Canada's Drug and
Health Technology Agency

CADTH Reimbursement Review

Panitumumab

Non-Sponsored Review

Therapeutic area: Left-sided metastatic colorectal cancer

Clinical and Pharmacoeconomic Report

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Abbreviations

AE	adverse event
CCC	Colorectal Cancer Canada
CCRAN	Colorectal Cancer Resource & Action Network
CI	confidence interval
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
FOLFIRI	5-fluorouracil, leucovorin, and irinotecan
FOLFOX	5-fluorouracil, leucovorin, and oxaliplatin
HR	hazard ratio
HRQoL	health-related quality of life
IQR	interquartile range
mCRC	metastatic colorectal cancer
mFOLFIRI	modified 5-fluorouracil, leucovorin, and irinotecan
mFOLFOX	modified 5-fluorouracil, leucovorin, and oxaliplatin
NMA	network meta-analysis
MSI-L	microsatellite instability-low
MSS	microsatellite stable
pMMR	proficient mismatch repair
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RR	risk ratio
SAE	serious adverse event
SD	standard deviation
VEGF	vascular endothelial growth factor
WDAE	withdrawal due to adverse event
XELOX	capecitabine (Xeloda) and oxaliplatin

Executive Summary

An overview of the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Panitumumab (Vectibix), 20 mg/mL solution for injection, IV infusion
Health Canada indication	For the treatment of previously untreated patients with nonmutated (wild-type) *RAS* metastatic colorectal carcinoma (mCRC) in combination with FOLFOX (infusional 5-fluorouracil, leucovorin, and oxaliplatin)
Indication under consideration for reimbursement	As per Health Canada indication
Health Canada approval status	Approved
NOC date	April 3, 2008
Requester	Provincial Advisory Group

Introduction

Colorectal cancer is among the most common cancer among adults. In Canada, there were an estimated 24,300 new cases in 2022, resulting in approximately 9,400 related deaths.[1] Advanced colorectal cancer represents a significant burden of disease. The 5-year survival rate for patients with metastatic colorectal cancer (mCRC) is less than 10%.[2]

The goals of therapy for most patients presenting with advanced colorectal cancer are to extend survival, reduce disease-related symptoms, and improve quality of life. The standard first line of therapy in Canada for mCRC is fluoropyrimidine-based chemotherapy combined with a targeted agent.[3,4] Commonly used chemotherapy regimens include 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) or 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI). Targeted agents include the vascular endothelial growth factor (VEGF) inhibitors bevacizumab and approved biosimilars as well as the epidermal growth factor receptor (EGFR) inhibitors cetuximab and panitumumab, which are used in patients with *RAS* wild-type (nonmutated) mCRC only.

The subject of this review is the combination of panitumumab with first-line chemotherapy for patients with left-sided mCRC that expresses wild-type *RAS*. Panitumumab has a Health Canada–approved indication for: "the treatment of previously untreated patients with nonmutated (i.e., wild-type) *RAS* mCRC in combination with FOLFOX."[5] We previously reviewed panitumumab for this indication in 2015; the pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommended funding panitumumab, in addition to combination chemotherapy, in patients who have a contraindication or intolerance to bevacizumab and who would otherwise be treated only with combination chemotherapy.[6] The manufacturer requested a subsequent review of panitumumab for the same indication based on new evidence in 2018; however, pERC did not recommend the reimbursement of panitumumab in patients who would otherwise be candidates to receive bevacizumab.[7]

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to our call for patient input and from clinical experts consulted by us for the purpose of this review.

Patient Input

This section was prepared by our staff based on the input provided by patient groups. The full patient group input is included in the Stakeholder Input document.

Two patient advocacy groups, Colorectal Cancer Canada (CCC) and Colorectal Cancer Resource & Action Network (CCRAN), submitted the patient input for this review. Both CCC and CCRAN are national nonprofit organizations committed to raising awareness, providing education about colorectal cancer, and advocating for improved patient outcomes.

The submissions were based on perspectives gathered from online surveys conducted by CCC with 16 respondents and by CCRAN with 77 respondents, telephone interviews conducted by CCC with 3 respondents and by CCRAN with 7 respondents, and a focus group discussion conducted by CCRAN with 9 respondents.

Respondents highlighted that fatigue, bloody stools, abdominal pain, and diarrhea were the most prevalent cancer-induced symptoms, and that the disease also impacted their mental well-being. Respondents highlighted the impact on patient's quality of life because they are unable to work, exercise, drive, concentrate, or participate in social activities, as well as the impact on caregiver's quality of life, including loss of lifestyle, time spent in medical appointments, struggle with managing treatment-induced side effects, loss of income, and physical and emotional exhaustion. Respondents noted that improvements in their physical condition (e.g., tumour shrinkage, tumour stability, reduction of pain and improved breath) and enhancements in their overall quality of life were the most desirable outcomes from new therapies, including improvement in mobility, sense of wellness, relief from side effects. With respect to panitumumab, respondents noted skin reactions (rash, dryness, itching) were the most challenging treatment-induced side effects and emphasized the importance of early support to manage the skin toxicity associated with panitumumab.

Clinician Input

Input From Clinical Experts

One clinical specialist with expertise in the diagnosis and management of colorectal cancer provided input on the condition.

Regarding mCRC with left-sided primary tumours expressing wild-type *RAS*, the clinical experts outlined the variability in public drug plans in Canada, with most funding first-line anti-VEGF therapy or anti-EGFR therapy only in instances of bevacizumab contraindications, although some provinces support first-line anti-EGFR therapy without the requirement for bevacizumab contraindications. In contrast, international guidelines[8,9] recommend first-line chemotherapy with anti-EGFR therapy and subsequent bevacizumab in the second line according to the clinical experts. The clinical experts also highlighted that current funding disparities

create inequities in access to treatment across provinces. The clinical experts noted that anti-EGFR therapy as part of first-line treatment without bevacizumab restrictions, with the option for second-line bevacizumab and third-line anti-EGFR therapy, would offer more options to physicians and eliminate the need to choose between upfront EGFR therapy or second-line bevacizumab.

The clinical experts suggested that patients who are eligible for first-line anti-EGFR treatment include those with left-sided tumours expressing wild-type *RAS*, while taking into account patient factors and physician discretion. Routine assessment through imaging and bloodwork are used to evaluate treatment responses. The goals of therapy at this stage are improving survival and enhancing quality of life as well as downstaging for potential resection whenever possible. The clinical experts highlighted notable side effects with anti-EGFR therapy, such as rash, hypomagnesemia, and infusion reactions. Discontinuation criteria for this treatment include disease progression, adverse events (AEs), patient choice, or circumstances enabling resection or ablation. The clinical experts indicated that panitumumab is administered in an outpatient setting by oncologists who do not need additional expertise.

Clinician Group Input

This section was prepared by us based on the input provided by clinician groups.

Clinician input was submitted by 2 clinician groups: Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee (OH-CCO GI DAC) and Canadian Gastrointestinal Oncology Evidence Network (CGOEN). Four members of the OH-CCO GI DAC and 6 members of CGOEN provided their input.

Clinician groups emphasized the unmet need in Canada for first-line treatment of left-sided mCRC expressing wild-type *RAS*, for which funding currently supports chemotherapy combined with bevacizumab but lacks routine access to anti-EGFR treatment. They pointed out that this creates a dilemma for oncologists because using anti-EGFR therapy in the first line makes patients ineligible for bevacizumab in the second line. As an exception to international treatment guidelines, clinician groups emphasized that Canada needs to align with standard care by offering panitumumab in the first line for left-sided mCRC expressing wild-type *RAS* and ensuring second-line access to bevacizumab. Both clinician groups noted that eligible patients for this treatment should have metastatic or locally advanced left-sided colorectal adenocarcinoma expressing wild-type *RAS*, have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1, and be able to tolerate systemic therapy. Those least suited for this treatment are patients with right-sided tumours or tumours with *RAS* mutations, or patients whose health status precludes the administration of multiagent chemotherapy. They also suggested that *RAS* testing is needed because tumours with *RAS* mutations, which are present in 50% of colorectal cancer cases, do not respond to this treatment. They noted that treatment response is assessed clinically using carcinoembryonic antigen values and imaging, with discontinuation recommended upon disease progression, unacceptable toxicity, or patient preference. Clinician groups indicated that treatment can be administered in the outpatient oncology setting.

Drug Program Input

The drug programs provided input on each drug being reviewed through our Reimbursement Review processes by identifying issues that may affect their ability to implement a recommendation. The

drug plans noted that although panitumumab (Vectibix) patent protection has lapsed, no biosimilar is presently accessible in the Canadian market, making panitumumab the exclusive source product. The drug plans indicated that mCRC is a complex therapeutic field with multiple lines of treatment options and subpopulations. Reimbursement of panitumumab in the first-line setting will also impact the use of bevacizumab and cetuximab, both in the second-line setting (in combination with backbone chemotherapy) and as single-agent treatment options in subsequent-line settings. For this review of panitumumab, the drug plans provided questions pertaining to the options for backbone chemotherapy and related concerns regarding additional clinic visits with different cycle lengths for some regimens, definition of "left-sided" mCRC, generalizability of clinician trial population to the Canadian context, access to subsequent therapies, frequency of imaging, frequency of dosing with panitumumab, and switching. These questions were addressed by the clinician experts consulted for this review. Clinical experts' responses have been included in the Responses to Questions From the Drug Programs.

Clinical Evidence

Protocol-Selected Studies

Description of Studies

Two published phase III, open-label randomized controlled trials (RCTs) were included in the systematic review: the PARADIGM study[10-12] and the CAIRO5 study.[13,14] The PARADIGM study was conducted in Japan; patients were randomized to receive panitumumab or bevacizumab, in combination with mFOLFOX6 (modified version of FOLFOX), for the first-line treatment of unresectable mCRC with wild-type *RAS*.[10] The population of interest presented and discussed in this review are the subset of 612 patients who had left-sided tumours. The primary outcome was overall survival.

The CAIRO5 study was conducted in the Netherlands; patients with left-sided wild-type *RAS* and *BRAF* tumours were randomized to receive panitumumab or bevacizumab, in combination with FOLFOX or FOLFIRI, for the first-line treatment of unresectable liver-only mCRC.[13] This constitutes a selected subpopulation of the overall mCRC indication for panitumumab who are expected to have a different disease trajectory. Therefore, the population of interest for this review are this subset of 236 patients who had left-sided tumours. The primary outcome was progression-free survival.

Study drugs were administered in the PARADIGM and CAIRO5 studies at the recommended dosage (i.e., panitumumab 6 mg/kg and bevacizumab 5 mg/kg administered as IV infusions every 2 weeks). All patients received appropriate concomitant backbone chemotherapy. Treatments were to be continued until disease progression, unacceptable toxicity, patient or physician decision, or curative-intent surgery. Findings from the PARADIGM and CAIRO5 studies were obtained in populations that were deemed to be younger and with a better performance status than patients routinely seen in clinical practice in Canada. This should be considered when generalizing the findings to patients in real-life conditions.

Efficacy Results

Efficacy results are outlined in Table 2. Improving survival in patients with cancer should remain the primary goal of therapy; as such, overall survival is the preferred and most reliable end point in oncology

trials.[15] Evidence from 1 study suggests that panitumumab may result in a clinically meaningful benefit on overall survival compared with bevacizumab in the first-line treatment of mCRC in patients with left-sided tumours expressing wild-type *RAS*, but there is uncertainty surrounding the magnitude of those findings. In the PARADIGM study, the use of panitumumab was associated with hazard ratios (HRs) in favour of this treatment versus bevacizumab for overall survival; the between-group difference in median survival observed in the study was considered clinically meaningful by both experts. Uncertainty surrounding the findings, due in part to issues with the risk of bias and imprecision, was expressed in the confidence intervals (CIs) that may also include the possibility of no clinically meaningful difference between treatments.

Additional efficacy outcomes assessed in the studies were considered relevant, but not as clinically meaningful as overall survival to inform treatment decisions according to the clinical experts. Evidence from these 2 studies suggest that panitumumab may not result in a clinically meaningful benefit on progression-free survival compared with bevacizumab in the first-line treatment of mCRC in patients with a left-sided tumour expressing wild-type *RAS* as well as in a subset of patients who have liver-only metastases. This is due to inconclusive results and substantial uncertainty surrounding the findings. In the PARADIGM and CAIRO5 studies, the HRs for progression-free survival were inconclusive and the between-group differences in median progression-free survival were not considered clinically meaningful by both experts. Progression-free survival may have been subject to assessment bias due to absence of a central review by assessors blinded to treatment assignment in these open-label trials. Uncertainty was also introduced because the underlying assumption of proportional hazards had been violated.

Evidence from 2 studies suggests that panitumumab may result in a clinically meaningful benefit on objective response rate compared with bevacizumab in the first-line treatment of mCRC in patients with left-sided tumours expressing wild-type *RAS* as well as in a subset of patients who have liver-only disease. However, there is substantial uncertainty surrounding the findings. The between-group differences observed in the PARADIGM and CAIRO5 studies were considered clinically meaningful by both experts, particularly in patients with potentially resectable disease, for whom reduction of tumour volume may result in successful surgery, as well as in patients with symptomatic disease to alleviate symptoms. However, there is uncertainty due to imprecision in the PARADIGM study because of the possibility that the lower end of the CI would constitute little to no difference. In addition, only limited statistical analyses were reported in the CAIRO5 study, precluding proper assessment of the between-group differences and the precision of the estimates.

Evidence from the 2 studies suggests that panitumumab may result in a clinically meaningful benefit on curative resection rate compared with bevacizumab in the first-line treatment of mCRC in patients with left-sided tumours expressing wild-type *RAS*, but not in a subset of patients who have liver-only disease which is expected to have a different disease trajectory. However, there is substantial uncertainty surrounding the findings. In the PARADIGM study, the between-group difference observed in favour of panitumumab was considered clinically meaningful by both experts; although the percentage may appear small, it would likely bring a significant benefit in patients for whom curative resection may be considered because successful curative resection constitutes a potential cure. In the CAIRO5 study, no difference was observed between panitumumab and bevacizumab. The outcome of curative resection rate is subject to limitations,

including the possibility of little to no difference due to imprecision as well as insufficient reporting of statistical analyses.

Panitumumab did not seem to have a clinically significant impact on duration of response compared to bevacizumab in the PARADIGM study. The magnitude of the between-group difference was not considered clinically meaningful by the experts, and the outcome in itself was not considered particularly informative for decision-making. Finally, the evidence did not inform on health-related quality of life (HRQoL) because no data were reported in the publications on this outcome.

Harms Results

Harms results are outlined in Table 2. High proportions of patients experienced at least 1 AE throughout the PARADIGM study follow-up, and the proportions were similar between treatment groups. Harms outcomes in this study were reported for the overall population of patients, regardless of tumour sidedness; this was considered appropriate by the clinical experts because harms outcomes are not expected to differ according to the tumour type (right-sided or left-sided). Dermatologic and soft tissue toxicities, as well as hypomagnesemia electrolyte disturbance, were reported more frequently in patients receiving panitumumab compared with patients receiving bevacizumab. The consulted clinical experts consulted indicated that it is common in clinical practice for patients undergoing treatment for mCRC to experience numerous AEs with the currently available agents, and that most may be considered tolerable and/or manageable by patients. It should be noted that patients and clinicians in the trial were aware of the treatment strategy received, which may have introduced bias in the reporting of subjective AEs.

More patients receiving panitumumab experienced grade 3 to 5 AEs in the CAIRO5 study compared with bevacizumab (listing not reported). Similarly, more patients receiving panitumumab experienced serious adverse events (SAEs) in both studies compared with bevacizumab. The withdrawal due to adverse events (WDAE) profile differed between the trials but, overall, these were reported more frequently with panitumumab than with bevacizumab. There were numerically more deaths reported in patients receiving panitumumab compared with bevacizumab; however, there were too few events to draw a strong conclusion regarding mortality due to AEs, and statistical significance was not reported, precluding any judgment on whether the difference would be meaningful. Mortality with panitumumab was for reasons that included known but rare toxicities from the drug, such as interstitial lung disease and other various infections and noninfectious pulmonary disorders.

