX/FOLFIRI + bev FOLFOX/FOLFIRI + cet	474	31.4	Transverse colon (excluded)	n.r.	2005–2012	108
FIRE-3 [21]	RAS WT/ BRAF unselected	FOLFIRI + cet FOLFIRI + bev	394	22.3	Splenic flexure	2014	2007–2012	72
PEAK [29]	RAS WT/ BRAF unselected	FOLFOX + bev FOLFOX + pani	143	25.2	Splenic flexure	2014	2009–2011	68

Abbreviations: PTL, primary tumour location; LC, left-sided colorectal cancer; RC, right-sided colorectal cancer; WT, wild-type; Cap, capecitabine; F(U), fluorouracil; FOL, folinic acid; I(RI), irinotecan; OX, oxaliplatin; Mito, mitomycin C; S, teysuno (S1); L, leucovorin; bev, bevacizumab; cet, cetuximab; pani, panitumumab; n.r., not reported.

Data Source: Reprinted from Eur J Cancer, vol.70 Holch,J.W. et al. The relevance of primary tumour location in patients with metastatic colorectal cancer: A meta-analysis of first-line clinical trials, page no. 90, Copyright (2017), with permission from Elsevier[25]

Table 2: Summary of (A) first-line and (B) second-line trials included in Arnold et al (2017) retrospective pooled analysis[26]

(A) First-line trials

Parameter	CRYSTAL (ESMO) (*RAS* wt)				PRIME (*RAS* wt)				PEAK (*RAS* wt/*BRAF* wt)				FIRE-3 (*RAS* wt)				*CALGB 80405 (RAS wt)*	
	FOLFIRI *N* = 189		FOLFIRI + cetux* *N* = 175		FOLFOX4 *N* = 208		FOLFOX4 + pani *N* = 208		FOLFOX6 + beva *N* = 68		FOLFOX6 + pani *N* = 75		FOLFIRI + beva *N* = 199		FOLFIRI + cetux *N* = 195		Both arms *N* = 474	
	R *n*=51	L *n*=138	R *n*=33	L *n*=142	R *n*=49	L *n*=159	R *n*=39	L *n*=169	R *n*=14	L *n*=54	R *n*=22	L *n*=53	R *n*=50	L *n*=149	R *n*=38	L *n*=157	R *n*=149	L *n*=325
Age, median years	59	58	61	60	61	62	62	61	66	60	64	60	66	63	68	64	61.7*	57.1*
Gender (Male, %)	47	70	48	65	NA	NA	NA	NA	NA	NA	NA	NA	56	70	63	76	48.9	70.1
ECOG, % 0 1 2	 63.0 33.0 4.0	 59 37 4	 39 61 0	 59 38 4	 55.1 38.8 6.1	 56.3 38.4 5.7	 56.4 38.5 5.1	 62.7 33.1 4.1	 64.3 35.7 0	 64.8 35.2 0	 45.5 54.5 0	 69.8 30.20	 54 44 2	 55 44 1	 39 58 3	 58 41 1	NA	NA
Prior adjuvant %	22	22.0	30	20.0	20.4	16.4	25.6	17.2	28.6	24.1	18.2	15.1	12	21	16	20	10.7	15.0
Liver metastases %	NA	NA	NA	NA	71.4	67.9	53.8	70.4	64.3	38.9	59.1	39.6	NA	NA	NA	NA	63.2	74.3
Liver metastases only, %	16	28	15	26	10.2	19.5	15.4	19.5	28.6	27.8	18.2	34.0	30	32	32	38	28.8	37.4
Extra-hepatic metastases only, %	NA	NA	NA	NA	18.4	12.6	30.8	10.1	7.1	33.3	22.7	26.4	NA	NA	NA	NA	36.7	25.6
BRAF mt, %	NA	NA	NA	NA	33.3	4.1	32.7	5.0	7.1	1.9	40.9	1.9	NA	NA	NA	NA	NA	NA

* Denotes mean age.

Data source: Arnold D, Lueza B, Douillard JY, Peeters M, Lenz HJ, Venook A, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Supplementary Tables. Ann Oncol. 2017 Aug 1;28(8):1713-29. Reproduced by permission of the Oxford University Press on behalf of the European Society for Medical Oncology.[26]

(B) Second-line trials

Parameter	**20050181(*RAS* wt)**			
	FOLFIRI ***N* = 187**		**FOLFIRI** **+ panitumumab** ***N* = 181**	
	Right-sided ***n* = 39**	**Left-sided** ***n* = 148**	**Right-sided** ***n* = 31**	**Left-sided** ***n* = 150**
Median age, years	62	60	60	61
ECOG 0 1 2	 48.7 43.6 7.7	 52.0 41.2 6.8	 35.5 54.8 9.7	 52 44 4
Prior adjuvant, %	15.4	16.2	29.0	20.7
Liver metastases, %	69.2	60.8	64.5	68.0
Liver metastases only, %	12.8	24.3	9.7	19.3
Extra-hepatic metastases only, %	17.9	14.9	25.8	12.7
BRAF mt, %	33.3	2.7	29.0	4.7

ECOG, Eastern Cooperative Oncology Group; FOLFIRI, fluorouracil, leucovorin and irinotecan; mt, mutant; wt, wild-type

NA, not available; ECOG, Eastern Cooperative Oncology Group; FOLFIRI, fluorouracil, leucovorin and irinotecan; mt, mutant; wt, wild-type
Data source: Arnold D, Lueza B, Douillard JY, Peeters M, Lenz HJ, Venook A, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Supplementary Tables. Ann Oncol. 2017 Aug 1;28(8):1713-29. Reproduced by permission of the Oxford University Press on behalf of the European Society for Medical Oncology.[26]

Arnold et al (2017) included 2,159 wild-type *RAS* patients (37.6%) with a known primary tumour location[26]; however, these values were not reported in Holch et al (2017)[25]. Patients with a right-sided tumour ranged from 18.2% to 41.0% in Holch et al (2017)[25] while 23.9% of patients had a right-sided tumour in Arnold et al (2017)[26]. Arnold et al (2017) reported that there was an imbalance between patients with a right-sided tumour across all trials; whereas Holch et al (2017) did not comment.[25,26]

Both of the reviews assessed the prognostic and predictive effect of tumour sidedness in patients with mCRC. Holch et al (2017) included data from 13 RCTs when testing the prognostic effect of tumour sidedness; however, only five trials were used when exploring the predictive effect of tumour sidedness (i.e. PRIME, CRYSTAL, CALGB/SWOG 80405, FIRE-3 AND PEAK).[25] On the other hand, Arnold et al (2017) used six trials in both the prognostic and predictive analyses (i.e. PRIME, CRYSTAL, 20050181, CALGB/SWOG 80405, FIRE-3 AND PEAK).[26]

Prognostic effect of tumour sidedness in patients with mCRC

Holch et al (2017) assessed the prognostic effect of primary tumour location in patients with mCRC.[25] The authors reported that patients with right-sided tumours had a poorer prognosis as compared to those with left-sided tumours on OS in 14 trials using a random effects model (HR: 1.56, 95% CI: 1.43 to 1.7; P <0.0001; I^2=46.9%).[25] Similar results were observed for PFS in 12 trials using a random effects model (HR: 1.33, 95% CI: 1.20 to 1.48; P <0.0001; I^2=54.8%).[25] The authors noted that there was significant heterogeneity among the pooled estimates of OS (I^2=46.9%) and PFS (I^2=54.8%). In order to explore the heterogeneity, Holch et al (2017) conducted a meta-regression. A meta-regression was conducted because it can help to explain how the treatment effect on OS or PFS will differ according to a unit change in an effect modifier, such as tumour sidedness.[65] Holch et al (2017) reported that the use of cetuximab was able to be explained with resulting residual heterogeneity for the OS estimate (I^2=7.7%). In other words, patients with a right-sided tumour who were treated with cetuximab plus chemotherapy had a poorer OS and PFS as compared to patients with a left-sided tumour (OS - P for interaction: 0.005 and PFS - P for interaction: 0.04).[25]

Arnold et al (2017) assessed the prognostic effect of tumour sidedness in each of the six trials included in the pooled analysis and for patients who were treated with 1) chemotherapy alone or chemotherapy plus bevacizumab or 2) chemotherapy plus cetuximab or chemotherapy plus panitumumab.[26] The prognostic effect of tumour sidedness was assessed by comparing the independent effects of the experimental and control arms on OS, PFS and ORR estimates. For the comparison between chemotherapy alone or chemotherapy plus bevacizumab, the authors reported that patients with right-sided tumours had a poorer prognosis as compared to those with left-sided tumours for OS (HR: 1.38, 95% CI: 1.17 to 1.63; P <0.001; I^2=12%), PFS (HR: 1.25, 95% CI: 1.06 to 1.47; P=0.008; I^2=0%) and ORR (OR: 0.56, 95% CI: 0.43 to 0.73; P <0.001; I^2=0%) using a fixed effects model. Similarly, those treated with chemotherapy plus cetuximab and/or panitumumab with a right-sided tumours had a poorer prognosis as compared to those with left-sided tumours for OS (HR: 2.03, 95% CI: 1.69 to 2.42; P <0.001; I^2=0%), PFS (HR: 1.59, 95% CI: 1.34 to 1.88; P<0.001; I^2=0%) and ORR (OR: 0.38, 95% CI: 0.28 to 0.50; P <0.001; I^2=48%) using a fixed effects model. It should be noted that Arnold et al (2017) pooled the effect of OS, PFS and ORR among five first-line trials and one second-line trial, which could increase the heterogeneity among the pooled estimates. Furthermore, these results should be interpreted with caution because the experimental and control arms from the six trials were treated independently, which breaks the randomization of the original trials. Breaking randomization will increase the risk of bias in the Arnold et al (2017) analysis because differences in response may reflect differences in the baseline risk and it fails to separate the effect from the intervention and control arms from other possible placebo effects.[66-68] Thus, the randomization that was initially performed in the six trials that were included in Arnold et al (2017) will be violated and the estimates from the pooled analysis will be confounded.

Predictive effect of tumour sidedness in patients with mCRC

Holch et al (2017) assessed the predictive effect of primary tumour location on OS, PFS and ORR in mCRC patients treated with anti-EGFR antibodies using data from two RCTs (i.e. PRIME and CRYSTAL).[25]

The CRYSTAL trial assessed the effect of chemotherapy plus cetuximab versus chemotherapy (N = 364) and the PRIME trial tested the effect of chemotherapy plus panitumumab versus chemotherapy (N = 416). Holch et al (2017) reported that the interaction test between anti-EGFR therapy and tumour sidedness was not significant for OS (P=0.10), PFS (P = 0.30) and ORR (P=0.20). The results suggest that there were no differences between patients with left-sided and right-sided tumours who were treated with anti-EGFR therapy. Additionally, the authors also explored the predictive effect of tumour sidedness on OS, PFS and ORR in mCRC patients treated with anti-EGFR or anti-VEGF antibodies using three RCTs (i.e. FIRE-3, CALGB/SWOG 80405, and PEAK).[25] Both the FIRE-3 and the CALGB/SWOG 80405 trials compared the effect of chemotherapy plus cetuximab versus chemotherapy plus bevacizumab (N = 394 and N = 474) while the PEAK trial compared chemotherapy plus panitumumab versus chemotherapy plus bevacizumab (N = 143). It was noted in the Submitter's NMA that the effect estimates for PEAK in the Holch et al (2017) analysis were incorrect.[48] Holch et al (2017) reported that the interaction test between anti-EGFR or anti-VEGF therapies and tumour sidedness were significant for OS (P<0.001), PFS (P<0.001) but not for ORR (P=0.41). This indicates that patients with a left-sided tumour experienced a protective effect of anti-EGFR or anti-VEGF therapies on OS and PFS as compared to those with right-sided tumour. Although these estimates demonstrate that treatment with an anti-EGFR or an anti-VEGF therapy is more beneficial in patients with left-sided tumours, these estimates represent a class effect so it is difficult to distinguish the effect of panitumumab or cetuximab.

Arnold et al (2017) also assessed the predictive effect of tumour sidedness on OS, PFS and ORR in mCRC patients who were treated with chemotherapy plus anti-EGFR (experimental arm) and either chemotherapy alone or chemotherapy plus bevacizumab (control).[26] To assess the predictive treatment effect on tumour sidedness, the authors conducted interaction tests using likelihood ratio test within Cox proportional hazards and logistic regression models. The effect estimates of interaction for OS, PFS and ORR were pooled using a fixed effects model. First, the authors assessed the predictive effect of tumour sidedness among the six RCTs that were included in the pooled analysis. For the trials that compared chemotherapy plus panitumumab to chemotherapy (i.e. PRIME and 20050181) and the trial that compared chemotherapy plus panitumumab to chemotherapy plus bevacizumab (i.e. PEAK), the effect of panitumumab did not differ among patients with a left or right-sided tumour for OS, PFS and ORR (P for interaction ≥ 0.05 for all). Secondly, among the six pooled trials, the predictive effect of chemotherapy plus anti-EGFR to chemotherapy alone and/or chemotherapy plus bevacizumab was significantly different for patients with a left or right-sided tumour for OS ($HR_{\text{left-sided tumour}}$: 0.75 [95% CI: 0.67 to 0.84] vs. $HR_{\text{right-sided tumour}}$: 1.12 [95% CI: 0.87 to 1.45]; P for interaction < 0.001) and PFS ($HR_{\text{left-sided tumour}}$: 0.78 [95% CI: 0.70 to 0.87] vs. $HR_{\text{right-sided tumour}}$: 1.12 [95% CI: 0.87 to 1.44]; P for interaction: 0.002). There was no difference between tumour sidedness and treatment for ORR (P for interaction: 0.07). Sensitivity analyses exploring the effect of anti-EGFR therapy (i.e. cetuximab and panitumumab) as compared to chemotherapy alone demonstrated that cetuximab maintained a significant predictive effect (P < 0.001) while the effect was attenuated for panitumumab (P = 0.47). These results suggest that patients with left-sided tumours may benefit from treatment with an anti-EGFR as compared to those with a right-sided tumour; however, this effect is more pronounced in patients treated with cetuximab. The pooled estimates should be interpreted with caution because the analysis was retrospective, there were imbalances in tumour sidedness across treatment arms which may be due to small sample sizes, adjustment for covariates across studies and the inclusion of second-line trials.

Discussion

Overall, the Holch et al (2017) and Arnold et al (2017) analyses have shown that tumour sidedness may be a prognostic factor but there is still some uncertainty with regards to the predictive effect of tumour sidedness.[7,26]

Both reviews demonstrated that *RAS* wild-type mCRC patients with a left-sided tumour have improved OS, PFS and ORR as compared to those with a right-sided tumour regardless of treatment.[25,26] These results have been supported by previous analyses.[58,63,69-71] However, the results from the meta-analysis and retrospective analysis should be interpreted with caution because of small sample sizes, uncontrolled confounders (i.e. *BRAF* status), breaking randomization and heterogeneity among

treatment groups. Thus, it would appear that *RAS* wild-type mCRC patients who have a left-sided tumour have better outcomes as compared to their right-sided counterparts.

Likewise, both Arnold and Holch showed that anti-EGFR therapies exerted a beneficial class effect in patients with left-sided tumors as compared to those with right-sided tumours.[7,26] It should be noted that both authors assessed the class effect of anti-EGFRs[72] rather than exploring the independent effects of cetuximab or panitumumab. Although cetuximab and panitumumab have similar mechanism of action and pharmacological effect, it is difficult it determine whether the treatment effect of anti-EGFRs was driven by cetuximab or by panitumumab.[72,73] Arnold et al (2017) reported that the treatment effect of panitumumab did not differ for patients with left-sided or right-sided tumours on OS, PFS and ORR using data from the PRIME, PEAK and 2005181 trials (P-value for interaction ≥ 0.05 for all).[26] These results were also observed in Boeckx et al (2017).[7] On the other hand, there was a more pronounced effect of cetuximab in patients with left-sided tumours on OS and PFS using data from the FIRE-3 and CALGB 80405 trials (P-value for interaction ≥ 0.05 for all).[26] Taken together, there is evidence to support the predictive effect of tumour sidedness in patients treated with anti-EGFRs; however, it is difficult to extrapolate the class effect[74] of anti-EGFRs because there is still uncertainty in magnitude of effect for panitumumab or cetuximub. Thus, there is a need for more long-term RCTs that stratify by tumour location in order to determine the predictive effect of tumour sidedness in *RAS* wild-type patients with mCRC.