Table 2: Summary of Key Results From the Studies Included in the Systematic Review

Outcome	PARADIGM[10] (left-sided tumours)		CAIRO5[13] (patients with a left-sided tumour)	
	Panitumumab N = 312	Bevacizumab N = 292	Panitumumab (group D) N = 116	Bevacizumab (group C) N = 114
Overall survival				
Number of patients with death from any cause, n (%)	218 (69.9)	230 (78.7)	Assessed in the study but NR in the publications	
Overall survival (months), median (95% CI)	37.9 (34.1 to 42.6)	34.3 (30.9 to 40.3)		
HR (95% CI)	0.82 (0.68 to 0.99)			
P value (stratified log-rank test)	0.03			
Progression-free survival				
Number of patients with disease progression or death from any cause, n (%)	217 (69.6)	224 (76.7)	106 (91)	99 (87)
Progression-free survival (months), median (95% CI)	13.1 (11.6 to 14.5)	11.9 (11.3 to 13.5)	10.4 (9.8 to 13.0)	10.8 (9.9 to 12.6)
HR (95% CI)	1.00 (0.83 to 1.20)		1.11 (0.84 to 1.48)[a]	
P value	NR		0.46	
Objective response rate (complete or partial response)				
Patients contributing to the analysis, n	308	287	116	114
Number of patients with complete or partial response, n (%)	247 (80.2)	197 (68.6)	93 (80)	60 (53)
95% CI	75.3 to 84.5	62.9 to 74.0	NR	
Absolute difference, % (95% CI)	11.2 (4.4 to 17.9)		NR	
P value	NR		< 0.0001	
Duration of response (in patients with complete or partial response)				
Duration of response (months), median (95% CI)	13.1 (11.1 to 14.8)	11.2 (9.6 to 13.1)	NR	
Curative resection rate	**R0**		**R0 or R1**	
Number of patients who achieved a curative resection,[b] n (%)	57 (18.3)	34 (11.6)	67 (58)	66 (58)
95% CI or P value	95% CI, 14.1 to 23.0	95% CI, 8.2 to 15.9	P = 1.00	
Absolute difference (95% CI), %	6.6 (1.0 to 12.3)		NR	
Patients with harms outcomes				
N	404	407	116	114

Outcome	PARADIGM[10] (left-sided tumours)		CAIRO5[13] (patients with a left-sided tumour)	
	Panitumumab N = 312	Bevacizumab N = 292	Panitumumab (group D) N = 116	Bevacizumab (group C) N = 114
AEs	Patients with any AEs		Patients with any grade 3 to 5 AEs	
n (%)	402 (99.5)	398 (97.8)	80 (69)	61 (54)
Patients with any SAEs, n (%)	72 (17.8)	44 (10.8)	49 (42)	41 (36)
Patients with any WDAEs, n (%)	96 (23.8)	75 (18.4)	5 (4)	3 (3)
Mortality, n (%)	10 (2.5)	2 (0.5)	3 (3)	1 (1)

AE = adverse event; CI = confidence interval; HR = hazard ratio; NR = not reported; R0 = excision of all colorectal cancer; R1 = microscopic tumour involvement in the resection margin; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Note: Analyses were not adjusted for multiplicity.

[a]Hazard ratio for bevacizumab vs. panitumumab.

[b]Curative resection based on study definition.

Sources: Watanabe et al. (2023)[10] and Bond et al. (2023).[13]

Indirect Evidence

Indirect evidence was considered to inform a comparison between panitumumab and cetuximab as well as to mitigate the limited reporting of SAEs for the comparison of panitumumab and bevacizumab in the included trials. Two network meta-analyses (NMAs) performed using the frequentist approach aimed to inform these comparisons.[16,17]

Cost Information

- Because we do not have access to an economic model to address the specified research question, the economic review included a comparison of the treatment costs of panitumumab in combination with first-line standard chemotherapy and those of comparators deemed to be appropriate based on clinical expert consultations and drug plan feedback.
- The 28-day per patient cost of panitumumab monotherapy is $5,446, which is more costly than bevacizumab monotherapy (28-day cost: $2,454) and less costly than cetuximab monotherapy (28-day cost: $7,884). The current standard-of-care treatment for patients with mCRC that express wild-type *RAS* consists of bevacizumab or cetuximab in combination with first-line standard chemotherapy; therefore, this review compared the cost of these regimens with panitumumab. Panitumumab and bevacizumab are used in combination with FOLFOX, FOLFIRI, or capecitabine (Xeloda) and oxaliplatin (XELOX) regimens, while cetuximab is used in combination with either FOLFOX or FOLFIRI. The 28-day per patient cost of panitumumab in combination with FOLFOX, FOLFIRI, and XELOX is $7,010, $10,181, and $5,879, respectively. The 28-day per patient cost of bevacizumab in combination with FOLFOX, FOLFIRI, and XELOX is $4,017, $7,189, and $2,887, respectively. The 28-day per patient cost of cetuximab in combination with FOLFOX and FOLFIRI is $9,448 and $12,619, respectively.

- When comparing panitumumab with bevacizumab (used in combination with FOLFOX, FOLFIRI, or XELOX), panitumumab results in a 28-day per patient incremental cost of $2,992. When comparing panitumumab with cetuximab (used in combination with FOLFOX or FOLFIRI), panitumumab results in a 28-day per patient incremental cost saving of $2,438. Across combination regimens, the incremental costs and incremental savings remain constant given that differences in the regimens are reflected by the use and drug acquisition costs of panitumumab, bevacizumab, or cetuximab. Costs are based on publicly available list prices and may not reflect actual prices paid by public drug plans in Canada.

Conclusions

Improving survival in patients with cancer remains the primary goal of therapy. As such, evidence from the PARADIGM study suggests that panitumumab may result in a clinically meaningful benefit for overall survival compared with bevacizumab in the first-line treatment of mCRC in patients with left-sided tumours expressing wild-type *RAS*. However, there is uncertainty surrounding the magnitude of those findings due in part to issues with redefinition of the primary population, confounding factors, and imprecision. Findings from the PARADIGM and CAIRO5 studies suggest potential benefits from panitumumab on the secondary outcomes of objective response rate and curative resection rate compared with bevacizumab in the first-line treatment of mCRC in patients with left-sided tumours expressing wild-type *RAS* and potentially in a subset of patients who have liver-only disease. These findings would be particularly relevant in patients for whom curative resection may be considered and in patients with symptomatic disease. However, the interpretation regarding clinical meaningfulness of the results is limited by imprecision because the CIs also include the possibility of little to no clinically meaningful difference between treatments and by limited reporting of statistical analyses. In the 2 studies, panitumumab did not seem to have a significant impact on progression-free survival and duration of response compared with bevacizumab. The evidence did not inform on HRQoL because no data were reported in the publications. The populations in the studies were deemed to be younger and with a better performance status than patients routinely seen in clinical practice in Canada. Two NMAs were reviewed to inform a comparison between panitumumab and cetuximab, and to mitigate the limited reporting of SAEs for the comparison of panitumumab and bevacizumab in the RCTs. However, substantial imprecision for nearly all comparison outcomes precluded any strong conclusion regarding the comparative effects of the drugs because CIs included the potential for no important difference between treatments or the possibility that either treatment could be favoured.

In the PARADIGM and CAIRO5 studies, high proportions of patients experienced harms events, of which dermatologic and soft tissue toxicities, as well as hypomagnesemia electrolyte disturbance, were reported more frequently in patients who received panitumumab compared with patients who received bevacizumab. SAEs and WDAEs were numerically higher with panitumumab than with bevacizumab. The harms profile reported in the PARADIGM and CAIRO5 studies appeared consistent with what is currently seen in clinical practice in Canada according to the clinical experts we consulted. There were too few events to draw a strong conclusion regarding mortality due to AEs; however, numerically more deaths were reported in patients receiving panitumumab for reasons that included known but rare toxicities from the drug, such

as interstitial lung disease and other various infections and noninfectious pulmonary disorders. As such, tolerability should be weighed against any potential gain in overall survival expected from treatment.

Results of the cost comparison of drug acquisition costs demonstrate that, when compared to bevacizumab (and used in combination with FOLFOX, FOLFIRI, or XELOX), the reimbursement of panitumumab is expected to increase treatment costs (incremental costs: $2,992 per patient per 28 days). Alternatively, when compared to cetuximab (and used in combination with FOLFOX or FOLFIRI), the reimbursement of panitumumab is anticipated to decrease treatment costs (incremental cost savings: $2,438 per patient per 28 days).

Based on the clinical review conclusions, panitumumab likely results in improved overall survival, improved objective response rate, and improved curative resection rate compared with bevacizumab. Given that panitumumab is associated with incremental costs and incremental benefit compared with bevacizumab, a cost-effectiveness analysis would be required to determine the cost-effectiveness of panitumumab relative to bevacizumab. Because this was not available, the cost-effectiveness of panitumumab relative to bevacizumab for the treatment of patients with mCRC that express wild-type *RAS* could not be determined. The clinical review further concluded that cetuximab may result in improved overall survival and improved progression-free survival relative to panitumumab; however, CIs were wide and often included the potential for no important difference between treatments. As such, it is uncertain whether differences between treatments exist. If it is expected that the clinical effects of panitumumab and cetuximab are similar, a comparison of drug acquisition costs may be appropriate.

Because bevacizumab is less costly than panitumumab, a price reduction of 55% would be required for the drug acquisition cost of panitumumab to be equal to bevacizumab. Costs associated with *RAS* and *BRAF* diagnostic testing, as well as administration costs, were not considered in this cost comparison. To adequately consider these alongside the health care resource implications associated with the comparative clinical benefits, a cost-effectiveness analysis of panitumumab in combination with standard first-line therapy compared with all current standard-of-care treatments would be required.

Introduction

Disease Background

Colorectal cancer is among the most common cancer among adults, with an estimated 24,300 new cases in 2022 in Canada, resulting in approximately 9,400 related deaths.[1] An estimated 25% of patients are diagnosed with metastatic (stage IV) disease and, among those with early-stage resectable colorectal cancer, an estimated 40% will experience a relapse within 3 to 5 years of diagnosis.[2] As such, advanced colorectal cancer represents a significant burden of disease. The 5-year survival rate for patients with mCRC is less than 10%.[2]

Standards of Therapy

Treatment Goals

The goals of therapy for most patients presenting with advanced colorectal cancer are to extend survival, reduce disease-related symptoms, and improve quality of life.

A minority of patients (approximately 10%) may be suitable for upfront resection of oligometastatic disease to the liver and lung, which may yield a curative outcome. Another 20% to 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 metastasectomy 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.[2]

For the majority of patients with unresectable mCRC, the goals of therapy are otherwise noncurative (palliative) and the primary treatment modality is systemic chemotherapy to extend survival and ameliorate or delay disease-related symptoms.[2]

Sidedness as a Determinant of Prognosis and Treatment

Anatomically, the right and the left colon arise from different embryonic origins; the proximal (right) colon arises from the midgut and receives it main blood supply via the superior mesenteric artery, whereas the distal (left) colon arises from the hindgut and is supplied by the inferior mesenteric artery.[2] Primary tumours that are distal to the colonic splenic flexure are conventionally defined as left-sided. It is recognized that right-sided colon cancers exhibit different molecular characteristics than left-sided colon cancers. Mismatch repair deficiency and *BRAF* mutations are observed more commonly in right-sided tumours, whereas *RAS* mutations are observed more commonly in left-sided tumours.[2]

Chemotherapy

The standard first line of therapy in Canada for mCRC is fluoropyrimidine-based chemotherapy combined with a targeted agent.[3,4] Fluoropyrimidines available in Canada include IV 5-fluorouracil, usually given with leucovorin; these drugs can be combined with oxaliplatin or irinotecan, administered as the commonly used regimens FOLFOX and FOLFIRI. Oxaliplatin in first-line regimen followed by irinotecan in second-line regimen, or the opposite sequence, are considered to be clinically equivalent approaches.[31,32]

Targeted Agents

Bevacizumab, a VEGF inhibitor, is a monoclonal antibody that blocks angiogenesis through binding to the VEGF ligand. The use of bevacizumab in combination with chemotherapy has been supported by several studies that have demonstrated an increase in progression-free survival.[33-35]

Cetuximab (chimeric) and panitumumab (humanized), EGFR inhibitors, are recombinant monoclonal antibodies to the EGFR that inhibit its downstream signalling pathways, including the *RAS* pathway. The anti-EGFR biologics cetuximab or panitumumab are currently used in the chemorefractory setting in patients with wild-type *RAS* (nonmutated) disease only. Retrospective analyses from several RCTs suggest that the effect of cetuximab is markedly better in patients with left-sided tumours (compared with patients with right-

sided tumours).[18,19] Common toxicities with this class of agents include significant skin rash (papulopustular eruptions), diarrhea, and hypomagnesemia. Infusion reactions may also occur.[2]

The subject of this review is the combination of panitumumab with first-line chemotherapy for left-sided mCRC that expresses wild-type *RAS*.

Drug

Panitumumab is a recombinant, fully human immunoglobulin G2 (IgG2) monoclonal antibody that binds with high affinity and specificity to human EGFR, a promotor of cell growth in normal epithelial tissues that is expressed on a variety of tumour cells, resulting in decreased VEGF production, inhibition of cell growth, and induction of apoptosis.[5]

Panitumumab has a Health Canada–approved indication for "the treatment of previously untreated patients with nonmutated (i.e., wild-type), *RAS* metastatic colorectal carcinoma in combination with FOLFOX."[5]

We previously reviewed panitumumab for this indication in 2015, and pERC recommended funding panitumumab, in addition to combination chemotherapy, in patients who have a contraindication or intolerance to bevacizumab and who would otherwise be treated only with combination chemotherapy.[6] The manufacturer requested a subsequent review of panitumumab for the same indication based on new evidence in 2018; however, pERC did not recommend the reimbursement of panitumumab in patients who would otherwise be candidates to receive bevacizumab.[7]

Guidance on the optimal sequencing of treatments for mCRC is provided in the provisional funding algorithm.[20]

The Provincial Advisory Group (PAG) and clinical experts consulted by us for this review indicated that there is an interest in clinical practice to use panitumumab as first-line treatment in patients with left-sided mCRC that expresses wild-type *RAS*. The PAG requested that we review panitumumab for this patient population and provide a reimbursement recommendation.

Stakeholder Perspectives

Patient Group Input

This section was prepared by our staff based on the input provided by patient groups. The full patient group input is included in the Stakeholder Input section at the end of this report.

Two patient advocacy groups, CCC and CCRAN, submitted the patient input for this review. Both CCC and CCRAN are national nonprofit organizations committed to raising awareness and providing education about colorectal cancer. They offer support to patients and their caregivers, advocating for improved patient outcomes in terms of longevity and quality of life. In addition, CCRAN extends its services to patients with cancer beyond the colorectal cancer domain by engaging in health technology assessment patient evidence submissions, educational events, and advocacy initiatives.

The submission from CCC was based on perspectives gathered through an online survey, conducted in English and French across Canada through CCC's monthly newsletter, which was posted on the social media platforms of CCC and other international colorectal cancer organizations and through outreach efforts by CCC's patient support specialists. Survey respondents resided in British Columbia, Alberta, Ontario, Quebec, Nova Scotia, Newfoundland and Labrador, and Prince Edward Island. Of the 16 respondents, 15 were patients and 1 was a caregiver, and 4 of the 16 respondents had experience with the drug under review. Three of the 16 respondents also agreed to participate in a qualitative interview by telephone or Zoom to expand on their experience with the drug under review.

CCRAN gathered experience from patients with mCRC regarding their cancer diagnosis and journey and drug therapies administered through a previously developed and administered online survey with respect to another therapy under review (i.e., trifluridine-tipiracil [Lonsurf] and bevacizumab). The survey was promoted through CCRAN's email blasts, social media channels, and support groups, surveying registered patients with colorectal cancer and caregivers residing in Canada. Of the 77 respondents, 60 were patients, 13 were caregivers, and 4 were patients who were also caregivers. Survey respondents resided in British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, and Nova Scotia. Through email blasts and social media, registered patients and caregivers who had firsthand experience with the therapy under review were requested to participate in a telephone interview to share their experiential treatment journey. Seven patients participated in the interview; the mean age of the patients who were interviewed was 52 years and the median age at the time of their diagnosis was 50 years. A focus group was also conducted with 9 patients with mCRC from across Canada via Zoom.

Respondents highlighted that colorectal cancer, being the third most common cancer and the second-leading cause of cancer-related death in Canada, has a profound and multifaceted impact on patients and their families. Respondents noted that despite advancements in treatment options, disease recurrence, often with a fatal course, is a reality for many patients, resulting in a median overall survival of approximately 30 months from the initiation of first-line systemic therapy. Fatigue, bloody stools, abdominal pain, and diarrhea were reported as the most prevalent cancer-induced symptoms, with fatigue being the most debilitating, hindering patients from performing everyday tasks and substantially reducing their quality of life. Respondents emphasized that these symptoms not only interfere with daily activities but also impact mental well-being, including fear of disease worsening or recurrence, constant worry, anxiety, depression, uncertainty and hopelessness about the future, and frustration. Respondents highlighted the impact on quality of life because they are unable to work, exercise, drive, concentrate, or participate in social activities. Caregivers also highlighted the numerous difficulties they face in caring for patients with colorectal cancer, including loss of lifestyle, time spent in medical appointments, struggle with managing treatment-induced side effects, loss of income, and physical and emotional exhaustion (caregiver burnout).

Respondents noted fatigue, diarrhea, hair loss, peripheral neuropathy, and nausea as the most common treatment-associated side effects. To manage these side effects, some respondents noted they often require additional medications, some of which may not be covered, resulting in out-of-pocket expenses. Access to new, effective therapies was deemed highly important by most respondents, and a significant percentage of respondents felt that their current drug options did not fully meet their needs. Respondents noted that

improvements in their physical condition (e.g., tumour shrinkage, tumour stability, reduction of pain, and improved breath) and enhancements in their overall quality of life were the most desirable outcomes from new therapies, including improvement in mobility, sense of wellness, and relief from side effects. Regarding panitumumab, respondents noted skin reactions (rash, dryness, itching), mouth sores, sore eyes, fatigue, and diarrhea are the most common side effects, with skin reactions being the most challenging to endure. Respondents emphasized the importance of early support to manage the skin toxicity associated with panitumumab. However, it was noted that patients appreciated the predictability of the "pani-induced rash" as a sign of potential clinical benefit. Further, despite the side effects, patients who were or are treated with panitumumab rated their overall quality of life relatively high and noted its potential in prolonging life, thus indicating that the potential benefits of the panitumumab treatment were worth the side effects.

Clinician Input

Input From Clinical Experts

All the review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of mCRC.