7.2 Critical appraisal of a manufacturer-submitted network meta-analysis (NMA) that assesses the efficacy of panitumumab plus chemotherapy versus active therapies for the first-line treatment of mCRC patients with left-sided primary tumours that express wild-type *RAS*.

Background

The pCODR systematic literature search identified two retrospective analyses that assessed the efficacy of chemotherapy plus panitumumab in patients with wild-type *RAS* mCRC with left-sided tumours.[7,8] Thus, there is a lack of direct evidence comparing chemotherapy with panitumumab to other active anti-cancer agents for the first-line treatment of mCRC patients with left-sided primary tumours that express wild-type *RAS*. Given the absence of head-to-head trials, the Submitter conducted a NMA.

No other indirect treatment comparisons have been conducted to chemotherapy with panitumumab to other therapeutic agents.

The objective of this section is to summarize and critically appraise the submitted NMA that provides evidence for the efficacy of chemotherapy with panitumumab in the first-line treatment of *RAS* wild-type mCRC patients with left-sided tumours.[48]

Review of Submitter's NMA

Objectives

The NMA was conducted by the Submitter to address two objectives:

- What is the comparative efficacy of chemotherapy plus panitumumab relative to chemotherapy alone, chemotherapy plus cetuximab, and chemotherapy plus bevacizumab in the treatment of wild-type *RAS* mCRC with left-sided tumours in the first-line treatment setting?
- What is the comparative efficacy of chemotherapy plus anti-EGFR (panitumumab or cetuximab) relative to chemotherapy alone, and chemotherapy plus anti-VEGF (bevacizumab) in the treatment of wild-type *RAS* mCRC with left-sided tumours in the first-line treatment setting?

Cetuximab was not considered a relevant comparator in the present pCODR review as suggested by the systematic review protocol because of its use in later lines of therapy in Canada. Thus, this present pCODR review will only present and critically appraise the treatment level NMA and not the class-level NMA.

Study Eligibility and Selection Process

The Submitter conducted a systematic review to identify eligible studies (criteria in Table 1) for the NMA.[48]

Table 1: Summary of PICOS Criteria for the Systematic Review and NMAs

Item	Description
Population	First line WT RAS mCRC with left-sided tumour.
Intervention	Panitumumab + chemotherapy (FOLFOX or FOLFIRI)
Comparators	**Treatment level:** Chemotherapy alone Chemotherapy + cetuximab Chemotherapy + Bevacizumab **Class level:** Chemotherapy alone Chemotherapy + anti-EGFR Chemotherapy + anti-VEGF
Outcomes	• PFS • OS
Study design	NMA of published RCTs

KEY: EGFR = epidermal growth factor receptor; FOLFIRI = FOL– Folinic acid F – Fluorouracil IRI – Irinotecan; FOLFOX = FOL– Folinic acid F – Fluorouracil OX – Oxaliplatin; mCRC = metastatic colorectal cancer; NMA = network meta-analysis; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; VEGF = vascular endothelial growth factor; WT = wild-type.

Data Source: NMA Report (2017)[48]

The following databases were searched for the systematic review: Ovid MEDLINE® (1946 to present), including Epub Ahead of Print and In-Process & Other Non-Indexed Citations, Embase (1988 to present) and EBM Reviews - Cochrane Central Register of Controlled Trials (March 2017). The search strategy was performed using a combination of controlled vocabulary and keywords and it was modified across databases. An amended RCT filter from Cochrane was also applied to the search. Studies that reported animal data or opinion pieces were excluded. The search was conducted on May 6, 2017.

The Submitter stated that two reviewers worked independently to screen titles and abstracts, as well as full text articles. The reviewers collected information on the study design (i.e. ClinicalTrials.gov Identifier, related publications and authors, year of study, interventions, and follow-up) and patient characteristics (i.e. median age, primary tumour location, liver metastases, prior adjuvant therapy, number of metastatic sites). The risk of bias was explored using the Cochrane Collaboration's tool for assessing the risk of bias.

Network Meta-Analysis Methodology

Prior to conducting an NMA, three assumptions must be met: heterogeneity, transitivity and consistency.[75] The Submitter commented that they were unable to explore heterogeneity due to a limited number of studies included in the NMA. For the transitivity assumption, the Submitter provided a descriptive comparison of the baseline characteristics across all of the trials included the NMA. Finally, to assess consistency, the Submitter compared the deviance information criterion (DIC) statistics using fitted consistency and inconsistency models; they plotted the posterior mean deviances of both the inconsistency and consistency models; and reported the qualitative estimates from the meta-analyses and pooled analysis of direct evidence.

Once the assumptions were tested, the Submitter performed two NMAs, a treatment-level NMA and a class-level NMA. The treatment-level NMA compared chemotherapy plus panitumumab relative to chemotherapy alone, chemotherapy plus cetuximab, and chemotherapy plus bevacizumab. The class-level NMA assessed the efficacy of chemotherapy with anti-EGFR (panitumumab or cetuximab) relative to chemotherapy alone, and chemotherapy with anti-VEGF (bevacizumab).

The Submitter used a Bayesian approach to conduct the treatment-level and class-level NMAs for each outcome. This was achieved by performing burn-in samples of more than 40,000 iterations and subsequent sampling iterations of 40,000 iterations or more using WinBugs. Estimates from the NMA

were obtained using both fixed and random-effects models but the final estimates and corresponding 95% credible intervals (CrI) were presented using a fixed effects model. A fixed effects model was used for the NMA because using a vague prior in a random effects model widens the CrIs.

Results

Included studies

The systematic review identified a total of 1,782 citations. Among those articles, 1,554 articles were included for title and abstract screening and the Submitter performed full-text screening of 304 articles.[48] From the full-text screening, 282 publications were excluded because of the intervention/comparator of interest (N=55), outcomes (N=53), population of interest (N=31), study design (N=60), SLR/meta-analysis design (N=26), full text not available (N=22) and left-sided tumour data not available (N=35). In total, 22 publications were included, which represents five unique studies. These five unique trials include: FIRE-3 (NCT00433927), PRIME (NCT00364013), PEAK (NCT00819780), CRYSTAL (NCT00154102) and CALGB/SWOG 80405 (NCT00265850) (Table 2).

The Submitter obtained the estimates of tumour sidedness in panitumumab-treated *RAS* wild-type patients from two meta-analyses (i.e. Holch and Arnold).[25,26] The Submitter noted that Holch et al (2017) used incorrect values for the estimates of PFS and OS from the PEAK trial.[25] In addition, Arnold et al (2017) included a second-line study, which lead to different results from the class-level NMA.[26]

Table 2: Trials included in the NMA

Trial/Study (NCT Number)	Comparison	Reference
FIRE-3 (NCT00433927)	FOLFIRI + bevacizumab vs. FOLFIRI + cetuximab	Heinemann et al., 2014[1]
PRIME (NCT00364013)	FOLFOX vs. FOLFOX + panitumumab.	Douillard et al., 2010[2]
PEAK (NCT00819780)	FOLFOX + bevacizumab vs. FOLFOX + panitumumab.	Schwartzberg et al., 2014[3]
CRYSTAL (NCT00154102)	FOLFIRI vs. FOLFIRI + cetuximab	Van Cutsem et al., 2009[4]
CALGB/SWOG 80405 (NCT00265850)	FOLFOX/FOLFIRI + bevacizumab vs. FOLFOX/FOLFIRI + cetuximab	Venook et al., 2014[5]

KEY: FOLFIRI = FOL– Folinic acid F – Fluorouracil IRI – Irinotecan; FOLFOX = FOL– Folinic acid F – Fluorouracil OX – Oxaliplatin.

Data Source: NMA Report (2017)[48]

Trial characteristics

Details of the populations, interventions, comparators and outcomes used in PRIME, PEAK, FIRE-3, CRYSTAL and CALGB/SWOG 80405 are reported in Table 3. The proportion of patients with a *RAS* wild-type status and a confirmed tumour side ranged from 30.4% in CRYSTAL to 66.6% in FIRE-3 (Table 3). In addition, 35.2% and 50.2% of patients in PRIME and PEAK had their *RAS* wild-type status and tumour side confirmed. Table 4 presents the baseline characteristics according to tumour location (right versus left) for patients receiving first-line therapy.

Table 3: Summary of the study and patient characteristics included in the NMA

Trial Name	First Author and Year of Publication (Primary Analysis Results)	Phase of Trial	Blinding	Biomarker Population	Treatment Line	Treatment Arms	Sample size	Median Age (years)	% Male	ECOG PS 0/1/2 (%)	Primary tumour location: Colon/ Rectum (%)	Liver only metastatic disease (%)	Prior adjuvant therapy (%)	Number of metastatic sites: 1 or 2 (%)	Median duration of follow-up (months)	Number of patients with RAS WT and tumour side confirmed	Patients with right-sided colorectal cancer (%)
FIRE-3	Heinemann 2014[1]	3	Open-label	KRAS WT/BRAF unselected	1st	FOLFIRI + bev FOLFIRI + cet	295 297	65 64	66 72	54/45/1 52/46/2	60/36*** 57/39	32 31	19 22	42**** 40	72	394	22.3
PRIME	Douillard 2010[2]	3	Open-label	KRAS WT/BRAF unselected	1st	FOLFOX FOLFOX + pani	590 593	61 62	62 67	56/38/6**	65/35 66/34	17 18	17 16	55 55	68	416	21.2
PEAK	Schwartzberg 2014[3]	2	Open-label	KRAS WT/BRAF unselected	1st	FOLFOX + bev FOLFOX + pani	143 142	61 63	67 61	64/36/0 63/37/0	64/36 68/32	27 26	NA	73 72	68	143	25.2
CRYSTAL	Van Cutsem 2009[4]	3	Open-label	KRAS WT/BRAF unselected	1st	FOLFIRI FOLFIRI + cet	599 599	61 61	55 61	59/37/4 58/38/4	59/41*** 55/44	18 20	17 19	85 86	60	364	23.1
CALGB/SWOG 80405	Venook 2014[5]*	3	Open-label	KRAS WT/BRAF unselected	1st	FOLFOX/FOLFIRI + bev FOLFOX/FOLFIRI + cet	559 578	59 59	62 60	NA	NA	NA	NA	NA	108	474	31.4

*Abstract only. **All randomly assigned patients. ***Remaining patients with 'colon or rectum' as the site of primary tumour, or with missing data. ****Patients with one metastatic site.
Note: Patient characteristics reported for KRAS WT patients unless otherwise noted.
KEY: bev = bevacizumab; cet = cetuximab; ECOG PS = Eastern Cooperative Oncology Group performance status; FOLFIRI = FOL– Folinic acid F – Fluorouracil IRI – Irinotecan; FOLFOX = FOL– Folinic acid F – Fluorouracil OX – Oxaliplatin; NA = not available; pani = panitumumab; WT = wild-type.

Data Source: NMA Report (2017)[48]

Table 4: Baseline characteristics according to tumour location (right versus left) for patients receiving first-line therapy

	CRYSTAL				PRIME				PEAK				FIRE-3				CALGB/SWOG 80405*	
	FOLFIRI N = 189		FOLFIRI + cet N =175		FOLFOX N = 208		FOLFOX + pani N = 208		FOLFOX + bev N = 68		FOLFOX + pani N = 75		FOLFIRI + bev N =199		FOLFIRI + cet N = 195		Both arms N = 474	
	R n=51	L n=138	R n=33	L n=142	R n=49	L n=159	R n=39	L n=169	R n=14	L n=54	R n=22	L n=53	R n=50	L n=149	R n=38	L n=157	R n=149	L n=325
Age (median, years)	59	58	61	60	61	62	62	61	66	60	64	60	66	63	68	64	61.7**	57.1**
Gender (male, %)	47	70	48	65	NA	NA	NA	NA	NA	NA	NA	NA	56	70	63	76	48.9	70.1
ECOG (%)																		
0	63	59	39	59	55.1	56.3	56.4	62.7	64.3	64.8	45.5	69.8	54	55	39	58	NA	NA
1	33	37	61	38	38.8	38.4	38.5	33.1	35.7	35.2	54.5	30.2	44	44	58	41		
2	4	4	0	4	6.1	5.7	5.1	4.1	0	0	0	0	2	1	3	1		
Prior adjuvant therapy (%)	22	22	30	20	20.4	16.4	25.6	17.2	28.6	24.1	18.2	15.1	12	21	16	20	10.7	15.0
Liver metastases (%)	NA	NA	NA	NA	71.4	67.9	53.8	70.4	64.3	38.9	59.1	39.6	NA	NA	NA	NA	63.2	74.3
Liver metastases only (%)	16	28	15	26	10.2	19.5	15.4	19.5	28.6	27.8	18.2	34.0	30	32	32	38	28.8	37.4
Extra-hepatic metastases only (%)	NA	NA	NA	NA	18.4	12.6	30.8	10.1	7.1	33.3	22.7	26.4	NA	NA	NA	NA	36.7	25.6
BRAF mt (%)	NA	NA	NA	NA	33.3	4.1	32.7	5.0	7.1	1.9	40.9	1.9	NA	NA	NA	NA	NA	NA

*Abstract only. **Denotes mean age.
KEY: bev = bevacizumab; cet = cetuximab; ECOG (PS) = Eastern Cooperative Oncology Group (performance status); FOLFIRI = FOL– Folinic acid F – Fluorouracil IRI – Irinotecan; FOLFOX = FOL– Folinic acid F – Fluorouracil OX – Oxaliplatin; mt = mutant; NA = not available; pani = panitumumab.
Source: Arnold et al., 2017.[12]

Data Source: NMA Report (2017)[48] and Arnold D, Lueza B, Douillard JY, Peeters M, Lenz HJ, Venook A, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Supplementary tables. Ann Oncol. 2017 Aug 1;28(8):1713-29. Reproduced by permission of the Oxford University Press on behalf of the European Society for Medical Oncology.[26]

The risk of bias for all the included trials was assessed using the Cochrane Collaboration's tool for assessing risk of bias (Figure 2). The Submitter reported that all included trials were open-label and the lack of blinding may bias the interpretation of subjective outcomes, such as PFS.

Figure 2: Risk of bias assessment

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
FIRE-3	+	+	−	−	+	+	+
PRIME	?	?	−	+	+	+	+
PEAK	+	?	−	?	+	+	+
CRYSTAL	+	?	−	+	?	+	+
CALGB/SWOG 80405	?	?	−	?	?	?	?

Based on Cochrane Collaboration's tool for assessing risk of bias.[57] Note that all studies were open-label.

Data Source: NMA Report (2017)[48]

The direct estimates of OS and PFS are presented in Table 5 and Table 6. The Submitter reported that chemotherapy plus panitumumab was associated with increased PFS as compared to chemotherapy in the *RAS* wild-type left-sided tumour subgroup from PRIME (Table 5). Similar results were observed in the CRYSTAL trial. There were no statistically significant treatment differences for PFS in the PEAK, CALGB/SWOG 80405 or FIRE-3 trials ($p > 0.05$ for all). Additionally, chemotherapy plus panitumumab was associated with increased OS as compared to chemotherapy (Table 6). Similar estimates were observed in the CRYSTAL, PEAK, CALGB/SWOG 80405 and FIRE-3 trials (Table 6). There was no difference in the treatment effect for OS using data from the PEAK trial.