Unmet Needs

The clinical experts noted that, for mCRC with left-sided primary tumours that express wild-type *RAS*, most public drug plans in Canada fund first-line anti-VEGF therapy (bevacizumab) or anti-EGFR therapy (panitumumab or cetuximab) in patients with bevacizumab contraindications. Only some provinces fund first-line anti-EGFR therapy without bevacizumab contraindication. Backbone chemotherapy can be 5-fluorouracil combined with either oxaliplatin or irinotecan, with most patients receiving 5-fluorouracil and irinotecan unless they are under consideration for resection. Second-line options include chemotherapy with agents that the patient has not received before. However, second-line bevacizumab is often not available due to the previously noted issue of a contraindication. In patients who have received first-line chemotherapy with bevacizumab and second-line chemotherapy, a third-line anti-EGFR therapy can be considered.

In contrast, the current paradigm of care in some countries (e.g., the US and European countries)[8,9] is to consider first-line chemotherapy with anti-EGFR therapy, and then subsequent bevacizumab with second-line chemotherapy according to the clinical experts we consulted. The clinical experts also suggested that it is reasonable to consider first-line bevacizumab with chemotherapy and third-line anti-EGFR therapy. Given the previously noted funding issues in Canada, oncologists face challenges when considering a survival benefit with first-line anti-EGFR therapy but then are not allowed to give second-line bevacizumab or give first-line bevacizumab and then third-line anti-EGFR therapy. The clinical experts also highlighted provincial differences with respect to funding result in inequity in access to treatment across the country.

The clinical experts noted that systemic therapy in mCRC is used for survival benefit. Although median survival is approximately 2 to 3 years, in some instances, tumour downsizing allows for local regional strategies like surgery or ablation, which can provide long-term survival of 5 years in approximately 30% of cases. These treatments not only enhance survival but also maintain or improve the quality of life.

Place in Therapy

The clinical experts noted that panitumumab should be used as part of first-line treatment without the restriction of bevacizumab contraindication and with the option for second-line treatment with bevacizumab. The clinical experts also noted that third-line anti-EGFR therapy may be more suitable for some patients. As such, patients who discontinue first-line treatment with panitumumab plus chemotherapy for reasons other than disease progression should have access to the drug as a single agent in the third-line setting. According to the clinical experts we consulted, by changing the treatment paradigm, treatment algorithms in Canada will align with those of international guidelines such as the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN)[8,9] and will ensure a harmonized standard in treatment across the country. The experts also noted that this will increase physician choice and eliminate the decision that clinicians must make between using upfront anti-EGFR and not giving a patient second-line bevacizumab.

Patient Population

The clinical experts noted that patients with left-sided tumours with wild-type *KRAS* would be eligible for first-line anti-EGFR treatment. Patient factors in combination with physician discretion should determine who would receive upfront anti-EGFR versus third-line treatment according to the clinical experts. The clinical experts also highlighted that patients already receive *RAS* testing as per provincial molecular testing programs.

Assessing Response to Treatment

The clinical experts highlighted that patients would undergo routine imaging and bloodwork as part of assessment for response to treatment, with the expectation that treatment would improve survival, quality of life, and doing instrumental activities of daily living and activities of daily living as well as increase downstaging for possible resection.

Rash, hypomagnesemia, and infusion reactions were some of the notable harms noted by the clinical experts.

Discontinuing Treatment

The clinical experts suggested that the evidence of disease progression, AEs such as rash or hypomagnesemia, or patient choice would result in drug discontinuation. The experts noted, however, that panitumumab as a single agent should remain accessible as a third-line option in the case of discontinuation due to excessive toxicity with panitumumab plus chemotherapy as first-line treatment without disease progression. The clinical experts further added that treatment would be discontinued in the circumstance of downsizing disease for resection or ablation because there would be no evidence of disease.

Prescribing Conditions

As per the clinical experts, panitumumab is given in an outpatient setting by oncologists and additional expertise is not necessary.

Clinician Group Input

We prepared this section based on the input provided by clinician groups. The full clinician group input is included in the Stakeholder Input document.

Clinician input was submitted by 2 clinician groups: OH-CCO GI DAC and CGOEN. OH-CCO GI DAC provides evidence-based clinical and health system guidance on drug-related issues, supporting CCO's mandate including the Provincial Drug Reimbursement Programs and the Systemic Treatment Program. CGOEN is a nationwide virtual network of GI oncology clinicians actively involved in advancing knowledge about GI cancer and its treatments, including participation in clinical trials, observational research, and contributions to clinical guidelines and health technology assessments at local, provincial, and national levels.

Four members of the OH-CCO GI DAC provided their input gathered jointly at a videoconference meeting, and 6 members of CGOEN provided their input based on the PARADIGM study.[10]

Unmet Needs

Both clinician groups noted that the goals of treatment are improving overall survival, delaying disease progressions, and improving symptoms and quality of life. They indicated that current funding in Canada for the first-line treatment of left-sided mCRC expressing wild-type *RAS*, with those who have microsatellite instability-low (MSI-L), microsatellite stable MSS, or proficient mismatch repair (pMMR) status, is chemotherapy (fluoropyrimidine with either irinotecan or oxaliplatin) combined with bevacizumab. A lack of routine access to anti-EGFR treatment in the first-line setting was emphasized by both clinician groups because EGFR monoclonal antibody therapy can only be used in bevacizumab ineligible patients. As such, EGFR monoclonal antibody therapy, if not used in the first line, can be used in the third-line setting after second-line chemotherapy. However, as noted by CGOEN, Canada is an exception. Treatment guidelines recommend EGFR monoclonal antibody therapy as a standard-of-care option for first-line treatment with chemotherapy without the need to be ineligible for bevacizumab and that patients receiving this treatment are also allowed to receive second-line bevacizumab. They noted that the current treatment approach in Canada creates a dilemma for oncologists because recommending first-line EGFR therapy with chemotherapy for survival means declaring the patient ineligible for bevacizumab, denying them access to this treatment (bevacizumab) in the second line. CGOEN also highlighted that there is a higher response rate with EGFR monoclonal antibody therapy and less risk of bleeding issues, which may help with respect to downsizing disease for potential metastasectomy.

Place in Therapy

Both clinician groups noted that, consistent with standard of care in other countries, panitumumab should be given in the first-line setting for *RAS* wild-type, left-sided mCRC, and that patients should have access to bevacizumab in the second-line setting.

Patient Population

Both clinician group indicated that patients best suited are those with metastatic or locally advanced left-sided colorectal adenocarcinoma expressing wild-type *RAS* and those who would otherwise be eligible for systemic chemotherapy. CGOEN added that eligible patients should have an ECOG performance status of 0 or 1 and be able to tolerate systemic therapy. OH-CCO GI DAC further noted that the designation of the left-sided tumours should be left to the discretion of the treating physician, because the definition of left-sided tumours is heterogeneous due to the differing inclusion criteria of the major trial.

As per the clinician groups, patients least suited would be those with a right-sided tumour, or a tumour with *RAS* mutations, or those patients whose health status precludes the administration of multiagent chemotherapy, including those with inadequate organ function for treatment or with and ECOG performance status of 2 or greater. One clinician group also noted that this treatment should not be used in the neoadjuvant setting for patients with resectable metastases (i.e., liver, lung).

CGOEN also noted that *RAS* testing, which is a part of standard of care for colorectal cancer, is needed because tumours with *RAS* mutations do not respond to treatment, and they represent 50% of cases of colorectal cancer.

Assessing Response to Treatment

Both clinical groups indicated that patients are assessed routinely clinically, using carcinoembryonic antigen values and cross-sectional imaging. Treatment is changed due to tolerance, progression, or patient preference.

Discontinuing Treatment

Both clinician groups suggested that treatment should be discontinued with disease progression, unacceptable toxicity, or patient preference. OH-CCO GI DAC further suggested that if patients are intolerant to chemotherapy, they should still have the option to continue with panitumumab alone.

Prescribing Conditions

Both clinician groups noted that the treatment can be administered in the outpatient oncology setting. CGOEN also indicated strong clinical familiarity in Canada with managing patients on EGFR monoclonal antibody therapy as well as use of tumour testing in the first-line setting to identify patients with mCRC expressing wild-type *RAS* as an accepted standard of care.

Additional Considerations

Indicating variations in testing access and timing among sites across jurisdictions in Canada, OH-CCO GI DAC highlighted the need for equitable access to *RAS* testing and timely turnaround of results across the provinces.

Drug Program Input

The drug programs provide input on each drug being reviewed through our non-sponsored review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts we consulted are summarized in Table 13.

The drug plans indicated that mCRC is a complex therapeutic field with multiple lines of treatment options and subpopulations. Reimbursement of panitumumab in the first-line setting will also impact the use of bevacizumab and cetuximab, both in the second-line setting (in combination with backbone chemotherapy) and as single-agent treatment options in the subsequent-line setting. The drug plans noted that the comparator in the PARADIGM study[10] was bevacizumab combined with mFOLFOX6; however, currently there are no drugs or regimens funded specifically for left-sided mCRC expressing wild-type *RAS*. The drug plans also highlighted that, as per the most recent (issued November 2021) provincial funding algorithm for mCRC,[20] in patients who have MSI-L, MSS, or pMMR, bevacizumab with or without chemotherapy (e.g., mFOLFOX, FOLFIRI, XELOX, or capecitabine [AVEX regimen]) is funded for the first-line treatment of mCRC. In those who have mCRC expressing wild-type *RAS* and *BRAF* and intolerance or contraindications to bevacizumab, panitumumab with or without multiagent chemotherapy is funded in first line in both left- and right-sided mCRC. The drug plans noted that *KRAS* and *NRAS* are part of reflex testing for newly diagnosed cases of advanced or mCRC or small bowel carcinoma in Ontario and other jurisdictions.

The drug plans noted that although panitumumab (Vectibix) patent protection has lapsed, no biosimilar is presently accessible in the Canadian market, making panitumumab the exclusive source product.

The drug plans also noted that panitumumab in combination with chemotherapy for the first-line treatment of patients with mCRC expressing wild-type *RAS* who have a contraindication or an intolerance to bevacizumab was previously reviewed by pCODR in 2015; however, this recommendation did not consider tumour sidedness.[6]

Industry Input

We prepared this section based on the input provided by the manufacturer of panitumumab.

The industry input was submitted by Amgen Canada Inc., the manufacturer of panitumumab (Vectibix) in Canada. Industry input was provided on the research protocol. They noted that the research protocol posted on our website is reflective of the treatment landscape for patients with mCRC with left-sided primary tumours that express wild-type *RAS*.

The manufacturer noted that panitumumab is approved by Health Canada for the treatment of previously untreated patients with nonmutated (wild-type) *RAS* mCRC in combination with FOLFOX and that patients with mCRC with left-sided primary tumours that express wild-type *RAS* represent approximately 70% to 80% of the total *RAS* wild-type mCRC population.[42] The manufacturer also noted that the prior review of panitumumab identified data limitations due to retrospective analyses,[7] which could now be addressed by the PARADIGM study, a phase III, prospective, RCT powered to detect a difference in overall survival specifically in patients with *RAS* wild-type left-sided primary tumours.

The manufacturer noted that experts and clinical practice guidelines[8,43-45] recommend the use of an EGFR inhibitors (cetuximab or panitumumab) in combination with chemotherapy in the first-line setting for patients with MSS and pMMR left-sided mCRC expressing *RAS* wild-type. The industry noted that studies suggest that first-line EGFR inhibitor use can increase VEGF expression levels sensitizing the tumour to subsequent VEGF

inhibitor treatment, which contrasts use of VEGF inhibitors in the first-line, which can lead to resistance to both VEGF inhibitors and EGFR inhibitors.[46,47]

The manufacturer indicated the PARADIGM study[10] and a prospective biomarker study[48] of participants included in the PARADIGM study as relevant publications.

Although there were no participants from Canada included in the PARADIGM study (which was conducted in centres in Japan), the manufacturer indicated that baseline disease characteristics and outcomes in the bevacizumab group were consistent with studies in other countries. Industry also noted previous pharmacokinetic analyses across 14 studies in multiple tumour types and postmarketing surveillance of patients from Japan with mCRC have shown that this population of patients has similar exposure, supporting the same dosing regimen and treatment outcomes with panitumumab as populations outside of Japan.[42,49]

Clinical Evidence

The clinical evidence included in the review of panitumumab is presented in 2 sections. The first section, the Systematic Review, includes studies that were selected according to an a priori protocol. The second section includes indirect evidence selected from the literature that met the selection criteria specified in the review. There would be a third section including long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review; however, none were considered relevant for inclusion in the review.

Systematic Review

Objectives

To perform a systematic review of the beneficial and harmful effects of panitumumab, added to standard chemotherapy, for the first-line treatment of patients with mCRC with left-sided primary tumours that express wild-type *RAS*.

Methods

Studies selected for inclusion in the systematic review included those meeting the selection criteria presented in Table 3. Outcomes included in our review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

Table 3: Inclusion Criteria for the Systematic Review

Criteria	Description
Patient population	Patients undergoing first-line treatment for mCRC who have left-sided primary tumours that express wild-type *RAS* Subgroup • ECOG performance status score
Intervention	Panitumumab 6 mg/kg IV infusion every 2 weeks in combination with first-line standard chemotherapy (i.e., FOLFOX or FOLFIRI)

Criteria	Description
Comparators	Bevacizumab 5 mg/kg IV infusion every 2 weeks in combination with first-line standard fluoropyrimidine-based chemotherapy (i.e., FOLFOX or FOLFIRI). Cetuximab 400 mg/m^2 initial IV infusion, followed by 250 mg/m^2 IV infusion every week in combination with first-line standard chemotherapy (i.e., FOLFOX or FOLFIRI).
Outcomes	**Efficacy outcomes:** • Overall survival • Progression-free survival • Objective response rate • Duration of response • Curative resection rate • HRQoL **Harms outcomes:** • AEs, SAEs, WDAEs, mortality **Harms of special interest:** • Dermatologic and soft tissue toxicity (i.e., dermatitis acneiform, pruritus, erythema, rash, skin exfoliation, paronychia, dry skin, and skin fissures). • Serious dermatologic and soft tissue toxicity (i.e., Stevens-Johnson syndrome, skin necrosis, and toxic epidermal necrolysis). • Hypersensitivity and infusion reactions (i.e., anaphylactic reactions, bronchospasm, dyspnea, fever, chills, edema, angioedema, and hypotension). • Pulmonary toxicity (i.e., interstitial pneumonitis and pulmonary fibrosis). • Electrolyte disturbances (i.e., hypomagnesemia and hypokalemia).
Study design	Published and unpublished phase III and IV RCTs

AE = adverse event; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = 5-fluorouracil, leucovorin, and irinotecan; FOLFOX = 5-fluorouracil, leucovorin, and oxaliplatin; HRQoL = quality of life; mCRC = metastatic colorectal cancer; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

An information specialist performed the literature search for clinical studies using a peer-reviewed search strategy according to the PRESS Peer Review of Electronic Search Strategies checklist.[21]

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run individually. Duplicates were removed manually in EndNote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the population, intervention, comparison, outcomes, and study (PICOS) framework and research questions. The main search concepts were panitumumab and colorectal cancer. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System (CTIS).

The search filters we developed were applied to limit retrieval to RCTs or controlled clinical trials. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. Refer to Appendix 1 for the detailed search strategies.

The initial search was completed on August 1, 2023. Regular alerts updated the search until the meeting of the Formulary Management Expert Committee (FMEC) on February 1, 2024.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from Grey Matters: A Practical Tool for Searching Health-Related Grey Literature. Included in this search were the websites of regulatory agencies (US FDA and European Medicines Agency). Google was used to search for additional internet-based materials. Refer to Appendix 1 for more information on the grey literature search strategy.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least 1 reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Protocol-Selected Studies

Characteristics of Included Studies

Two published phase III, open-label RCTs were identified from the literature for inclusion in the systematic review (Appendix 2, Figure 1): the PARADIGM study[10-12] and the CAIRO5 study.[13,14] The included studies are summarized in Table 4. A list of excluded studies is presented in Appendix 3.