Table 5: Summary of direct (A) PFS and (B) OS in the wild-type *RAS* with left-sided tumour subpopulation

(A) Progression-Free Survival

Study	Treatment 1 (n)	Treatment 2 (n)	PFS HR (95% CI)
PRIME	FOLFOX (159)	FOLFOX+ panitumumab (169)	0.72 (0.57, 0.90)
CRYSTAL	FOLFIRI (138)	FOLFIRI+Cetuximab (142)	0.50 (0.34, 0.72)
PEAK	FOLFOX+Bevacizumab (54)	FOLFOX+ panitumumab (53)	0.68 (0.45, 1.04)
CALGB/SWOG 80405	FOLFOX/ FOLFIRI+Bevacizumab (152)	FOLFOX/ FOLFIRI+ Cetuximab (173)	0.84 (0.66, 1.06)
FIRE-3	FOLFIRI+Bevacizumab (149)	FOLFIRI+Cetuximab (157)	0.90 (0.71, 1.14)

KEY: CI = confidence interval; FOLFIRI = FOL– Folinic acid F – Fluorouracil IRI – Irinotecan; FOLFOX = FOL– Folinic acid F – Fluorouracil OX – Oxaliplatin; HR = hazard ratio; PFS = progression-free survival; WT = wild-type.
Source: Arnold et al., 2017.[12]

Data Source: NMA Report (2017)[48]

(B) Overall survival

Study	Treatment 1 (n)	Treatment 2 (n)	OS HR (95% CI)
PRIME	FOLFOX (159)	FOLFOX+ panitumumab (169)	0.73 (0.57, 0.93)
CRYSTAL	FOLFIRI (138)	FOLFIRI+Cetuximab (142)	0.65 (0.50, 0.86)
PEAK	FOLFOX+Bevacizumab (54)	FOLFOX+ panitumumab (53)	0.77 (0.46, 1.28)
CALGB/SWOG 80405	FOLFOX/ FOLFIRI+Bevacizumab (152)	FOLFOX/ FOLFIRI+ Cetuximab (173)	0.77 (0.59, 0.99)
FIRE-3	FOLFIRI+Bevacizumab (149)	FOLFIRI+Cetuximab (157)	0.63 (0.48, 0.85)

KEY: CI = confidence interval; FOLFIRI = FOL– Folinic acid F – Fluorouracil IRI – Irinotecan; FOLFOX = FOL– Folinic acid F – Fluorouracil OX – Oxaliplatin; HR = hazard ratio; OS = overall survival; WT = wild-type.
Source: Arnold et al., 2017.[12]

Data Source: NMA Report (2017)[48]

Assumptions of the NMA

As previously mentioned, three assumptions must be met prior to conducting an NMA. The Submitter stated that they were unable to assess heterogeneity due to the limited number of trials informing the NMA.

To explore the transitivity assumption, the Submitter provided a descriptive comparison of the baseline characteristics across all of the trials included the NMA. The Submitter commented that the baseline characteristics appeared to be well balanced for the subgroup of patients with left-sided tumours.[10] They did note more imbalances in the subgroup of patients with right-sided tumours. This imbalance may be a result of small sample sizes. However, the Submitter reported that there was heterogeneity among the panitumumab and cetuximab RCTs, such as differences in median age, liver-only metastatic disease, and number of metastatic sites. For instance, the PRIME and PEAK trials included a lower proportion of patients with one metastatic site than in the FIRE-3 and CRYSTAL trials. Despite this apparent heterogeneity, the Submitter stated that "*…any differences in patient/study characteristics across studies in the left-sided sub-groups are likely biased against panitumumab, lending credibility to the conclusions from our NMA.*"[10]

For the final assumption, consistency, the Submitter explored for consistency by comparing the DIC statistics in fitted consistency and inconsistency models, plotting the posterior mean deviances of both the inconsistency and consistency models, and comparing the qualitative estimates from the meta-analyses and pooled analysis of direct evidence. Although the consistency models indicated that there was no evidence of inconsistency, the Submitter stated that the results from PEAK and the treatment-level NMA results for PFS for chemotherapy plus panitumumab versus chemotherapy plus bevacizumab differed. This discrepancy arose because the NMA flagged the PEAK trial as an outlier and gave more weight to the other studies included in the network.

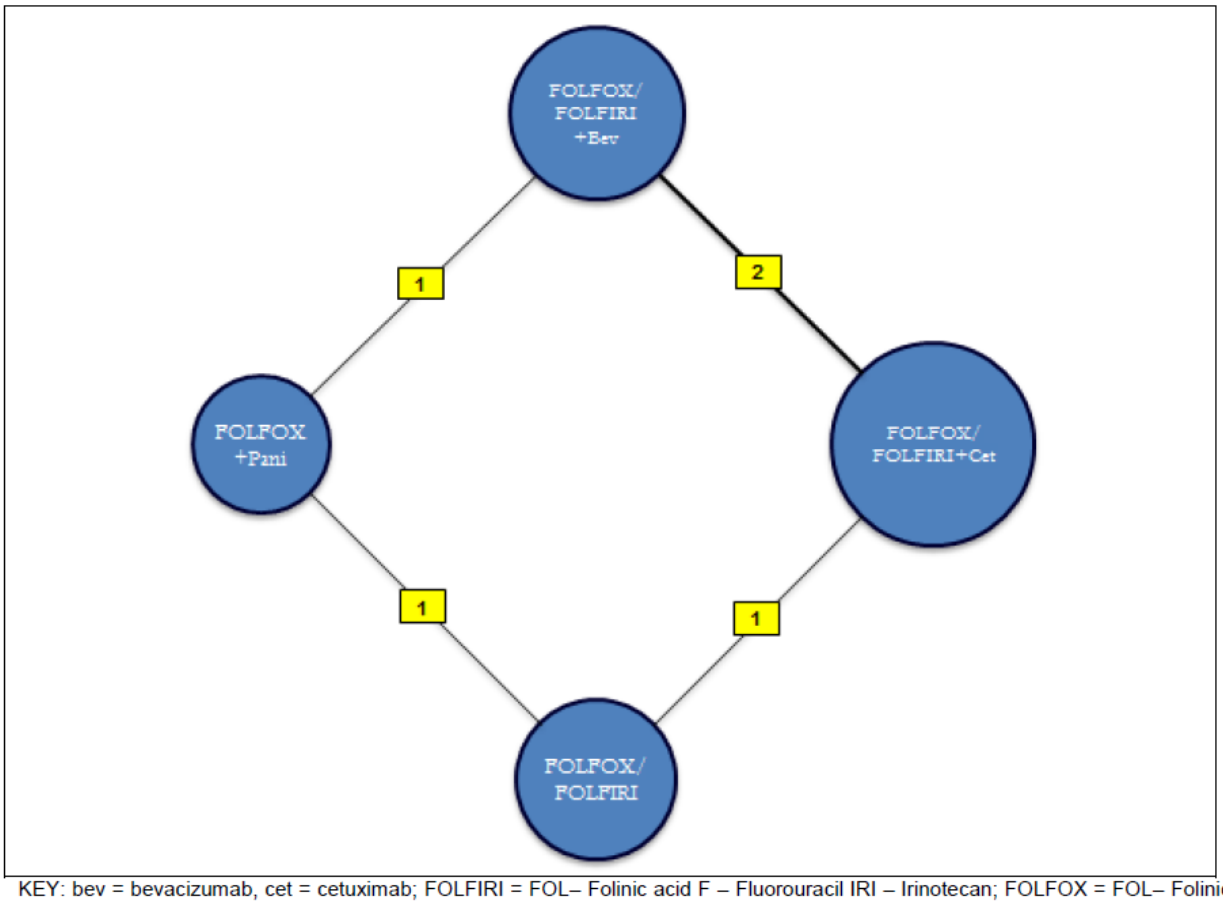
Indirect Treatment Comparison

Since the three assumptions of the NMA were met, the Submitter performed two Bayesian NMAs. The treatment-level NMA compared chemotherapy plus panitumumab relative to chemotherapy alone, chemotherapy plus cetuximab, and chemotherapy plus bevacizumab. The comparison between chemotherapy plus panitumumab to chemotherapy plus cetuximab will not be reported. On the other hand, the class-level NMA assessed the efficacy of chemotherapy with anti-EGFR (panitumumab or

cetuximab) relative to chemotherapy alone, and chemotherapy with anti-VEGF (bevacizumab). The results of the class-level NMA will not be presented.