Table 4: Details of Included Studies

Detail	PARADIGM	CAIRO5
Design and population		
Study design	Phase III, open-label RCT	Phase III, open-label RCT
Locations	Multicentre, 197 study sites in Japan	Multicentre, 46 study sites in the Netherlands and 1 study site in Belgium
Patient enrolment dates	May 2015 to June 2017	November 13, 2014, to January 31, 2022
Randomized (N)	N = 823 (overall population); randomized in a 1:1 ratio Left-sided tumour population (subgroup): • N = 316 panitumumab • N = 296 bevacizumab	N = 530 (overall population) Left-sided tumour population (subgroup): • N = 118 panitumumab (group D) • N = 118 bevacizumab (group C)
Inclusion criteria for overall population	• Patients aged ≥ 20 to < 80 years • Diagnosis of unresectable adenocarcinoma originating in the large intestine • Wild-type *RAS* according to adequate *KRAS* or *NRAS* testing • No prior chemotherapy for mCRC (relapse	• Patients aged ≥ 18 years • Histologically proven colorectal cancer with known *RAS* and *BRAF* mutation status • Previously untreated and unresectable liver-only metastases (as centrally assessed) • Measurable metastases according to RECIST

Detail	PARADIGM	CAIRO5
	had to be > 24 weeks after the final dose of adjuvant or neoadjuvant fluoropyrimidine therapy, if any received) • ECOG performance status score of 0 or 1 • Presence of at least 1 evaluable lesion according to RECIST 1.1 • Adequate kidney and liver function • Life expectancy of at least 3 months	1.1 • WHO performance status of 0 or 1 • Life expectancy of more than 12 weeks • No contraindications for liver surgery or ablation • Resectable primary tumour (if still in situ) • Adequate organ function
Exclusion criteria for overall population	• Patients previously treated with oxaliplatin in the adjuvant or neoadjuvant setting • Radiotherapy within 4 weeks • Brain metastasis or synchronous or metachronous cancers • Significant or poorly controlled concomitant disease/condition (protocol specified)	• Extrahepatic metastases • Previous systemic or local treatment for metastases • Previous adjuvant chemotherapy within the prior 6 months • Major cardiovascular event within the prior 12 months • Other significant or poorly controlled concomitant disease or condition • Other primary malignancy within the prior 5 years (excepting of adequately treated in situ carcinoma of any organ, basal cell carcinoma of the skin, or a second primary colorectal cancer)
Drugs		
Intervention	Panitumumab 6 mg/kg administered as an IV infusion every 2 weeks	Group D: Panitumumab 6 mg/kg administered as an IV infusion every 2 weeks for a maximum of 12 cycles
Comparator(s)	Bevacizumab 5 mg/kg administered as an IV infusion every 2 weeks	Group C: Bevacizumab 5 mg/kg administered as an IV infusion every 2 weeks for a maximum of 12 cycles
Concomitant medications and treatments	mFOLFOX6 every 2 weeks administered as follows: • oxaliplatin 85 mg/m^2 IV on day 1 • leucovorin 200 mg/m^2 IV on day 1 • fluorouracil IV bolus 400 mg/m^2 on day 1 • fluorouracil 2,400 mg/m^2 continuous IV infusion on days 1 to 3	FOLFOX or FOLFIRI (investigator's choice) based on patient preference, administered every 2 weeks for a maximum of 12 cycles: • oxaliplatin 85 mg/m^2 IV on day 1 (FOLFOX) • or • irinotecan 180 mg/m^2 IV on day 1 (FOLFIRI) Both with • folinic acid 400 mg/m^2 IV on day 1 • fluorouracil IV bolus 400 mg/m^2 on day 1 • fluorouracil 2,400 mg/m^2 continuous IV infusion over 46 hours
Duration		
Follow-up	Median follow-up of 61 months	Median follow-up of 49.9 months (95% CI, 44.5 to 52.5 months)

Detail	PARADIGM	CAIRO5
Outcomes		
Primary end point	Overall survival in patients with left-sided primary tumours (as per protocol revision)	Progression-free survival
Secondary and exploratory end points	**Secondary:** • overall survival in the overall population (with hierarchical testing procedure) • progression-free survival • response rate • duration of response • rate of successful curative-intent resection **Exploratory:** • percentage of early tumour shrinkage • best percentage change from baseline in target lesions (depth of response) • disease control rate • time to treatment failure • AEs	**Secondary:** • R0 and R1 resection rate • secondary progression-free survival • overall survival • objective response rate • toxicity • postoperative morbidity • curative resection rate • pathological complete response rate of resected lesions
Notes		
Publications (included in the systematic review as sources of information)	• Watanabe et al. (2023)[10] • Yoshino et al. (2017)[11] (rationale and design) • Muro et al. (2019)[12] (abstract)	• Bond et al. (2023)[13] • Huiskens et al. (2015)[14] (protocol)
Funding sources	• Takeda Pharmaceutical Company Limited	• Dutch Colorectal Cancer Group • Roche and Amgen

AEs = adverse events; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FOLFIRI = 5-fluorouracil, leucovorin, and irinotecan; FOLFOX = 5-fluorouracil, leucovorin, and oxaliplatin; mCRC = metastatic colorectal cancer; RCT = randomized controlled trial; RECIST = Response Evaluation Criteria in Solid Tumors version 1.1.
Sources: Watanabe et al. (2023)[10] and Bond et al. (2023).[13]

Study Design

The PARADIGM study[10] was performed in Japan; patients were randomized in a 1:1 ratio to receive panitumumab or bevacizumab, in combination with mFOLFOX6, for the first-line treatment of unresectable mCRC expressing wild-type *RAS*. The trial was initially designed to include and assess the primary outcome in the overall population of patients with right-sided or left-sided tumours. However, a protocol revision was made after enrolment completion but before the first interim analysis to perform the primary outcome assessment in patients who had a left-sided tumour, defined as a tumour originating in the descending colon, sigmoid colon, rectosigmoid, or rectum. The rationale from this change came from findings of other RCTs reported at the time the study was performed.[18,19,22] The population of interest presented and discussed in this review are the subset of 612 patients who had left-sided tumours.

Treatment allocation was performed using a minimization method, with a random component for the following allocation factors:

- study site

- age (< 65 or ≥ 65 years)
- liver metastasis (presence or absence).

Patients and investigators were not blinded to treatment assignment; the rationale was not discussed in the published articles.

The CAIRO5 study[13] was performed in the Netherlands; patients with left-sided wild-type *RAS* and *BRAF* tumours were randomized in a 1:1 ratio to receive panitumumab or bevacizumab, in combination with FOLFOX or FOLFIRI, for the first-line treatment of unresectable liver-only mCRC. The trial also included a comparison of treatments for patients who had a right-sided tumour; however, the population of interest presented and discussed in this review are the subset of 236 patients who had left-sided tumours. Note that at the advice of the data safety and monitoring board, accrual of patients with left-sided wild-type tumours expressing *RAS* into the trial was discontinued due to futility in March 2022.

Randomization was performed centrally using a minimization technique and stratified by the following allocation factors:

- resectability of liver metastases (potentially resectable or permanently unresectable)
- serum lactate dehydrogenase concentration (normal or abnormal)
- treatment choice (irinotecan or oxaliplatin).

Patients were assigned to treatment groups via a masked web-based allocation procedure. Patients and investigators were not blinded to treatment assignment; however, surgeon and radiologist members of the central liver expert panel were blinded to treatment allocation.

Inclusion and Exclusion Criteria

The study populations differed between the trials. Patients were eligible for the PARADIGM study if they were aged between 20 and 80 years and had previously untreated unresectable mCRC with *RAS* wild-type. In the CAIRO5 study, patients were eligible if they were aged 18 years or older and had previously untreated and unresectable liver-only metastases; as such, the study included patients with both potentially resectable and permanently unresectable disease, with no extrahepatic metastases. In both trials, the presence of at least 1 evaluable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 was required. In addition, patients needed to have a good performance status, as measured by ECOG performance status (< 2) in the PARADIGM study and by the WHO performance status (< 2) in the CAIRO5 study. Additional inclusion criteria included a life expectancy of at least 12 weeks in both studies as well as adequate kidney and liver function in the PARADIGM study and no contraindications for liver surgery or ablation in the CAIRO5 study.

Patients were not eligible for the PARADIGM study if they had been previously treated with oxaliplatin in the adjuvant or neoadjuvant setting or if the mCRC relapse was within 24 weeks of the final dose of an adjuvant fluoropyrimidine chemotherapy. Patients were also excluded if they received recent radiotherapy; if they had brain metastasis, synchronous, or metachronous cancers; or if they had a concomitant significant or poorly controlled condition among a protocol-specified list.

Patients were not eligible for the CAIRO5 study if they had extrahepatic metastases, adjuvant chemotherapy within the prior 6 months, or any previous systemic or local treatment for metastases. Patients were also excluded if they had a major cardiovascular event within the prior 12 months, another primary malignancy within the prior 5 years, or a concomitant significant or poorly controlled condition.

Interventions

The intervention evaluated in the PARADIGM study was panitumumab 6 mg/kg, and the comparator was bevacizumab 5 mg/kg. All patients in both groups received concomitant chemotherapy with mFOLFOX6.

The CAIRO5 study evaluated the use of bevacizumab 5 mg/kg, which was compared to panitumumab 6 mg/kg. All patients in both groups received concomitant chemotherapy with either mFOLFOX6 or FOLFIRI. The choice of backbone chemotherapy regimen (FOLFOX or FOLFIRI) was upon local investigators' choice based on patient preference. Treatments were administered for a maximum of 12 cycles.

Both panitumumab and bevacizumab in the 2 studies were administered as IV infusions every 2 weeks, and were to be discontinued upon disease progression, unacceptable toxicity, patient or physician decision, or curative-intent surgery. In the PARADIGM study, in case of discontinuation of study drug, recommendations for second- and subsequent-line treatments were as follows:

- second-line treatment — combination of bevacizumab or anti-EGFR antibody with an irinotecan-based chemotherapy was strongly recommended
- subsequent-line treatment — any approved drugs, used appropriately.

There were no recommendations for second- and subsequent-line treatments in the CAIRO5 study. Patient follow-up was to be maintained, and subsequent treatments received were to be documented; however, these were not reported in the publications.

In the PARADIGM study, prespecified supportive care and concomitant medications were recommended for use throughout the study period in case of neutropenia, nausea or vomiting, allergic reactions, hypertension, pulmonary fibrosis, and hepatitis B. Other symptomatic therapies were also allowed (e.g., in the presence of panitumumab-related AEs) at the investigator's discretion. Prespecified criteria were defined for dose reduction or suspension and discontinuation of study treatment and supportive care measures. No information was reported in the publications regarding the use of supportive care and concomitant medications in the CAIRO5 study.

Outcomes

A list of efficacy end points identified in the review protocol that were assessed in the clinical trial included in this review are provided in Table 5.

Table 5: Summary of Outcomes of Interest Identified in the Review Protocol

Outcome Measure	PARADIGM	CAIRO5
Overall survival	Primary	Secondary
Progression-free survival	Secondary	Primary
Objective response rate	Secondary	Secondary
Duration of response	Secondary	NR
Curative resection rate	Secondary	Secondary
HRQoL	NR	NR
AEs	Secondary	Secondary
SAEs	Secondary	Secondary
WDAEs	Secondary	Secondary
Mortality	Secondary	Secondary

AE = adverse event; HRQoL = health-related quality of life; NR = not reported; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

Overall survival was the primary efficacy outcome in the PARADIGM study and was assessed as a secondary outcome in the CAIRO5 study. It was defined in both trials as time from randomization to death from any cause. Overall survival is widely recognized as the gold-standard goal of therapy in the treatment of cancer.[15] The clinical experts we consulted emphasized that overall survival is indeed the most relevant outcome in clinical practice.

Progression-free survival was the primary efficacy outcome in the CAIRO5 study and was assessed as a secondary outcome in the PARADIGM study. It was defined in both studies as time from randomization to progressive disease or death. In the CAIRO5 study, disease progression was assessed using RECIST version 1.1. In the PARADIGM study, progression-free survival in patients undergoing curative-intent resection covered the time period up until preoperative diagnostics confirmed no progressive disease. In patients who discontinued study treatments due to reasons other than disease progression or death, progression-free survival covered the time period up until progressive disease, death, or patient being censored at the last follow-up date. No definition for disease progression was reported in the PARADIGM publications.

Objective response rate and curative-intent resection were secondary outcomes in both studies. In the PARADIGM study, objective response rate was defined as the proportions of patients with complete or partial response as the best overall response; no specific definition was reported about how response was assessed. The rate of successful curative-intent resection was defined as a postoperative R0 status. In the CAIRO5 study, objective response rate included patients with partial or complete response according to RECIST version 1.1; tumour response was assessed locally by the investigator and centrally by a masked panel. Curative-intent resection was defined as R0 or R1 resection, with R1 (microscopic tumour involvement in the resection margin) referred to as complete local treatment.

Statistical Analysis

PARADIGM Study

Initially, the sample size calculation was based on all participants. It was estimated that having 800 patients, resulting in 570 expected deaths, would enable the study to achieve 80% power, at a 1-sided significance level of 0.025. However, the primary analysis was amended in May 2019, following a protocol revision, to assess the primary outcome of overall survival in patients with left-sided tumours, with a 1-sided type I error of 0.0125 in each group (i.e., patients with left-sided tumours and all patients enrolled).

An interim analysis of overall survival was preplanned when approximately 70% of the targeted number of events had occurred (280 events among patients with left-sided tumours). A 1-sided alpha of 0.00308 was allocated to this analysis for patients with left-sided tumours. At the time of this interim analysis (November 2019), the independent data monitoring committee recommended continuation of the trial. In July 2020, the primary analysis was amended to implement a hierarchical testing procedure to test overall survival first among patients with left-sided tumours followed by the overall population.

Based on Monte-Carlo simulations, 420 deaths among patients with left-sided tumours would provide 80% power to detect an HR for overall survival of 0.74 at a 1-sided significance level of 0.02101. The HR of 0.74 was assumed based on results from a previous trial (TRICOLORE)[23] in which the median overall survival was 33.6 months. Considering the alpha spent for the interim analysis of overall survival among patients with left-sided tumours (1-sided alpha of 0.00308), a 1-sided alpha of 0.01159 was allocated to the final analysis, yielding a 1-sided significance level of 0.02101 for the primary analysis.

The study was designed to test for superiority of panitumumab relative to bevacizumab. Efficacy analyses were performed in the full analysis set, which included all patients who were randomized and had received at least 1 dose of the study drug and who met what the investigators considered to be the major eligibility criteria (not reported). For safety analyses, the safety population consisted of all randomized patients who received study treatment in the overall population.

The primary outcome was overall survival in patients with left-sided tumours, which was estimated with the use of a stratified log-rank test, adjusted for stratification factors used at randomization at a 2-sided alpha of 0.04202. Results were expressed using an HR with confidence interval using a stratified Cox model (stratified by the randomization factors of age and presence of liver metastases). A Cox analysis with step function for a time-varying coefficient was performed because there was a violation of the proportional hazards assumption in post hoc analyses. The Kaplan-Meier technique was used to generate survival curves. Patients were censored at the last confirmed date of survival or the date of data cut-off, whichever was earlier. Progression-free survival was analyzed among patients with an evaluable lesion using methods similar to the analysis of overall survival. Specifically, a stratified log-rank test was performed and a stratified Cox model was used to calculate between-group HRs with 2-sided 95% CIs. Kaplan-Meier curves of event-free survival were generated for each treatment group.

The point estimate and 95% CI for the difference in overall response rate was calculated via frequency analysis and the Cochran-Mantel-Haenszel test was performed using the same stratification factors as

used for randomization other than study site. Details of the analyses of curative resection rate and duration of response were not reported. There was no prespecified threshold for statistical significance established for between-group comparison of secondary outcomes; the study relied on the primary outcome of overall survival for clinical relevance. Analyses were not adjusted for multiplicity. Missing data were not imputed.

CAIRO5 Study

The sample size calculation estimated that having at least 256 events of disease progression or death would enable the study to achieve 80% power, at a 2-sided significance level of 5%, to detect a HR of 0.70 for progression-free survival in group C versus group D, including an interim analysis and assuming a median progression-free survival of 11.6 months in group C (bevacizumab).

Because the study was ongoing, emergence of new data on the lack of benefit of anti-EGFR treatments in some patients resulted in a protocol amendment to also consider tumour sidedness and *BRAF* mutation status for randomization, which initially only included *RAS* mutation status. With this amendment, patients with right-sided tumours with *BRAF* mutations would not be allocated to the bevacizumab and panitumumab comparison (groups C and D).

The study was designed to test for superiority of bevacizumab relative to panitumumab in patients with left-sided wild-type *RAS* and *BRAF* tumours only. Efficacy and safety analyses were performed in the modified intention-to-treat population (patients without withdrawal of consent before starting study treatment or violation of major entry criteria, including no mCRC or previous liver surgery for colorectal cancer liver metastases).

The primary outcome was progression-free survival, which was estimated with the use of a 2-sided stratified log-rank test. Patients without disease progression or who did not die were censored on their last clinical visit date. Results were expressed using a HR with CI using a stratified Cox proportional hazards analysis. The authors reported that the proportional hazards assumption was met based on testing for independence between scaled Schoenfeld and time. The Kaplan-Meier technique was used to generate survival curves. Overall survival results were not analyzed or reported because the study's statistical team did not consider the data to be mature. The secondary outcomes of objective response rate, curative resection rate, and harms (AEs, SAEs, WDAEs, mortality) were compared using the Fisher exact test. For response outcomes, patients without postbaseline measurements were classified as not evaluable and were excluded from the analysis. No information was reported in the publications about whether these analyses were adjusted for multiplicity.

Critical Appraisal

Internal Validity

Study Design, Intervention, and Comparators

The PARADIGM study was designed to evaluate the superiority of panitumumab over bevacizumab in the first-line treatment of patients with unresectable mCRC with *RAS* wild-type. The CAIRO5 study was designed to evaluate the superiority of bevacizumab over panitumumab in patients with untreated and unresectable

liver-only metastases. The populations of interest for this review from both studies were patients with left-sided wild-type *RAS* tumours.

The trials were randomized but were not blinded. By having an open-label design, the studies were susceptible to assessment and reporting biases because knowledge of treatment assignment could influence investigators' assessment of subjective efficacy and patient-reported outcomes, such as subjective AEs and tumour response outcomes (e.g., objective response rate, duration of response, progression-free survival). Ideally, anticancer drug trials should be blinded, when possible, with centralized review of tumour-based outcomes.[27]

In the PARADIGM study, there was no central assessment of the tumours, whereas in the CAIRO5 study, only an assessment of resectability was performed both locally by the investigator and centrally by a masked panel. It is not possible to determine the impact or direction of a potential bias that knowledge of treatment assignment may have had on other outcomes, such as subjective AEs.

Upon further disease progression in the PARADIGM study, the study drug regimen was discontinued and followed by the investigator's best choice of treatment. There were recommendations for second- and subsequent-line treatments, which were representative of clinical practice according to the clinical experts. The various therapies received by patients after disease progression were reported in Watanabe et al.[10] There was imbalance between treatment groups for the specific therapy received, including that 45% of patients in the panitumumab group received subsequent bevacizumab, whereas 46% of patients in the bevacizumab group received subsequent panitumumab. Although it cannot be confirmed whether imbalances in subsequent treatments would have favoured either treatment groups, the clinical experts we consulted considered bias in the overall survival results due to differences in subsequent treatments to be unlikely, considering the limited impact on survival of any therapy at this later stage of advanced disease. However, the estimated effect of panitumumab relative to bevacizumab on overall survival is reflective of the effect of the intervention drugs followed by subsequent treatments that were reflective of clinical practice in Canada.

Selection, Allocation, and Disposition of Patients

In both trials, patients were randomized at a ratio of 1:1 using appropriate methods to achieve prognostic balance and conceal allocation until group assignment. In the CAIRO5 study, the efficacy assessments were performed in a prespecified subset of patients who had a left-sided tumour; in the PARADIGM study, the assessments were performed in a subset of patients who had a left-sided tumour following a protocol revision. Selecting a subgroup of the population based on 1 single disease characteristic — although there is a valid rationale provided — may have introduced selection bias because randomization was not stratified in this subgroup. However, reported baseline demographic and disease characteristics in both studies were equally balanced between treatment groups in patients with left-sided tumours, suggesting that known confounding factors are not likely to have a significant impact on the results. The potential impact of unknown confounders and direction of potential bias are unknown.

In the PARADIGM study, high proportions of patients in both groups discontinued treatment; however, there were differences between treatment groups in reasons for discontinuation. Numerically fewer patients who

received panitumumab discontinued due to disease progression compared with patients who received bevacizumab, while numerically more patients in the panitumumab group discontinued due to curative-intent surgery or AEs. These high treatment discontinuation rates are expected given the stage of the disease and AE profiles of the drugs; however, they remain a concern because their potential impact on the results is uncertain.

Patient disposition was not detailed in the CAIRO5 publications. Therefore, there is a concern about the potential impact on the results of discontinuation, the magnitude and direction of which cannot be assessed.

Outcome Measures

The primary efficacy outcome in the PARADIGM study was overall survival, which is the preferred and most reliable end point in oncology trials.[15] In the CAIRO5 study, the primary efficacy outcome was progression-free survival, which was considered relevant, although not as clinically meaningful to inform treatment decisions according to the clinical experts we consulted. Progression-free survival is a surrogate outcome for overall survival and does not always correlate with overall survival.[15]

Additional efficacy outcomes in the trials included objective response rates and curative resection rates. In the PARADIGM study, in the absence of prespecified criteria, response rate may have been subjective to investigators' assessment. According to the clinical experts, an objective response rate would be particularly relevant in patients with potentially resectable disease, for whom reduction of tumour volume may result in successful surgery, as well as in patients with symptomatic disease to alleviate symptoms.

Statistical Analysis

The PARADIGM study had sufficient power for the analysis of the primary outcome. In the CAIRO5 study, at the advice of the data safety and monitoring board, accrual of patients into the trial who had left-sided wild-type tumours expressing *RAS* was discontinued due to futility in March 2022. With 205 events of disease progression or death reported, it is likely that the study did not have sufficient power for the analysis of the primary outcome because the study calculations planned for at least 256 events to achieve 80% power at a 2-sided significance level of 5% to detect an HR of 0.70. The imprecision is reflected in the CI, and its width will inform certainty in the judgment of the effect.

In the PARADIGM study, analyses were not adjusted for multiplicity, whereas in the CAIRO5 study, the authors of the publications did not describe any methods for accounting for multiplicity of comparisons for the key outcomes in the study. Therefore, there is the possibility of an increased risk of type I error (false-positive conclusions) for statistically significant results.

The methods used for the analysis were appropriate for time-to-event outcomes (stratified Cox model adjusted for stratification factors used at randomization in PARADIGM; stratified Cox proportional hazards analysis in CAIRO5). In both studies, however, the underlying assumption of proportional hazards was violated for the primary outcome assessment; based on visual inspection of the Kaplan-Meier plots for overall survival (PARADIGM) and progression-free survival (CAIRO5), there was crossing of the curves. In the PARADIGM study, testing with a Cox analysis with step function for a time-varying coefficient was performed; given that the interpretation of the HR is limited, the investigators presented separate HRs for

the first 28 months of the study and from 28 months to the end of follow-up in a post hoc analysis, which was appropriate. The post hoc analysis concluded that the HR differed between the first 28 months of the study (HR = 1.04; 95% CI, 0.80 to 1.35) compared with the last 28 months until end of follow-up (HR = 0.63; 95% CI, 0.49 to 0.83).[10] In the CAIRO5 study, the authors reported that the proportional hazards assumption was met based on testing for independence between scaled Schoenfeld and time; however, test results were not reported. Given the aforementioned crossing of the Kaplan-Meier curves, it may not be appropriate to interpret the overall HR because the HR varies over time (i.e., the treatment effect changes direction).

In both studies, between-group differences with CIs were not reported for many of the outcomes in the trial. As such, interpretation of these outcomes data is limited.

External Validity

Patient Selection

The inclusion and exclusion criteria in the PARADIGM and CAIRO5 studies were deemed clinically relevant and reasonable by the clinical experts. However, the patients in the studies differed slightly from the population typically seen by the experts in clinical practice in Canada because they were younger and had a better performance status, as shown by the baseline performance status in the studies. This should be considered when generalizing the findings from the studies to real-life patients.

Race and ethnicity are not expected to be meaningful prognostic factors in mCRC; therefore, the clinical experts had no concern over the fact that the PARADIGM study was performed exclusively in Japan, whereas the CAIRO5 study was performed almost exclusively in the Netherlands. Moreover, as per the clinical experts, clinical practice within these 2 countries is expected to be aligned with that of Canada.

The CAIRO5 study included a population who presented with selected disease characteristics (i.e., liver-only, potentially surgically resectable tumour); according to the clinical experts, this patient subpopulation accounts for approximately 15% of cases of mCRC and the disease trajectory is expected to differ from the overall mCRC disease trajectory.

Treatment Regimen and Length of Follow-Up

The administration of panitumumab in both studies was in line with the Health Canada recommended dosage in oncology and what would be used in the reimbursement population. Treatment duration and follow-up were considered adequate in the context of the disease.

The concomitant backbone chemotherapy regimen used in the PARADIGM study was mFOLFOX6, a modified version of FOLFOX. The concomitant backbone chemotherapy regimen used in CAIRO5 was mainly FOLFOX as well, which is the concomitant chemotherapy recommended per the Health Canada indication. A small proportion of patients received concomitant FOLFIRI instead; the clinical experts indicated that these regimens (i.e., mFOLFOX6, FOLFOX, and FOLFIRI) are considered interchangeable in clinical practice and they are expected to have similar efficacy.

In the PARADIGM study, there were recommendations for second- and subsequent-line treatments that were representative of clinical practice in Canada according to the clinical experts. Therefore, the estimated effect

of panitumumab relative to bevacizumab on overall survival in this study is reflective of the effect of the intervention drugs followed by subsequent treatments that are consistent with clinical practice in Canada.

Outcome Measures

Outcome measures of efficacy were considered relevant to clinical practice by the experts we consulted for this review and were suggested to be relevant by the patient groups. Focus was placed on overall survival for interpretation of the results, which was reported in the PARADIGM study but not in the CAIRO5 study because this remains the primary goal of therapy. Other efficacy outcomes reported were not as clinically meaningful to inform treatment decisions according to the clinical experts. However, outcomes of HRQoL and symptoms, were not reported in either of the trials; therefore, there is currently no information regarding the impact of panitumumab relative to bevacizumab on these outcomes that were identified as important to patients based on the input received.

Results of the Included Studies

Baseline Characteristics

Baseline characteristics were balanced between treatment groups in the PARADIGM study and in the CAIRO5 study. Full details regarding baseline characteristics are provided in Watanabe et al[10] for the PARADIGM study and in Bond et al[13] for the CAIRO5 study.

In the PARADIGM study, the median age of patients was 65.5 years (range, 28 to 79 years); 68% of patients were male and 33% were female. The proportions of patients within each of the ECOG performance status scores for the panitumumab and bevacizumab treatment arms were as follows: 84% and 79% of patients, respectively, had a performance status of 0, and 16% and 21%, respectively, had a performance status of 1. A total of 50% of patients in both groups had at least 2 organs with metastases; 70% of patients in both groups had liver disease. Prior treatments included primary tumour resection in 59% of patients in the panitumumab arm and 66% of patients in the bevacizumab arm; only 5% of patients per treatment arm received previous adjuvant chemotherapy.

In the CAIRO5 study, the median age of patients was 60 years (interquartile range [IQR], 52 to 69 years); 62% of patients were male and 38% were female. The proportions of patients within each of the WHO performance status scores in the panitumumab and bevacizumab treatment arms were as follows: 59% and 65% of patients, respectively, had a performance status of 0, and 41% and 35%, respectively, had a performance status of 1 (1 patient in the panitumumab group had a performance status of 2). Prior treatments included primary tumour resection in 30% of patients in the panitumumab arm and 34% of patients in the bevacizumab arm; only 4% of patients received previous adjuvant chemotherapy. As for resectability, 83% of patients had a potentially resectable tumour according to central expert panel assessment. Of the 116 patients assigned to and treated with panitumumab, a total of 103 (89%) patients chose FOLFOX as backbone chemotherapy, whereas 13 (11%) patients chose FOLFIRI. Similarly, of the 114 patients assigned to and treated with bevacizumab, 105 (92%) patients chose FOLFOX, whereas 9 (8%) patients chose FOLFIRI.

Patient Disposition

In the PARADIGM study (N = 823), 411 patients were randomly assigned to receive panitumumab, while 412 patients were randomized to receive bevacizumab. Of these, 316 patients in the panitumumab arm and 296 patients in the bevacizumab arm had left-sided tumours and were the population of interest for this review. High discontinuation rates were reported (311 of 316 patients and 292 of 296 patients, respectively); the most frequent reason was disease progression. However, there were differences between treatment groups in reasons for discontinuation: in the panitumumab group, 130 patients (41%) discontinued due to disease progression, 84 patients (27%) due to curative-intent resection, and 69 patients (22%) due to AEs. In the bevacizumab group, 144 patients (49%) discontinued due to disease progression, 54 patients (18%) due to curative-intent resection, and 52 patients (18%) due to AEs.

In the CAIRO5 study (N = 530), 236 patients had a left-sided tumour that expressed wild-type *RAS*; of these patients, 118 per group were randomly assigned to receive panitumumab or bevacizumab. Patient disposition was not detailed in the publications. However, the authors reported that 36 patients in each treatment arm received no local treatment (i.e., no surgery); of these patients, some received maintenance treatment with fluorouracil with or without study drug. This was the case for 8 patients who might not have received panitumumab and 18 patients who might not have receive bevacizumab.

Exposure to Study Treatments

In the PARADIGM study, for the key efficacy outcomes of overall survival and progression-free survival in patients with left-sided tumours, the median follow-up at the cut-off date of January 14, 2022, was 61.3 months (IQR, 57.2 to 65.2 months) in the panitumumab arm, and 61.0 months (IQR, 57.1 to 66.2 months) in the bevacizumab arm. In the CAIRO5 study, the median follow-up at the time of the analysis was 49.9 months (95% CI, 44.5 to 52.5 months) in the panitumumab arm (group D) and in the bevacizumab arm (group C).

Subsequent Treatments

Upon further disease progression in both the PARADIGM and CAIRO5 studies, the study drug regimen was discontinued and followed by the investigator's best choice of treatment. There were recommendations for second- and subsequent-line treatments in the PARADIGM study but not in the CAIRO5 study.

In the PARADIGM study, these recommendations were representative of clinical practice according to the clinical experts. The various therapies received by patients after disease progression were reported in Watanabe et al.[10] There was an imbalance between treatment groups for the specific therapy received, including that 45% of patients in the panitumumab group received subsequent bevacizumab, whereas 46% of patients in the bevacizumab group received subsequent panitumumab.

In the CAIRO5 study, patient follow-up was to be maintained, and the subsequent treatment received was to be documented; however, the various therapies received by patients after disease progression were not reported in the publications.

Efficacy Results

Only those efficacy outcomes identified in the review protocol are reported subsequently. Results are summarized in Table 6.

Table 6: Summary of Efficacy Outcomes for the Studies Included in the Systematic Review

Outcome	PARADIGM[10] (left-sided tumours)		CAIRO5[13] (patients with left-sided tumours)	
	Panitumumab N = 312	Bevacizumab N = 292	Panitumumab (group D) N = 116	Bevacizumab (group C) N = 114
Overall survival				
Number of patients with death from any cause, n (%)	218 (69.9)	230 (78.7)	Assessed in the study but NR in the publications	
Overall survival (months), median (95% CI)	37.9 (34.1 to 42.6)	34.3 (30.9 to 40.3)		
HR (95% CI)	0.82 (0.68 to 0.99)			
P value (stratified log-rank test)	0.03			
Kaplan-Meier estimated survival probabilities			Assessed in the study but NR in the publications	
3 years	53%	47%		
4 years	42%	33%		
5 years	32%	21%		
Progression-free survival				
Number of patients with disease progression or death from any cause, n (%)	217 (69.6)	224 (76.7)	106 (91)	99 (87)
Progression-free survival (months), median (95% CI)	13.1 (11.6 to 14.5)	11.9 (11.3 to 13.5)	10.4 (9.8 to 13.0)	10.8 (9.9 to 12.6)
HR (95% CI)	1.00 (0.83 to 1.20)		Bevacizumab vs. panitumumab 1.11 (0.84 to 1.48)	
P value	NR		0.46	
Objective response rate (complete or partial response)				
Number of patients contributing to the analysis	308	287	116	114
Number of patients with complete or partial response, n (%)	247 (80.2)	197 (68.6)	93 (80)	60 (53)
95% CI	75.3 to 84.5	62.9 to 74.0	NR	
Absolute difference, % (95% CI)	11.2 (4.4 to 17.9)		NR	
P value	NR		0.0001	
Duration of response (in patients with complete or partial response)				
Duration of response (months), median (95% CI), months	13.1 (11.1 to 14.8)	11.2 (9.6 to 13.1)	NR	
Curative resection rate	**R0**		**R0 and R1**	

Outcome	PARADIGM[10] (left-sided tumours)		CAIRO5[13] (patients with left-sided tumours)	
	Panitumumab N = 312	Bevacizumab N = 292	Panitumumab (group D) N = 116	Bevacizumab (group C) N = 114
Number of patients who achieved a curative resection,[a] n (%)	57 (18.3)	34 (11.6)	67 (58)	66 (58)
95% CI or P value	95% CI, 14.1 to 23.0	95% CI, 8.2 to 15.9	P = 1.00	
Absolute difference, % (95% CI)	6.6 (1.0 to 12.3)		NR	

CI = confidence interval; HR = hazard ratio; NR = not reported; R0 = excision of all colorectal cancer; R1 = microscopic tumour involvement in the resection margin.
Note: Analyses were not adjusted for multiplicity.
[a]Curative resection based on study definition.
Sources: Watanabe et al. (2023)[10] and Bond et al. (2023).[13]

Overall Survival

Overall survival was the primary efficacy outcome in the PARADIGM study. The use of panitumumab was associated with a stratified HR of 0.82 (95.798% CI, 0.68 to 0.99; P = 0.03) versus bevacizumab. The median survival time was 37.9 months (95.798% CI, 34.1 to 42.6 months) in the panitumumab group and 34.3 months (95.798% CI, 30.9 to 40.3 months) in the bevacizumab group. The magnitude of the between-group difference in median survival time was considered clinically meaningful by the clinical experts we consulted.

Overall survival probabilities in the panitumumab group compared with the bevacizumab group in the PARADIGM study were 53% versus 47% at 3 years, 42% versus 33% at 4 years, and 32% versus 21% at 5 years (95% CIs not reported); however, between-group differences, with associated CIs, were not reported. In the Kaplan-Meier plot, provided in Watanabe et al.,[10] the curves followed a similar pattern, but were not parallel and appeared to cross at approximately 28 months. The investigators presented separate HRs for the first 28 months of the study and from 28 months to the end of follow-up in a post hoc analysis, which was appropriate. The post hoc analysis concluded that the HR differed between the first 28 months of the study (HR = 1.04; 95% CI, 0.80 to 1.35) compared with the last 28 months until end of follow-up (HR = 0.63; 95% CI, 0.49 to 0.83).[10]

Overall survival was assessed as a secondary outcome in the CAIRO5 study; however, results for this outcome were not reported in any publication at the time of this review.

Progression-Free Survival

In the PARADIGM study, the use of panitumumab was associated with a stratified HR of 1.00 (95% CI, 0.83 to 1.20) versus bevacizumab for progression-free survival. The median progression-free survival time was 13.1 months (95% CI, 11.6 to 14.5 months) in the panitumumab group and 11.9 months (95% CI, 11.3 to 13.5 months) in the bevacizumab group. The magnitude of the between-group difference was considered not particularly clinically meaningful by the clinical experts we consulted. In the Kaplan-Meier plot, provided in Watanabe et al.,[10] the curves followed a similar pattern. The Kaplan-Meier estimates of the probability of

progression-free survival at clinically relevant follow-up times, either within groups or between groups, were not reported.