Five trials informed the four pairwise comparisons in the treatment-level NMA (Figure 3). The treatment-level NMA consisted of 1,346 *RAS* wild-type patients with a confirmed left-sided tumour. Three single trials informed the comparisons between 1) chemotherapy to chemotherapy plus panitumumab, 2) chemotherapy plus panitumumab to chemotherapy plus bevacizumab and 3) chemotherapy plus cetuximab to chemotherapy. Two trials informed the comparison between chemotherapy plus bevacizumab to chemotherapy plus cetuximab.

Figure 3: Treatment-level evidence network for PFS and OS

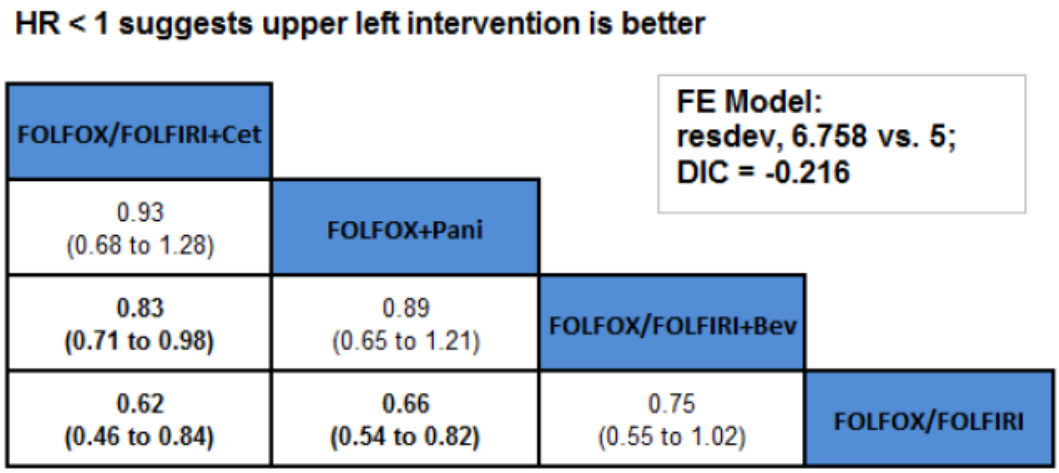


KEY: bev = bevacizumab, cet = cetuximab; FOLFIRI = FOL– Folinic acid F – Fluorouracil IRI – Irinotecan; FOLFOX = FOL– Folinic acid F – Fluorouracil OX – Oxaliplatin; OS = overall survival; pani = panitumumab; PFS = progression-free survival.

Data Source: NMA Report (2017)[48]

Using a Bayesian NMA, the Submitter showed that chemotherapy plus panitumumab was associated with an increased PFS as compared to chemotherapy in *RAS* wild-type mCRC patients with a left-sided tumour (HR: 0.66, 95% CrI: 0.54 to 0.82) (Figure 4). In contrast, there was no significant difference between chemotherapy plus panitumumab and chemotherapy plus bevacizumab on PFS (HR: 0.89, 95% CrI: 0.65 to 1.21).

Figure 4: Pairwise comparisons from the fixed effects NMA assessing the effect of chemotherapy with panitumumab relative to comparators on PFS

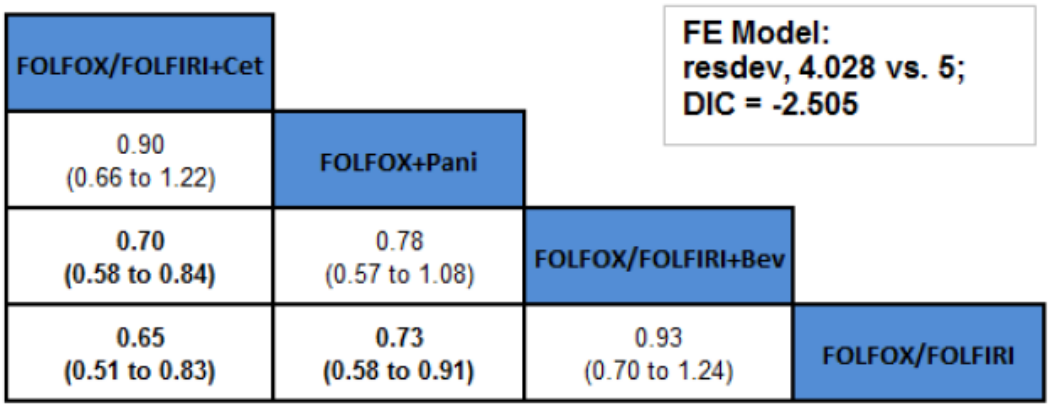


Pairwise comparisons from the fixed-effects model are shown in terms of summary HRs and 95% CrIs. Each value reflects a comparison between treatments belonging to the intersecting column and row, with additional benefit indicated for the treatment in the column. Model fit statistics are also presented. Results in bold font denote statistically significant findings.
KEY: bev = bevacizumab, cet = cetuximab; CrI=credible interval; DIC=deviance information criteria; FE=fixed effects; ; FOLFIRI = FOL– Folinic acid F – Fluorouracil IRI – Irinotecan; FOLFOX = FOL– Folinic acid F – Fluorouracil OX – Oxaliplatin; HR=hazard ratio; NMA = network meta-analysis; pani = panitumumab; PFS = progression-free survival; resdev= residual deviance.

Data Source: NMA Report (2017)[48]

Chemotherapy plus panitumumab was associated with improved OS relative to chemotherapy in *RAS* wild-type mCRC patients with a left-sided tumour (HR: 0.73, 95% CrI: 0.58 to 0.91) (Figure 5). There was no association between chemotherapy plus panitumumab and chemotherapy plus bevacizumab on OS (HR: 0.78, 95% CrI: 0.57 to 1.08).

Figure 5: Pairwise comparisons from the fixed effects NMA assessing the effect of chemotherapy with panitumumab relative to comparators on OS



Pairwise comparisons from the fixed-effects model are shown in terms of summary HRs and 95% CrIs. Each value reflects a comparison between treatments belonging to the intersecting column and row, with additional benefit indicated for the treatment in the column. Model fit statistics are also presented. Results in bold font denote statistically significant findings.
KEY: bev = bevacizumab, cet = cetuximab; CrI=credible interval; DIC=deviance information criteria; FE=fixed effects; ; FOLFIRI = FOL– Folinic acid F – Fluorouracil IRI – Irinotecan; FOLFOX = FOL– Folinic acid F – Fluorouracil OX – Oxaliplatin; HR=hazard ratio; NMA = network meta-analysis, OS = overall survival; pani = panitumumab; resdev= residual deviance.

Data Source: NMA Report (2017)[48]

Table 6 shows a summary of the ranks and probabilities for the treatment-level NMA assessing the effect of chemotherapy with panitumumab relative to comparators on PFS and OS. For the estimates derived from the Bayesian NMA, the Submitter provided the mean rank with 95% CrIs and probability of the estimate being the best, second best and so on. In addition, the Submitter generated estimates from a Surface under the cumulative ranking curve (SUCRA) as an additional method to assess ranking and uncertainty. A higher percentage reflects a higher relative probability that an intervention is among the best options. For PFS, the SUCRA values were highest for chemotherapy plus cetuximab (FE: 88.4% and RE: 74.5%) followed by chemotherapy plus panitumumab (FE: 70.0% and RE: 67.7%). Furthermore, chemotherapy plus panitumumab had the highest probability of ranking second best mean treatment ranking (FE: 43.2% and RE: 30.4%). Similar results were observed for OS.