Progression-free survival was the primary efficacy outcome in the CAIRO5 study. The median survival time was 10.4 months (95% CI, 9.8 to 13.0 months) in the panitumumab group and 10.8 months (95% CI, 9.9 to 12.6 months) in the bevacizumab group. Because the study tested the superiority of bevacizumab over panitumumab, the use of bevacizumab was associated with a stratified HR of 1.11 (95% CI, 0.84 to 1.48; P = 0.46) versus panitumumab. In the Kaplan-Meier plot, provided in Bond et al.,[13] the curves followed a similar pattern, but were not parallel and appeared to cross at several time points. Kaplan-Meier estimates of the probability of progression-free survival at clinically relevant follow-up times, either within groups or between groups, were not reported.

Objective Response Rate

Response rates in the PARADIGM study included patients with either partial or complete response, which was observed in 80.2% (95% CI, 75.3% to 84.5%) of patients in the panitumumab group and in 68.6% (95% CI, 62.9% to 74.0%) of patients in the bevacizumab group. No statistical comparison was reported. The magnitude of the between-group difference (point estimate, 11.2%; 95% CI, 4.4% to 17.9%) was considered clinically meaningful by the clinical experts we consulted. However, there is uncertainty due to imprecision because the lower end of the confidence interval (i.e., 4.4%) may constitute little to no difference.

Response rates in the CAIRO5 study included patients with either partial or complete response, which was observed in 80% (95% CI not reported) of patients in the panitumumab group and in 53% (95% CI not reported) of patients in the bevacizumab group (P < 0.0001). The magnitude of the between-group difference (point estimate = 27%; 95% CI not reported) was considered clinically meaningful by the clinical experts we consulted; however, the precision of the effect estimate is unknown because the 95% CI was not reported. One patient in the panitumumab group achieved a complete response; all other patients in both arms had a partial response.

Duration of Response

In the PARADIGM study, the median duration of response (in patients with a partial or a complete response) was 13.1 months (95% CI, 11.1 to 14.8 months) in the panitumumab group and 11.2 months (95% CI, 9.6 to 13.1 months) in the bevacizumab group. No statistical comparison between treatment groups was reported. The magnitude of the between-group difference (point estimate = 1.9 months; 95% CI not reported) was not considered clinically meaningful by the clinical experts we consulted.

No data were reported in the publications for the outcome of duration of response for CAIRO5.

Curative Resection Rate

In PARADIGM, the proportions of patients with curative resection, i.e., who were able to undergo surgery with excision of all colorectal cancer after study treatment (R0), was 18.3% (95% CI, 14.1% to 23.0%) of patients receiving panitumumab and 11.6% (95% CI, 8.2% to 15.9%) in patients receiving bevacizumab. This resulted in an absolute difference between groups of 6.6% (95% CI, 1.0% to 12.3%). The clinical experts we consulted highlighted that although the percentage may appear small, it would be clinically meaningful for patients for

whom curative resection may be considered, as successful curative resection constitutes a potential cure. However, there is uncertainty due to imprecision, as the lower end of the confidence interval (i.e., 1.0%) may constitute little to no difference.

In CAIRO5, the proportion of patients with curative resection (i.e., all liver metastases treated with an R0 or R1 resection or ablation) was 58% in each group.

Health-Related Quality of Life

No data were reported in the publications for the outcome of HRQoL for PARADIGM and CAIRO5.

Harms Results

Only those harms identified in the review protocol are reported here. Refer to Table 7 for detailed harms data. Harms outcomes were reported for the overall population of patients in the PARADIGM study, regardless of tumour sidedness. This was considered appropriate by the clinical experts because it is not expected there would be any differences in harms outcomes according to the tumour sidedness (right-sided or left-sided).

Adverse Events

In the PARADIGM study, the proportion of patients who experienced an AE was 99.5% in the panitumumab group and 97.8% in the bevacizumab group. The most frequently reported AEs in the panitumumab and bevacizumab groups, respectively, included, but were not limited to, peripheral sensory neuropathy (70.8% and 73.7%), acne-like dermatitis (74.8% and 3.2%), stomatitis (61.6% and 40.5%), decreased appetite (55.7% and 50.6%), paronychia (52.0% and 4.9%), decreased neutrophil count (50.0% and 55.3%), and dry skin (46.0% and 9.3%).

In the CAIRO5 study, the proportion of patients who experienced a grade 3 to 5 AE was 69% in the panitumumab group and 54% in the bevacizumab group. Grade 1 to 2 AEs were not reported. According to the authors, the most frequently reported AEs in the panitumumab and bevacizumab groups, respectively, included neutropenia (21% and 25%, respectively), skin toxicity (25% and 1%), hypertension (7% and 18%), and diarrhea (16% and 4%).

Serious Adverse Events

The proportion of patients who experienced SAEs in the PARADIGM study was numerically higher in the panitumumab group, with 17.8% of patients reporting any SAE compared to 10.8% of patients in the bevacizumab group.

In CAIRO5, the proportion of patients who experienced SAEs was numerically higher in the panitumumab group, with 42% of patients reporting any SAE compared to 36% of patients in the bevacizumab group.

Withdrawals Due to Adverse Events

The proportion of patients who experienced WDAEs in the PARADIGM study was numerically higher in the panitumumab group, with 23.8% of patients withdrawing due to an AE compared to 18.4% of patients in the bevacizumab group.

In the CAIRO5 study, the proportion of patients who experienced WDAEs was 4% in the panitumumab group compared to 3% of patients in the bevacizumab group.

Table 7: Summary of Key Harms Outcomes in Studies Included in the Systematic Review

Outcome	PARADIGM[10] (overall population)		CAIRO5[13] (patients with left-sided tumour)	
	Panitumumab N = 404	Bevacizumab N = 407	Panitumumab (group D) N = 116	Bevacizumab (group C) N = 114
AEs	**Patients with any AEs**		**Patients with any grade 3 to 5 AEs**	
n (%)	**402 (99.5)**	**398 (97.8)**	**80 (69)**	**61 (54)**
Most common events (≥ 20%), n (%)				
Peripheral sensory neuropathy	286 (70.8)	300 (73.7)	NR	
Acne-like dermatitis	302 (74.8)	13 (3.2)	NR	
Stomatitis	249 (61.6)	165 (40.5)	NR	
Decreased appetite	225 (55.7)	206 (50.6)	NR	
Paronychia	210 (52.0)	20 (4.9)	NR	
Decreased neutrophil count	202 (50.0)	225 (55.3)	NR	
Dry skin	186 (46.0)	38 (9.3)	NR	
Nausea	160 (39.6)	161 (39.6)	NR	
Fatigue	159 (39.4)	162 (39.8)	NR	
Diarrhea	151 (37.4)	136 (33.4)	NR	
Dysgeusia	125 (30.9)	94 (23.1)	NR	
Hypomagnesemia	121 (30.0)	7 (1.7)	NR	
Palmar-plantar erythrodysesthesia syndrome	94 (23.3)	57 (14.0)	NR	
Constipation	93 (23.0)	107 (26.3)	NR	
Decreased platelet count	86 (21.3)	80 (19.7)	NR	
Patients with any SAEs, n (%)	**72 (17.8)**	**44 (10.8)**	**49 (42)**	**41 (36)**
Patients with any WDAEs, n (%)	**96 (23.8)**	**75 (18.4)**	**5 (4)**	**3 (3)**
Mortality, n (%)	**10 (2.5)**	**2 (0.5)**	**3 (3)**	**1 (1)**
Causes of death				
Interstitial lung disease	4	0	NR	NR
Lung disorder	1	0	NR	NR
Pneumonia	1	0	NR	NR
Pneumonia with pancytopenia	1	0	NR	NR
Pneumonitis	1	0	NR	NR

Outcome	PARADIGM[10] (overall population)		CAIRO5[13] (patients with left-sided tumour)	
	Panitumumab N = 404	Bevacizumab N = 407	Panitumumab (group D) N = 116	Bevacizumab (group C) N = 114
Sepsis and peritonitis	1	0	NR	NR
Cerebral hemorrhage	1	0	NR	NR
Respiratory failure	0	1	NR	NR
Unspecified	0	1	NR	NR
Cardiac arrest	NR	NR	1	0
Pulmonary embolism	NR	NR	1	0
Abdominal sepsis	NR	NR	1	0
Multiorgan failure	NR	NR	0	1

AE = adverse event; N/A = not applicable; NR = not reported; SAE = serious adverse event; WDAE = withdrawal due to adverse events.
Sources: Watanabe et al. (2023)[10] and Bond et al. (2023).[13]

Mortality

In the PARADIGM study, 10 patients (2.5%) who received panitumumab and 2 patients (0.5%) who received bevacizumab died during the study of causes that were unrelated to disease progression (those deaths were captured under harms outcomes). Common causes of deaths in the panitumumab and bevacizumab groups included interstitial lung disease (n = 4 and n = 0, respectively) as well as various infectious and noninfectious lung disorders (additional details are provided in Table 7.

In the CAIRO5 study, 3 patients (3%) who received panitumumab, and 1 patient (1%) who received bevacizumab died during the study of causes that were unrelated to disease progression (those deaths were captured under harms outcomes). Causes of deaths were cardiac arrest, pulmonary embolism, and abdominal sepsis in the panitumumab group, and multiorgan failure in the bevacizumab group.

Harms of Special Interest

In the PARADIGM study, dermatologic and soft tissue toxicity was reported more frequently in patients receiving panitumumab compared to patients receiving bevacizumab; these included acne-like dermatitis (74.8% versus 3.2%, respectively), paronychia (52.0% versus 4.9%), and dry skin (46.0% versus 9.3%). Regarding electrolyte disturbance, hypomagnesemia was reported more frequently in patients receiving panitumumab compared to patients receiving bevacizumab (30.0% versus 1.7%, respectively).

The CAIRO5 publications reported on patients with grade 3 or higher AEs, which were experienced by 71.8% of patients in the panitumumab group and 64.9% of patients in the bevacizumab group. The most frequently reported in the panitumumab and bevacizumab groups was decreased neutrophil count (31.9% and 35.4%, respectively). Among the prespecified harms of special interest, the most frequently reported in the panitumumab and bevacizumab groups, respectively, were as follows:

- Dermatologic and soft tissue toxicity

    - acne-like dermatitis (17.1% and 0%)
    - paronychia (9.4% and 0.2%)
    - dry skin (7.7% and 0.2%)
    - stomatitis (6.7% and 1.7%)
- Electrolyte disturbances:
    - hypomagnesemia (8.2% and 0%)
    - hypokalemia (5.2% and 0.7%)

Detailed SAEs were not reported in the PARADIGM publications; therefore, it is unknown whether patients experienced serious dermatologic and soft tissue toxicity (including Stevens-Johnson syndrome, skin necrosis, and toxic epidermal necrolysis), or serious hypersensitivity and infusion reactions (including anaphylactic reactions, bronchospasm, dyspnea, fever, chills, edema, angioedema, and hypotension) throughout the study duration.

In the PARADIGM study, pulmonary toxicity, including interstitial lung disease, was reported more frequently as a cause of death in patients receiving panitumumab compared to patients receiving bevacizumab.

No information was reported in the CAIRO5 publications regarding the harms of special interest identified in the review protocol. However, the publication reported on patients with grade 3 to 5 AEs. The most frequently reported grade 3 AE was neutropenia (14% of patients receiving panitumumab compared to 18% of patients receiving bevacizumab). Among the prespecified harms of special interest, the most frequently reported in the panitumumab and bevacizumab groups, respectively, were as follows:

- Dermatologic and soft tissue toxicity
    - skin toxicity (grade 3, 23% and 1%; grade 4, 2% and 0%)
    - mucositis or stomatitis (grade 3, 9% and 4%)
    - paronychia (grade 3, 3% and 0%)
- Serious dermatologic and soft tissue toxicity
    - Stevens-Johnson syndrome (grade 3, 1% and 0%)
- Electrolyte disturbances
    - hypokalemia (grade 3, 5% and 4%)
    - hypomagnesemia (grade 3, 3% and 0%)
    - hyponatremia (grade 3, 2% and 0%)
- Hypersensitivity and infusion reactions
    - infusion-related reaction (grade 3, 1% and 1%)

Indirect Evidence

Search and Selection Methods

Because both RCTs included in the systematic review compared panitumumab to bevacizumab, indirect evidence was considered to inform a comparison between panitumumab and cetuximab. In addition, the reporting of SAEs for the comparison of panitumumab and bevacizumab was limited in both included trials. A focused literature search for indirect treatment comparisons dealing with panitumumab and mCRC was run in MEDLINE (1946 to present) on August 1, 2023. No limits were applied to the search. Conference abstracts were excluded from the search results. The literature search results were screened by 1 reviewer to identify any indirect comparisons fulfilling the PICO criteria outlined in Table 3 (aside from study design). Updated literature searches were conducted up to February 1, 2024.

Included Indirect Comparisons

A total of 318 records were identified from the initial literature search. After title and abstract screening, 9 full-text articles were reviewed and 2 NMAs were included.[16,17] Of the 7 excluded NMAs, 3 did not specifically assess mCRC expressing wild-type *RAS*,[24-26] 1 evaluated neoadjuvant treatment strategies for rectal cancer,[27] 1 grouped all anti-EGFR therapies into a single treatment node in the NMA,[28] 1 examined third-line treatments for colorectal cancer,[29] and 1 was excluded as it investigated the same population, interventions, comparators, and outcomes as the included NMAs but was less up to date.[30] No additional eligible NMAs were identified from the updated literature searches.

Methods of Included Network Meta-Analyses

Of the systematic reviews contributing to each NMA, Wu et al. (2020)[17] aimed to include RCTs that assessed first-line treatment for patients with *RAS* or *BRAF* wild-type mCRC and to perform a subgroup analysis based on tumour location (i.e., left- versus right-sided tumours), and Choi et al. (2022)[16] aimed to include RCTs that assessed first- or second-line treatment for patients with *RAS* wild-type mCRC. Wu et al. (2020) evaluated both efficacy and harms outcomes, whereas Choi et al. (2022)[16] aimed to assess the risks of serious AEs. In each systematic review, the authors searched multiple electronic databases (at minimum MEDLINE [PubMed] and the Cochrane Central Register of Controlled Trials) and both also mentioned manually scanning the reference lists of eligible studies. The date of the last search ranged from March 2018 to February 2022. In all systematic reviews, study selection and data extraction were performed independently in duplicate with discrepancies resolved by consensus or discussion with a third reviewer. The risk of bias of the included RCTs was appraised at the study level using version 2.0 of the Cochrane Risk of Bias tool in both NMAs, which was also performed independently in duplicate with discrepancies resolved by consensus or discussion with a third reviewer in these studies.

In terms of statistical analyses, both NMAs were performed using the frequentist approach. Wu et al. (2020)[17] assessed heterogeneity of pairwise comparisons using Cochran Q test and I^2 values and evaluated publication bias via visual inspection of funnel plots and the Egger test. The analysis was conducted using a random-effects model but the rationale for selecting this approach was not described. Inconsistency between the direct and indirect evidence within the network was examined by testing the design-by-treatment interaction. In the NMA by Choi et al. (2022),[16] heterogeneity was assessed using I^2 values and

the assessment of publication bias was not reported. Additionally, the authors selected the fixed-effect model when heterogeneity was low (i.e., I^2 < 50%), whereas the random-effects model was applied when heterogeneity was high (i.e., I^2 > 50%), and Cochran Q was used to assess inconsistency. In terms of subgroup analyses, Wu et al. (2020)[17] conducted analyses according to *KRAS*, *RAS*, or *BRAF* wild-type mCRC and compared results for left- versus right-sided tumours, whereas Choi et al. (2022)[16] conducted analyses based on first- versus second-line treatment.

Results of Included NMAs

Characteristics of Included NMAs

The NMA by Wu et al. (2020)[17] for first-line treatment in patients with *RAS* wild-type mCRC included 8 trials, whereas the NMA by Choi et al. (2022)[16] for this same patient population included 4 trials (Table 8). The NMA by Choi et al. (2022)[16] did not include trials in which an active therapy was compared to chemotherapy alone. The ATOM trial[31] was included in the NMA by Choi et al. (2022)[16] but not in the NMA by Wu et al. (2020)[17] because it was published after the date last searched (March 2018).