Table 6: Summary of the ranks and probabilities for the treatment-level NMA assessing the effect of chemotherapy with panitumumab relative to comparators on (A) PFS and (B) OS

(A) Progression-free survival

Treatment	Model	SUCRA	Probability of Each Rank				Mean Rank (95% CrI)
			1st	2nd	3rd	4th	
FOLFOX/FOLFIRI + Cet	**FE**	**88.4%**	**65.9%**	**33.2%**	**0.9%**	**0.0%**	**1.3 (1, 2)**
	RE	74.5%	46.9%	34.3%	14.1%	4.7%	1.8 (1, 4)
FOLFOX + Pani	**FE**	**70.0%**	**33.5%**	**43.2%**	**23.3%**	**0.0%**	**1.9 (1, 3)**
	RE	67.7%	39.7%	30.4%	23.3%	6.6%	2 (1, 4)
FOLFOX/FOLFIRI + Bev	**FE**	**40.5%**	**0.6%**	**23.5%**	**72.7%**	**3.2%**	**2.8 (2, 4)**
	RE	42.7%	8.9%	26.9%	47.7%	16.5%	2.7 (1, 4)
FOLFOX/FOLFIRI	**FE**	**1.1%**	**0.0%**	**0.1%**	**3.1%**	**96.8%**	**4 (3, 4)**
	RE	15.1%	4.5%	8.4%	15.0%	72.2%	3.5 (1, 4)

Results in bold font denote findings from the more suitable fixed effects model for NMA based on the geometric structure of the network.

KEY: bev = bevacizumab; cet = cetuximab; CrI=credible interval; FE=fixed effects; FOLFIRI = FOL– Folinic acid F – Fluorouracil IRI – Irinotecan; FOLFOX = FOL– Folinic acid F – Fluorouracil OX – Oxaliplatin; NMA = network meta-analysis; pani = panitumumab; PFS = progression-free survival; RE = random effects; SUCRA = Surface Under the Cumulative Ranking (SUCRA) curve.

(B) Overall Survival

Treatment	Model	SUCRA	Probability of Each Rank				Mean Rank (95% CrI)
			1st	2nd	3rd	4th	
FOLFOX/FOLFIRI + Cet	**FE**	**91.9%**	**75.9%**	**24.1%**	**0.0%**	**0.0%**	**1.2 (1, 2)**
	RE	83.0%	61.6%	28.5%	7.3%	2.6%	1.5 (1, 4)
FOLFOX + Pani	**FE**	**72.4%**	**24.1%**	**69.1%**	**6.7%**	**0.2%**	**1.8 (1, 3)**
	RE	67.7%	30.9%	47.1%	15.9%	6.0%	2 (1, 4)
FOLFOX/FOLFIRI + Bev	**FE**	**25.1%**	**0.0%**	**6.6%**	**62.1%**	**31.3%**	**3.2 (2, 4)**
	RE	29.2%	3.5%	15.7%	45.7%	35.1%	3.1 (1, 4)
FOLFOX/FOLFIRI	**FE**	**10.6%**	**0.0%**	**0.2%**	**31.2%**	**68.6%**	**3.7 (3, 4)**
	RE	20.1%	4.0%	8.7%	31.0%	56.3%	3.4 (1, 4)

Results in bold font denote findings from the more suitable fixed effects model for NMA based on the geometric structure of the network.

KEY: bev = bevacizumab; cet = cetuximab; CrI=credible interval; FE=fixed effects; FOLFIRI = FOL– Folinic acid F – Fluorouracil IRI – Irinotecan; FOLFOX = FOL– Folinic acid F – Fluorouracil OX – Oxaliplatin; NMA = network meta-analysis; pani = panitumumab; PFS = progression-free survival; RE = random effects; SUCRA = Surface Under the Cumulative Ranking (SUCRA) curve.

Data Source: NMA Report (2017)[48]

Critical Appraisal of the ITC

The quality of the ITC provided by the Submitter was assessed according to the recommendations made by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons. Details of the critical appraisal are presented below.

Table 7: Adapted ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis†

ISPOR Questions	Details and Comments‡
1. Is the population relevant?	**Yes, in part.** The indication under review was to assess the efficacy and safety of panitumumab, in combination with chemotherapy, for the first-line treatment of mCRC patients with left-sided primary tumours that express wild-type *RAS*. The studies included in the treatment-level NMA were PRIME, PEAK, CRYSTAL, CALGBSWOG 80405 and FIRE-3. All of these trials included *RAS* wild-type carriers with untreated mCRC. Data was also available on tumour sidedness.
2. Are any critical interventions missing?	**No.** The Submitter included all relative interventions for this patient population in the systematic review. However, for the purpose of the review, comparisons between panitumumab plus chemotherapy to cetuximab will not be considered because this is not a relevant comparator in Canada.
3. Are any relevant outcomes missing?	**Yes.** In the NMA, the Submitter included OS and PFS but they did not consider other outcomes, such as overall response rate, safety outcomes and HRQoL.
4. Is the context (e.g., settings and circumstances) applicable to your population?	**Yes.** The settings of the five included trials were similar.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	**Yes.** The Submitter provided a summary of the systematic literature review process used in the NMA. In the summary, the Submitter described the information sources they used, their search strategy and their study selection criteria.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	**Yes.** The trials form one connected network of RCTs.
7. Is it apparent that poor quality studies were included thereby leading to bias?	**No.** The Submitter assessed the risk of bias of all included studies using the Cochrane Collaboration's tool for assessing risk of bias. The Submitters noted that the lack of blinding across the five trials will not impact objective outcomes (i.e. OS); however, it might bias the interpretation of subjective outcomes (i.e. PFS).
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	**Unclear.**
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	**Yes.** The Submitter provided a qualitative assessment of heterogeneity (Table 3 and 4); however, the Methods team felt that performing subgroup analyses and a test for difference would have been more informative.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	**Yes.** The Submitter noted that there was heterogeneity among the trials included in the NMA. This includes differences in median age, liver-only metastatic disease and number of metastatic sites. The Submitter commented that the baseline characteristics appeared to be well balanced for the subgroup of patients with left-sided tumours.[10] They did note more imbalances in the subgroup of patients with right-sided tumours. This imbalance may be a result of small sample sizes.
11. Were statistical methods used that	**Yes.** The Submitter used a Bayesian NMA.

ISPOR Questions	Details and Comments‡
preserve within-study randomization? (No naïve comparisons)	
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	Yes. The Submitter explored for consistency by comparing the deviance and DIC statistics in fitted consistency and inconsistency models; plotting the posterior mean deviances of both the inconsistency and consistency models; and comparing the qualitative estimates from the meta-analyses and pooled analysis of direct evidence.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Yes. The reported findings from the NMA represent the combined direct and indirect estimates. However, it was noted that the direct estimates were reported as study-level estimates and pair-wise meta-analysis. Yet, the results using the various approaches had a similar direction and magnitude of treatment effect.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	No. The Submitter stated that they were unable to adjust for imbalances in effect modifiers because the NMA was based on sub-group data (i.e., not feasible to get sub-group of sub-group data), and the network only consisted of one or two studies within each connection.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	Yes. The Submitter also provided both fixed and random-effects models. However, they emphasized the final results using a fixed effects model. Their rationale for using a fixed effects model was due to the lack of clinical trials. They stated that the use of a random-effects model with a vague prior on the between study variance exerts a large degree of influence on the CrIs because there are insufficient studies to reign in the prior and provide an accurate estimate of the between study variance. The use of the random effects model with a vague prior was problematic in the treatment-level NMA because treatments that were originally associated with statistically significant reductions in PFS or OS were no longer associated with significant reductions, limiting external validity of the model.
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Not applicable.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	No. The Submitter reported, and the Methods Team does recognize, that they were unable to perform any subgroup analysis or meta-regression analysis due to the limited number of studies included in the NMA.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes. This representation was presented in Figure 3.
19. Are the individual study results reported?	Yes. The Submitter provided the baseline characteristics of the trials used in the NMA as well as the effect estimates of PFS and overall survival.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	Yes. The Submitter has provided the direct comparisons of OS and PFS from the PRIME and PEAK trials.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes. The Submitter provided the PFS and OS HR and 95% CrIs from the NMA.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Yes. The rankings of the interventions are reported in Table 6.
23. Is the impact of important patient characteristics on treatment effects reported?	No.

ISPOR Questions	Details and Comments‡
24. Are the conclusions fair and balanced?	The NMA Report provided by the Submitter did not make any strong conclusions. The treatment-level NMA suggests that chemotherapy plus panitumumab was associated with improved PFS (HR: 0.66 [95% CrI: 0.54 to 0.82]) and OS (HR: 0.73 [95% CrI: 0.58 to 0.91]) as compared to chemotherapy alone. The effect of chemotherapy plus panitumumab versus chemotherapy plus bevacizumab on PFS and OS were attenuated. However, it was noted that the treatment-level NMA was informed by a limited sample size. Although the Submitter provided a well conducted NMA, there was no other patient important outcomes include in the NMA. Thus, it is difficult to determine the overall clinical benefit of panitumumab versus chemotherapy or chemotherapy plus bevacizumab.
25. Were there any potential conflicts of interest?	**Not reported.**
26. If yes, were steps taken to address these?	**Not reported.**

HRQoL = health-related quality of life; ISPOR = International Society For Pharmacoeconomics and Outcomes Research; ITC = indirect treatment comparison; ORR = objective response rate; PFS = progression-free survival.
† Jansen et al[75]
‡Bolded comments are considered a weakness of the ITC.

Conclusion

The Submitter provided an NMA that compared chemotherapy plus panitumumab to chemotherapy plus bevacizumab and chemotherapy alone in *RAS* wild-type mCRC patients with left-sided tumours. The results of the NMA indicated that chemotherapy plus panitumumab had a protective effect on OS and PFS relative to chemotherapy (PFS HR: 0.66 [95% CrI: 0.54 to 0.82] and OS HR: 0.73 [95% CrI: 0.58 to 0.91]). There was no difference between chemotherapy plus panitumumab versus chemotherapy plus bevacizumab on PFS and OS. Following review of feedback by the Submitter on the pCODR pERC Initial Recommendation, the Methods Team re-iterated that the current review was for panitumumab and the treatment-level NMA was reviewed rather than the class-level NMA (i.e. class-level of anti-EGFR therapies cetuximab and panitumumab). Following review of feedback by the Submitter on the pCODR pERC Initial Recommendation, the Methods Team noted that although several studies and meta-analyses were conducted to support panitumumab in left-sided tumours, all studies used the same sources of trial data of panitumumab (i.e. PEAK and PRIME); therefore, the additional analyses do not constitute new data but additional analyses of the same data. A meta-analysis is a statistical analysis that combines the results of multiple studies and therefore, are limited by the data combined. The results of the NMA indicated that chemotherapy plus panitumumab had a protective effect on OS and PFS relative to chemotherapy (PFS HR: 0.66 [95% CrI: 0.54 to 0.82] and OS HR: 0.73 [95% CrI: 0.58 to 0.91]). There was no difference between chemotherapy plus panitumumab versus chemotherapy plus bevacizumab on PFS and OS. Overall, the NMA was well designed and of high quality since the assumptions of the NMA were met. However, there is limited evidence to support the credibility of the subgroup analysis that assessed the comparative efficacy of chemotherapy plus panitumumab in patients with left and right-sided tumours in Boeckx et al (2017)[7], thus, highlighting concerns with the data incorporated into the NMA. Hence, there is uncertainty in whether there is a differential treatment response to panitumumab in *RAS* wild-type patients with left or right-sided tumours, and therefore, it is difficult to draw conclusions on the estimates from the NMA.

8 COMPARISON WITH OTHER LITERATURE

None identified.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR 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 left sided 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 CADTH 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. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

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 CADTH 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

1. Literature search via OVID platform

Search Strategy:

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** September 2017**, Embase** 1974 to 2017 October 11**, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Search Strategy:

#	Searches	Results
1	(Vectibix* or Vectibex* or panitumumab* or ABX-EGF or Abenix*).ti,ab,ot,kf,hw.	8838
2	(339177-26-3 or 6A901E312A).rn,nm.	6775
3	1 or 2	9036
4	exp Colorectal neoplasms/ or exp Colorectal tumor/ or exp Rectal cancer/	386772
5	(colorectal or colon or rectal or rectum or sigmoid or anal or anus or perianal or circumanal).ti,ab,kf,kw. and (cancer* or neoplas* or tumo?r* or carcinoma* or CRC).ti,ab.	545444
6	4 or 5	631578
7	3 and 6	6134
8	7 use cctr	223
9	7 use ppez	1110
10	8 or 9	1333
11	*panitumumab/	1257
12	(Vectibix* or Vectibex* or panitumumab* or ABX-EGF or Abenix*).ti,ab.	4143
13	11 or 12	4328

14	Colorectal neoplasms/ or Colorectal tumor/ or Rectal cancer/	170063
15	(colorectal or colon or rectal or rectum or sigmoid or anal or anus or perianal or circumanal).ti,ab,kw. and (cancer* or neoplas* or tumo?r* or carcinoma* or CRC).ti,ab.	544399
16	14 or 15	573000
17	13 and 16	3137
18	17 use oemezd	1977
19	10 or 18	3310
20	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial).pt.	1107618
21	Randomized Controlled Trial/	973245
22	exp Randomized Controlled Trials as Topic/	268720
23	"Randomized Controlled Trial (topic)"/	137521
24	Controlled Clinical Trial/	550150
25	exp Controlled Clinical Trials as Topic/	279627
26	"Controlled Clinical Trial (topic)"/	9362
27	Randomization/	175456
28	Random Allocation/	192700
29	Double-Blind Method/	400161
30	Double Blind Procedure/	143879
31	Double-Blind Studies/	262664
32	Single-Blind Method/	71676

33	Single Blind Procedure/	29846
34	Single-Blind Studies/	73208
35	Placebos/	318294
36	Placebo/	315209
37	Control Groups/	114057
38	Control Group/	113963
39	(random* or sham or placebo*).ti,ab,hw,kf,kw.	3736915
40	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	737956
41	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	2487
42	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.	2406910
43	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	90146
44	allocated.ti,ab,hw.	162354
45	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	101095
46	or/20-45	5348770
47	19 and 46	1063
48	exp animals/	46800506
49	exp animal experimentation/ or exp animal experiment/	2172743
50	exp models animal/	1623274
51	nonhuman/	5337095
52	exp vertebrate/ or exp vertebrates/	45500454

53	or/48-52	48381749
54	exp humans/	37381426
55	exp human experimentation/ or exp human experiment/	409714
56	or/54-55	37383645
57	53 not 56	10999761
58	47 not 57	1062
59	conference abstract.pt.	2741036
60	58 not 59	759
61	58 and 59	303
62	limit 61 to yr="2012 -Current"	224
63	60 or 62	983
64	limit 63 to english language	939
65	remove duplicates from 64	644

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Add to builder	Query	Items found
#9	Add	Search **#7 AND #8**	3
#8	Add	Search **Publisher[sb]**	532059
#7	Add	Search **#2 AND #5 AND #6**	191
#6	Add	Search **#3 OR #4**	254595

Search	Add to builder	Query	Items found
#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]))**	1239947
#4	Add	Search **(colorectal[tiab] OR colon[tiab] OR rectal[tiab] OR rectum[tiab] OR sigmoid[tiab] OR anal[tiab] OR anus[tiab] OR perianal[tiab] OR circumanal[tiab] OR CRC[tiab]) AND (cancer*[tiab] OR neoplas*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab])**	212839
#3	Add	Search **Colorectal neoplasms[MeSH] OR Colorectal tumor[MeSH] OR Rectal cancer[MeSH]**	174910
#2	Add	Search **panitumumab[nm] OR Vectibix*[tiab] OR Vectibex*[tiab] OR panitumumab*[tiab] OR ABX-EGF[tiab] OR Abenix*[tiab]**	1415

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: Vectibix/panitumumab, metastatic colorectal carcinoma (mCRC)

   Select international agencies including:

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

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

   Search: Vectibix/panitumumab, metastatic colorectal carcinoma (mCRC)

Conference abstracts:

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

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

Search: Vectibix/panitumumab, metastatic colorectal carcinoma (mCRC)-last 5 years

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 (September 2017) 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 concepts were panitumumab (vectibix) and colorectal carcinoma (CRC).

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 January 4, 2018.

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. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. 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.

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. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

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

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.

Data Analysis

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

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 clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the PAG, and by Registered Clinicians.

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