Table 8: Primary Study Overlap Across the Included NMAs for First-Line Treatment in *RAS* Wild-Type mCRC

Trial name	Included in Wu et al. (2020)	Included in Choi et al. (2022)
Cetuximab + chemotherapy vs. chemotherapy		
CRYSTAL[32]	Yes	No
OPUS[33]	Yes	No
TAILOR[34]	Yes	No
Panitumumab + chemotherapy vs. chemotherapy		
PRIME[35]	Yes	No
VOLFI[36]	Yes	No
Bevacizumab + chemotherapy vs. cetuximab + chemotherapy		
FIRE-3[18]	Yes	Yes
CALGB 80405[37]	Yes	Yes
ATOM[31]	No	Yes
Bevacizumab + chemotherapy vs. panitumumab + chemotherapy		
PEAK[38]	Yes	Yes

Sources: Wu et al. (2020)[17] and Choi et al. (2022).[16]

Characteristics of the NMAs and the RCTs included in them are presented in Table 9. The NMA by Wu et al. (2020)[17] included 2,544 patients, although it was unclear how many were included in the left-sided tumour subgroup, and Choi et al. (2022)[16] included 2,130 patients. In both NMAs, trial comparisons formed closed loops with few studies (range, 1 to 4) per comparison. The NMA by Wu et al. (2020)[17] included treatment nodes for chemotherapy alone, chemotherapy plus bevacizumab, chemotherapy plus cetuximab, and chemotherapy plus panitumumab. The NMA by Choi et al. (2022)[16] included the same treatment nodes

except chemotherapy alone. Notably, in the NMA by Choi et al. (2022),[16] effect estimates for panitumumab versus cetuximab were not reported. Although the comparison between panitumumab and bevacizumab is already informed by 2 head-to-head RCTs, the NMA was still considered relevant because the reporting of SAEs was scant in the included RCT publications. Outcomes analyzed in the NMA by Wu et al. (2020)[17] were overall survival, progression-free survival, objective response rate, curative resection rate, time to response, duration of response, early tumour shrinkage, and AEs. Choi et al. (2022)[16] assessed hematological, cardiovascular, dermatological, gastrointestinal, renal, and neurological SAEs.

Table 9: Characteristics of the NMAs and Their Included Trials

Author (year)	RCTs (patients)	Relevant comparisons (vs. panitumumab)	Outcomes analyzed
Wu et al. (2020)[17]	8 (2,544)	• Bevacizumab + chemotherapy • Cetuximab + chemotherapy	• OS • PFS • ORR • Curative resection rate • Time to response • Duration of response • Early tumour shrinkage • AEs

Choi et al. (2022)[16]	4 (2,130)	• Bevacizumab + chemotherapy	• Serious AEs:
			  ○ hematological
			  ○ cardiovascular
			  ○ dermatological
			  ○ gastrointestinal
			  ○ renal
			  ○ neurologic

AE = adverse event; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.
Sources: Wu et al. (2020)[17] and Choi et al. (2022).[16]

In both included NMAs, there was limited reporting of trial and patient characteristics and limited assessment of heterogeneity between included trials. For trials included in the NMA by Wu et al. (2020),[17] study eligibility criteria for ECOG status were either 0 to 1 or 0 to 2. In addition, 3 trials included in this NMA compared cetuximab plus chemotherapy versus chemotherapy alone, 2 compared panitumumab plus chemotherapy versus chemotherapy alone, 2 compared bevacizumab plus chemotherapy versus cetuximab plus chemotherapy, and 1 trial compared bevacizumab plus chemotherapy versus panitumumab plus chemotherapy, and background chemotherapy in these trials included FOLFIRI, FOLFOX4, mFOLFOX6, FOLFOXIRI, or mFOLFOXIRI; trials included in this NMA evaluating panitumumab used FOLFOX4, FOLFOXIRI, mFOLFOXIRI, or mFOLFOX6 as background chemotherapy. For trials included in the NMA by Choi et al. (2022),[16] 3 compared bevacizumab plus chemotherapy versus cetuximab plus chemotherapy and 1 compared bevacizumab plus chemotherapy versus panitumumab plus chemotherapy with background

chemotherapy in these trials including FOLFIRI or mFOLFOX6; the 1 trial included in this NMA evaluating panitumumab used mFOLFOX6 as background chemotherapy.

In terms of overall risk of bias, trials included in the NMA by Wu et al. (2020)[17] were deemed to have either an unclear (6 of 8 studies; 75%) or high (2 of 8 studies; 25%) risk of bias. Trials deemed to have an overall unclear risk of bias were generally judged to have unclear allocation concealment, performance bias, or selective outcome reporting; trials deemed to have an overall high risk of bias were judged to have a high risk of bias for selective outcome reporting. In contrast, in the NMA by Choi et al. (2022),[16] 3 of 4 studies (75%) were deemed to have an overall high risk of bias and 1 study (25%) was deemed to have an overall unclear risk of bias. Notably, trials deemed to have an overall high risk of bias were judged to have a high risk of bias in the measurement of the outcomes, whereas the trial deemed to have an overall unclear risk of bias was judged to have unclear risk of bias in the measurement of the outcomes. One of the trials at overall high risk of bias also had unclear risk of bias in the selection of the reported result.

Efficacy Results of Included NMAs

Comparative effects for efficacy outcomes were only reported in the NMA by Wu et al. (2020),[17] which included a subgroup analysis on patients with left-sided mCRC expressing wild-type *RAS* (Table 10).[17] The effect estimates for both panitumumab versus bevacizumab and panitumumab versus cetuximab were reported.

Table 10: Efficacy Results of the Left-Sided *RAS* Wild-Type Subgroup Analysis From the NMA by Wu et al. (2020)

Outcome	Effect estimate for panitumumab vs. bevacizumab	Effect estimate for panitumumab vs. cetuximab
Overall survival, HR (95% CI)	0.69 (0.38 to 1.23)	1.25 (0.75 to 2.08)
Progression-free survival, HR (95% CI)	0.78 (0.44 to 1.38)	1.10 (0.65 to 1.85)
Objective response rate, OR (95% CI)	1.07 (0.65 to 1.76)	0.68 (0.43 to 1.09)

CI = confidence interval; HR = hazard ratio; NMA = network meta-analysis.
Source: Wu et al. (2020).[17]

Overall Survival

For the comparison between panitumumab versus bevacizumab, the HR for OS was 0.69 (95% CI, 0.38 to 1.23), with the point estimate favouring panitumumab. For the comparison between panitumumab versus cetuximab, the HR for OS was 1.25 (95% CI, 0.75 to 2.08), with the point estimate favouring cetuximab. These effect estimates were affected by imprecision, such that the 95% CIs included the potential that either drug in each comparison could be favoured. The results for the assessments of statistical heterogeneity, inconsistency, and publication bias for this analysis were not reported.

Progression-Free Survival

For the comparison between panitumumab and bevacizumab, the HR for PFS was 0.78 (95% CI, 0.44 to 1.38), with the point estimate favouring panitumumab. For the comparison between panitumumab versus cetuximab, the HR for PFS was 1.10 (95% CI, 0.65 to 1.85), with the point estimate favouring cetuximab. These effect estimates were affected by imprecision, such that the 95% CIs included the potential that either drug in each comparison could be favoured. The extent of statistical heterogeneity present in this analysis was not reported. The assessments of inconsistency and publication bias for this outcome were reported for the overall analysis only (i.e., not for any subgroup analyses). The authors reported that they did not detect any significant differences between the direct and indirect evidence and that there was no evidence of publication bias for this outcome.

Objective Response Rate

For the comparison between panitumumab versus bevacizumab, the OR for ORR was 1.07 (95% CI, 0.65 to 1.76), with the point estimate favouring panitumumab. For the comparison between panitumumab versus cetuximab, the OR for ORR was 0.68 (95% CI, 0.43 to 1.09), with the point estimate favouring cetuximab. These effect estimates were affected by imprecision, such that the 95% CIs included the potential that either drug in each comparison could be favoured. The extent of statistical heterogeneity present in this analysis was not reported. The assessments of inconsistency and publication bias for this outcome were reported for the overall analysis only (i.e., not for any subgroup analyses). The authors reported that they did not detect any significant differences between the direct and indirect evidence and that there was no evidence of publication bias for this outcome.

Duration of Response

Comparative effect estimates for duration of response were not reported in any of the included NMAs.

Curative Resection Rate

Comparative effect estimates for curative resection rate were not reported in any of the included NMAs.

Health-related Quality of Life

HRQoL was not reported in any of the included NMAs.

Harms Results of Included NMAs

Comparative effects for harms reported in the NMA by Choi et al. (2022)[16] are presented in Table 11, which included a subgroup analysis on first-line treatment for mCRC; however, a subgroup analysis based on tumour location was not conducted.[16] Only the effect estimates for panitumumab versus bevacizumab and cetuximab versus bevacizumab were reported (i.e., the effects between panitumumab versus cetuximab were not reported in this NMA).

Results for the SAEs of thrombocytopenia, nausea, fatigue, peripheral neuropathy, paronychia, hypokalemia, hypocalcemia, and dehydration were inconclusive due to wide CIs that included the possibility of both benefit and harm for panitumumab relative to bevacizumab. The results for the relative risk of hypertension favoured panitumumab (risk ratio [RR] = 0.05; 95% CI, 0.00 to 0.80), whereas the results for the relative risk of

rash (RR = 22.00; 95% CI, 5.44 to 88.98), mucositis (RR = 5.61; 95% CI, 1.66 to 18.94), and hypomagnesemia (RR = 21.00; 95% CI, 1.24 to 354.90) favoured bevacizumab. Assessments for statistical heterogeneity, inconsistency, and publication bias for this analysis were not reported.

Table 11: Serious AE Results of the First-Line Treatment Subgroup Analysis From the NMA by Choi et al. (2022)

Outcome	Effect estimate for panitumumab vs. bevacizumab RR (95% CI)
Hematological	
Thrombocytopenia	5.00 (0.24 to 103.21)
Gastrointestinal	
Nausea	2.00 (0.18 to 21.80)
Neurological	
Fatigue	1.25 (0.61 to 2.57)
Peripheral neuropathy	0.20 (0.01 to 4.13)
Cardiovascular	
Hypertension	0.05 (0.00 to 0.80)
Dermatological	
Rash	22.00 (5.44 to 88.98)
Paronychia	2.00 (0.18 to 21.80)
Mucositis	5.61 (1.66 to 18.94)
Renal	
Hypomagnesemia	21.00 (1.24 to 354.90)
Hypokalemia	2.14 (0.90 to 5.09)
Hypocalcemia	5.00 (0.24 to 103.21)
Dehydration	6.00 (0.73 to 49.19)

AE = adverse event; CI = confidence interval; RR = risk ratio.
Source: Choi et al. (2022).[16]

Critical Appraisal of Included Network Meta-Analyses

The included NMAs were not informed by an a priori registered protocol. As such, there is risk of bias in the selection of the reported results. The search strategies of both systematic reviews were comprehensive because they searched multiple bibliographic databases and employed an additional strategy (reference list scanning). The NMA by Wu et al. (2020) may be missing newer studies that were published after the date last searched (March 2018), so there is the potential for bias due to missing evidence in the synthesis. The NMA by Wu et al. (2020)[17] included RCTs in which the interventions of interest were compared to chemotherapy alone, whereas Choi et al. (2022)[16] did not include such studies, reducing the overlap of

primary studies included in these NMAs. Further, the 2 NMAs focused on different outcomes. In all cases, the methods for study selection and data extraction were adequate to minimize the risk of error. The risk of bias was assessed using appropriate tools; however, in the NMA by Choi et al. (2022)[16] trials were rated as overall low risk of bias, even when 1 or more domains contributing to the overall risk of bias was rated as high risk, which is inconsistent with the guidance for the use of the tool. Risk of bias was assessed at the level of the study, rather than at the level of the reported result, ignoring that the risk of bias can differ per reported result within a study. Based on the reported information, analysis methods across the NMAs generally appeared appropriate; however, model parameters (i.e., assessment of model fit) and assessments of heterogeneity, inconsistency, and publication bias were not presented for most analyses included in this review.

Although both NMAs used the same risk of bias tool and there was generally consistent overlap in the included trials, each NMA came to different conclusions regarding overall risk of bias. Wu et al. (2020)[17] determined that overall risk of bias was either unclear or high across included trials, whereas Choi et al. (2022)[16] judged that the included trials mostly had a low risk of bias. Overall, differences in their risk of bias assessments were related to the domains of allocation concealment, performance bias, measurement bias, and selective outcome reporting. Notably, Wu et al. (2020)[17] evaluated both efficacy and safety, whereas Choi et al. (2022) only focused on SAEs, which may, at least in part, explain the differences in their respective risk of bias assessments. As noted previously, in the NMA by Choi et al. (2022),[16] the judgment of overall risk of bias was not aligned with the guidance for use of the tool.

The assessment of clinical and methodological heterogeneity in the included NMAs was limited, which challenged the transitivity assumption. In both cases, there was insufficient information reported by the authors of the NMAs to judge the degree of heterogeneity in potential treatment effect modifiers across the various RCTs. Although the evidence networks formed a closed loop, there were a limited number of trials included in each NMA. Nearly all comparison outcomes were affected by imprecision which reduced the certainty of the effect estimates, including the size and direction of the effect. The CIs were wide and often included the potential for no important difference between treatments or that either treatment could be favoured, especially for efficacy outcomes.

For the efficacy outcomes presented in the NMA by Wu et al. (2020),[17] the subgroup analysis results were directly relevant and most applicable to patients with left-sided mCRC expressing wild-type *RAS*. For the safety outcomes presented in the NMA by Choi et al. (2022),[16] the results represented patients who received first-line treatment for mCRC regardless of tumour sidedness, indicating potential indirectness regarding the patient population of interest for these outcomes. However, this was considered appropriate by the clinical experts because it is not expected that there would be any differences in harms outcomes according to the tumour sidedness (right-sided or left-sided).

Although a number of clinically relevant outcomes were considered, comparative effects for several important efficacy outcomes that may be of high relevance to these patients (i.e., duration of response, curative resection rate, and HRQoL) were not reported.

Other Relevant Evidence

No long-term extension study or additional relevant study was considered to address important gaps in the evidence included in the systematic review.

Economic Evidence

Because this review is part of our Non-Sponsored Reimbursement Review program, in which an application filed by a sponsor is absent, we do not have access to an economic model for panitumumab in combination with first-line standard chemotherapy for the treatment of left-sided mCRC that expresses wild-type *RAS*. As a result, the economic review consists of a cost comparison between panitumumab in combination with first-line standard chemotherapy and appropriate comparators for the first-line treatment of patients with mCRC who have left-sided primary tumours that express wild-type *RAS*.

The comparators presented in the Table 12 have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on each product's respective product monographs and validated by clinical experts. If discrepancies in dosing between the product monograph and clinical practice in Canada were noted, the dose specified by the clinical experts was used. Pricing for comparator products was based on publicly available list prices.

The clinical expert feedback we obtained indicated that there are 2 distinct comparators used in combination with 3 distinct chemotherapy regimens: bevacizumab plus FOLFOX, bevacizumab plus FOLFIRI, bevacizumab plus XELOX, cetuximab plus FOLFOX, and cetuximab plus FOLFIRI (Table 12). Results of the cost comparison demonstrate that, over a 28-day cycle, panitumumab is more costly than bevacizumab when used in combination with FOLFOX, FOLFIRI, or XELOX. In addition, panitumumab is less costly than cetuximab, when used in combination with FOLFOX or FOLFIRI, over a 28-day cycle. Note that results may differ by jurisdiction if there are differences in their list prices for the drugs under review compared to those presented in Table 12.

Table 12: Cost Comparison Table for mCRC

Treatment	Strength or concentration	Form	Price[a] ($)	Recommended dosage	Daily cost ($)[a]	Average 28-day cost ($)[a]
Panitumumab (Vectibix)	**20 mg/mL**	**5 mL vial**	**641.7700**	**6 mg/kg every 2 weeks**	**194**	**5,446**
Panitumumab + FOLFOX						
Panitumumab (Vectibix)	20 mg/mL	5 mL vial	641.7700	6 mg/kg every 2 weeks	194	5,446
Oxaliplatin (generic)	5 mg/mL	10 mL vial 20 mL vial 40 mL vial	36.2700 72.5400 145.0800	85 mg/m^2 every 2 weeks	8	223

Treatment	Strength or concentration	Form	Price[a] ($)	Recommended dosage	Daily cost ($)[a]	Average 28-day cost ($)[a]
Folic acid (Leucovorin)	10 mg/mL	5 mL vial 50 mL vial	68.9430[b] 350.1900	400 mg/m^2 every 2 weeks	36	1,014
Fluorouracil bolus	50 mg/mL	100 mL vial	160.9000	400 mg/m^2 every 2 weeks	2	47
Fluorouracil infusion	50 mg/mL	100 mL vial	160.9000	2,400 mg/m^2 every 2 weeks	10	280
Panitumumab + FOLFOX					**250**	**7,010**
Panitumumab + FOLFIRI						
Panitumumab (Vectibix)	20 mg/mL	5 mL vial	641.7700	6 mg/kg every 2 weeks	194	5,446
Irinotecan (generic)	20 mg/mL	2 mL vial 5 mL vial 25 mL vial	208.3400 520.8500 2,604.2500	180 mg/m^2 every 2 weeks	121	3,394
Folic acid (Leucovorin)	10 mg/mL	5 mL vial 50 mL vial	68.9430[b] 350.1900	400 mg/m^2 every 2 weeks	36	1,014
Fluorouracil bolus	50 mg/mL	100 mL vial	160.9000	400 mg/m^2 every 2 weeks	2	47
Fluorouracil infusion	50 mg/mL	100 mL vial	160.9000	2,400 mg/m^2 every 2 weeks	10	280
Panitumumab + FOLFIRI					**363**	**10,181**
Panitumumab + XELOX						
Panitumumab (Vectibix)	20 mg/mL	5 mL vial	641.7700	6 mg/kg every 2 weeks	194	5,446
Oxaliplatin (generic)	5 mg/mL	10 mL vial 20 mL vial 40 mL vial	36.2700 72.5400 145.0800	130 mg/m^2 every 3 weeks	8	228
Capecitabine (Xeloda)	150 mg 500 mg	Tab	0.4575[c] 1.5250[c]	1,000 mg/m^2 twice daily from days 1 to 14 of 21-day cycle	7	205
Panitumumab + XELOX					**209**	**5,879**
Bevacizumab + FOLFOX						
Bevacizumab (Bambevi) Bevacizumab (Zirabev)	25 mg/mL	4 mL vial 16 mL vial	347.0000 1,388.0000	5 mg/kg every 2 weeks	88	2,454
Oxaliplatin (generic)	5 mg/mL	10 mL vial 20 mL vial 40 mL vial	36.2700 72.5400 145.0800	85 mg/m^2 every 2 weeks	8	223

Treatment	Strength or concentration	Form	Price[a] ($)	Recommended dosage	Daily cost ($)[a]	Average 28-day cost ($)[a]
Folic acid (Leucovorin)	10 mg/mL	5 mL vial 50 mL vial	68.9430[b] 350.1900	400 mg/m^2 every 2 weeks	36	1,014
Fluorouracil bolus	50 mg/mL	100 mL vial	160.9000	400 mg/m^2 every 2 weeks	2	47
Fluorouracil infusion	50 mg/mL	100 mL vial	160.9000	2,400 mg/m^2 every 2 weeks	10	280
Bevacizumab + FOLFOX					**144**	**4,017**
Bevacizumab + FOLFIRI						
Bevacizumab (Bambevi) Bevacizumab (Zirabev)	25 mg/mL	4 mL vial 16 mL vial	347.0000 1,388.0000	5 mg/kg every 2 weeks	88	2,454
Irinotecan (generic)	20 mg/mL	2 mL vial 5 mL vial 25 mL vial	208.3400 520.8500 2,604.2500	180 mg/m^2 every 2 weeks	121	3,394
Folic acid (Leucovorin)	10 mg/mL	5 mL vial 50 mL vial	68.9430[b] 350.1900	400 mg/m^2 every 2 weeks	36	1,014
Fluorouracil bolus	50 mg/mL	100 mL vial	160.9000	400 mg/m^2 every 2 weeks	2	47
Fluorouracil infusion	50 mg/mL	100 mL vial	160.9000	2,400 mg/m^2 every 2 weeks	10	280
Bevacizumab + FOLFIRI					**257**	**7,189**
Bevacizumab + XELOX						
Bevacizumab (Bambevi) Bevacizumab (Zirabev)	25 mg/mL	4 mL vial 16 mL vial	347.0000 1,388.0000	7.5 mg/kg every 3 weeks	88	2,454
Oxaliplatin (generic)	5 mg/mL	10 mL vial 20 mL vial 40 mL vial	36.2700 72.5400 145.0800	130 mg/m^2 every 3 weeks	8	228
Capecitabine (Xeloda)	150 mg 500 mg	Tab	0.4575[c] 1.5250[c]	1,000 mg/m^2 twice daily from days 1 to 14 of 21-day cycle	7	205
Bevacizumab + XELOX					**103**	**2,887**
Cetuximab + FOLFOX						
Cetuximab (Erbitux)	2 mg/mL	50 mL vial	378.7500	Initiation: 400 mg/m^2; maintenance: 250 mg/m^2 weekly	282	7,884

Treatment	Strength or concentration	Form	Price[a] ($)	Recommended dosage	Daily cost ($)[a]	Average 28-day cost ($)[a]
Oxaliplatin (generic)	5 mg/mL	10 mL vial 20 mL vial 40 mL vial	36.2700 72.5400 145.0800	85 mg/m^2 every 2 weeks	8	223
Folic acid (Leucovorin)	10 mg/mL	5 mL vial 50 mL vial	68.9430[b] 350.1900	400 mg/m^2 every 2 weeks	36	1,014
Fluorouracil bolus	50 mg/mL	100 mL vial	160.9000	400 mg/m^2 every 2 weeks	2	47
Fluorouracil infusion	50 mg/mL	100 mL vial	160.9000	2,400 mg/m^2 every 2 weeks	10	280
Cetuximab + FOLFOX					**337**	**9,448**
Cetuximab + FOLFIRI						
Cetuximab (Erbitux)	2 mg/mL	50 mL vial	378.7500	Initiation: 400 mg/m^2; maintenance: 250 mg/m^2 weekly	282	7,884
Irinotecan (generic)	20 mg/mL	2 mL vial 5 mL vial 25 mL vial	208.3400 520.8500 2,604.2500	180 mg/m^2 every 2 weeks	121	3,394
Folic acid (Leucovorin)	10 mg/mL	5 mL vial 50 mL vial	68.9430[b] 350.1900	400 mg/m^2 every 2 weeks	36	1,014
Fluorouracil bolus	50 mg/mL	100 mL vial	160.9000	400 mg/m^2 every 2 weeks	2	47
Fluorouracil infusion	50 mg/mL	100 mL vial	160.9000	2,400 mg/m^2 every 2 weeks	10	280
Cetuximab + FOLFIRI					**451**	**12,619**

FOLFIRI = 5-fluorouracil, leucovorin, and irinotecan; FOLFOX = 5-fluorouracil, leucovorin, and oxaliplatin; mCRC = metastatic colorectal cancer; XELOX = capecitabine (Xeloda) and oxaliplatin.

Note: All prices are from the Delta IQVIA database (accessed October 2023),[1] unless otherwise indicated, and do not include dispensing fees. Recommended dosage is based on Cancer Care Ontario monographs,[39] unless otherwise indicated. For dosing that depends on weight or body surface area, we assumed 70.72 kg or 1.81 m^2 that was validated by clinical expert feedback. Total cost estimates per regimen are based on the least costly combination of the component drugs, with wastage considered for single-use vials.

[a]When initiation and maintenance dosages differ, cost is based on the maintenance dose, unless otherwise stated. Costs for 21-day treatment regimens have been prorated to a 28-day period.

[b]Alberta Health Care Insurance Plan.[40]

[c]Ontario Drug Benefit Formulary.[41]

Price Reduction Analysis

Because panitumumab is more costly than bevacizumab, an analysis was conducted to determine the price reduction required for the drug acquisition cost of panitumumab to equate that of the least costly comparator. Considering constant chemotherapy regimen costs across combination regimens, a 55% price reduction is necessary for the acquisition cost of panitumumab to equal that of bevacizumab.

Table 13: Price Reduction Analyses

Scenario	Submitted price ($)	Reduction needed (%)	Reduced price ($)	Savings relative to submitted price[a] ($)
Price reduction required to equal least costly comparator (bevacizumab)	641.77	55	288.80	352.97

[a]Savings from the sponsor list price per patient per unit.

Issues for Consideration

The reimbursement of panitumumab for the treatment of patients with mCRC that expresses wild-type *RAS* may be associated with additional costs outside of drug acquisition costs. To determine eligible patients, *RAS* and *BRAF* diagnostic testing is required. Costs associated with diagnostic testing have not been evaluated in this review. The clinical expert feedback we obtained for this review noted that *RAS* and *BRAF* diagnostic testing would not be limited to patients treated with panitumumab because it would be similarly required among patients treated with bevacizumab and cetuximab combination regimens. Hence, the inclusion of diagnostic testing costs is not likely to result in cost differences between panitumumab and comparators.

No cost-effectiveness studies conducted in Canada were identified based on a literature search conducted on October 31, 2023.

Discussion

Summary of Available Evidence

Two published phase III, open-label RCTs were included in the systematic review: the PARADIGM study[10-12] and the CAIRO5 study.[13,14] The PARADIGM study[10] was performed in Japan; patients were randomized to receive panitumumab or bevacizumab, in combination with mFOLFOX6, for the first-line treatment of unresectable mCRC expressing wild-type *RAS*. The subset of 612 patients who had left-sided tumours are the population of interest presented and discussed in this review. The primary outcome was overall survival.

The CAIRO5 study[13] was performed in the Netherlands; patients with left-sided *RAS* and *BRAF* wild-type tumours were randomized to receive panitumumab or bevacizumab, in combination with FOLFOX or FOLFIRI, for the first-line treatment of unresectable liver-only mCRC. This constitutes a selected subpopulation of the overall mCRC indication for panitumumab, who are expected to have a different disease trajectory. The subset of 236 patients who had left-sided tumours are the population of interest for this review. The primary outcome was progression-free survival.

Study drugs were administered in the PARADIGM and CAIRO5 studies at the recommended dosage (i.e., panitumumab 6 mg/kg and bevacizumab 5 mg/kg administered as IV infusions every 2 weeks). All patients received appropriate concomitant backbone chemotherapy. Treatments were to be continued until disease progression, unacceptable toxicity, patient or physician decision, or curative-intent surgery.

Findings from the PARADIGM and CAIRO5 studies were obtained in populations that were deemed to be younger and with a better performance status than patients routinely seen in clinical practice. This should be considered when generalizing the findings to patients in real-life conditions. By having an open-label design, the studies were susceptible to assessment and reporting biases for subjective efficacy (e.g., tumour response outcomes) and harms outcomes. High treatment discontinuation rates, although expected given the disease and AE profiles of the drugs, remain a concern. The impact and direction of these sources of bias are uncertain.

One NMA was included to inform a comparison between panitumumab and cetuximab. A second NMA was included to inform on SAEs for the comparison of panitumumab and bevacizumab because the reporting of SAEs was scant in the included trial publications.

Interpretation of Results

Efficacy

Improving survival should remain the primary goal of therapy for patients with cancer; as such, overall survival is the preferred and most reliable end point in oncology trials.[15] In the PARADIGM study, the use of panitumumab was associated with HRs in favour of this treatment versus bevacizumab for overall survival in patients with previously untreated mCRC with left-sided tumours that express wild-type *RAS*. The between-group difference in median survival of approximately 3.6 months observed in the study was considered clinically meaningful by both experts. Results for overall survival were not expected to have been impacted by the open-label design due to the objectivity of the outcome; however, patients with left-sided tumours constituted a subgroup of the initial overall population, which may have affected the efficacy of randomization to evenly distribute patient variables. The variety of treatments received after disease progression also constitutes a potential confounding factor. Uncertainty surrounding the findings is hereby expressed by the wide CIs, which also include the possibility of no clinically meaningful difference between treatments. Therefore, evidence from 1 study suggests that panitumumab likely results in a clinically meaningful benefit on overall survival compared with bevacizumab in the first-line treatment of mCRC in patients with left-sided tumours expressing wild-type *RAS*, but there is uncertainty surrounding the magnitude of those findings.

Additional efficacy outcomes assessed in the studies included progression-free survival; however, it was not considered clinically meaningful to inform treatment decisions according to the clinical experts. Panitumumab did not seem to have a significant impact on progression-free survival compared to bevacizumab in either of the 2 studies because the HRs were inconclusive and did not favour 1 treatment over the other. In the PARADIGM study, the between-group difference in median progression-free survival of approximately 1.2 months observed in the study in favour of panitumumab was not considered clinically meaningful by both experts. In the CAIRO5 study, the between-group difference was approximately 0.4 months and favoured bevacizumab. Progression-free survival was not subject to confounding from the treatments received upon disease progression; however, it may have been subject to assessment bias due to absence of central review by assessors blinded to treatment assignment. Uncertainty was also introduced because the underlying assumption of proportional hazards was violated based on statistical testing and

visual inspection of the Kaplan-Meier plots. Therefore, evidence from 2 studies suggest that panitumumab may not result in a clinically meaningful benefit on progression-free survival compared with bevacizumab in the first-line treatment of mCRC in patients with left-sided tumours expressing wild-type *RAS*, as well as in a subset of patients who have liver-only disease. This is due to inconclusive results and substantial uncertainty surrounding the findings.

The results suggest potential benefits of panitumumab on other secondary outcomes, such as objective response rate. There was a between-group difference of 11.2% observed in the PARADIGM study and a between-group difference of 27% in the CAIRO5 study. These were considered clinically meaningful by both experts, particularly in patients with potentially resectable disease, for whom reduction of tumour volume may result in successful surgery, as well as in patients with symptomatic disease to alleviate symptoms. However, these were not measured in the trials. There is uncertainty surrounding those findings, including uncertainty due to imprecision in the PARADIGM study considering the possibility that the lower end of the confidence interval would constitute little to no difference. In addition, only limited statistical analyses were reported in the CAIRO5 study, precluding proper assessment of the between-group differences and the precision of the estimates. Therefore, evidence from these 2 studies suggests that panitumumab may result in a clinically meaningful benefit on objective response rate compared with bevacizumab in the first-line treatment of mCRC in patients with left-sided tumours expressing wild-type *RAS* as well as in a subset of patients who have liver-only disease. However, there is substantial uncertainty surrounding the findings.

Panitumumab did not seem to have a clinically significant impact on duration of response compared to bevacizumab in the PARADIGM study. The magnitude of the between-group difference was approximately 1.9 months which was not considered clinically meaningful by the experts and the outcome in itself was not considered particularly informative for decision-making.

Results from the 2 studies were inconsistent regarding potential benefits from panitumumab on curative resection rate. In the PARADIGM study, the between-group difference of 6.6% observed in the study in favour of panitumumab was considered clinically meaningful by both experts; although the percentage may appear small, it would likely be a significant benefit in patients for whom curative resection may be considered because successful curative resection constitutes a potential cure. In the CAIRO5 study, no difference was observed between panitumumab and bevacizumab. Issues with inconsistency may be mitigated by the fact that patients with liver-only disease are expected to have a different natural disease trajectory. Nevertheless, the outcome of curative resection rate is subject to similar limitations as those described for objective response rate, including the possibility of little to no difference due to imprecision as well as insufficient reporting of statistical analyses. Therefore, evidence from the 2 studies suggests that panitumumab may result in a clinically meaningful benefit on curative resection rate compared with bevacizumab in the first-line treatment of mCRC in patients with left-sided tumours expressing wild-type *RAS*, but not in a subset of patients who have liver-only disease. However, there is substantial uncertainty surrounding the findings.

The evidence did not inform on HRQoL because no data were reported in the publications for the outcome.

Indirect evidence was considered to inform a comparison between panitumumab and cetuximab as well as to mitigate the limited reporting of SAEs for the comparison of panitumumab and bevacizumab in the

included trials. Two NMAs performed using the frequentist approach aimed to inform these comparisons.[16,17] The assessments of clinical and methodological heterogeneity in the included NMAs were limited, which challenged the transitivity assumption, and there was a limited number of trials included in each NMA. Consequently, nearly all comparison outcomes were affected by imprecision, which reduced the certainty of the effect estimates, including the size and direction of the effect. CIs were wide and often included the potential for no important difference between treatments or the possibility that either treatment could be favoured, especially for efficacy outcomes.

Harms

A high proportion of patients experienced at least 1 AE during the PARADIGM study follow-up and the proportions were similar between treatment groups. Harms outcomes in this study were reported for the overall population of patients, regardless of tumour sidedness. This was considered appropriate by the clinical experts because it is not expected that there would be any differences in harms outcomes according to the tumour side (right-sided or left-sided). Dermatologic and soft tissue toxicities, as well as hypomagnesemia electrolyte disturbance, were reported more frequently in patients who received panitumumab compared to patients who received bevacizumab. The clinical experts we consulted indicated that it is common for patients undergoing treatment for mCRC in clinical practice to experience numerous AEs, and that most may be considered tolerable and/or manageable by patients. Patients and clinicians in this trial were aware of the treatment strategy received, and this may have introduced bias in the reporting of subjective AEs.

More patients who received panitumumab experienced grade 3 to 5 AEs in the CAIRO5 study compared with bevacizumab (listing not reported). More patients who received panitumumab experienced SAEs compared with those who received bevacizumab in both the PARADIGM and CAIRO5 studies. The WDAEs profile differed between the trials but these were reported more frequently with panitumumab than with bevacizumab. There were too few events to draw a strong conclusion regarding mortality due to AEs; however, there were numerically more deaths reported in the group that received panitumumab for reasons that included known but rare toxicities from the drug, such as interstitial lung disease and other various infections and noninfectious pulmonary disorders.

Cost

- The 28-day per patient cost of panitumumab monotherapy is $5,446, which is more costly than bevacizumab monotherapy (28-day cost: $2,454) and less costly than cetuximab monotherapy (28-day cost: $7,884). Because the current standard-of-care treatment for patients with mCRC that expresses wild-type *RAS* consists of bevacizumab or cetuximab in combination with first-line standard chemotherapy, this review compared the cost of these regimens with panitumumab. Panitumumab and bevacizumab are used in combination with FOLFOX, FOLFIRI, or XELOX regimens, whereas cetuximab is used in combination with either FOLFOX or FOLFIRI. The 28-day per patient cost of panitumumab in combination with FOLFOX, FOLFIRI, and XELOX is $7,010, $10,181, and $5,879, respectively. The 28-day per patient cost of bevacizumab in combination with FOLFOX,

FOLFIRI, and XELOX is $4,017, $7,189, and $2,887, respectively. The 28-day per patient cost of cetuximab in combination with FOLFOX and FOLFIRI is $9,448 and $12,619, respectively.

- When comparing panitumumab with bevacizumab (used in combination with FOLFOX, FOLFIRI, or XELOX), panitumumab results in 28-day per patient incremental costs of $2,992. When comparing panitumumab with cetuximab (used in combination with FOLFOX or FOLFIRI), panitumumab results in 28-day per patient incremental cost savings of $2,438. Across combination regimens, the incremental costs and incremental savings remain constant because the differences in the regimens are reflected by the use and drug acquisition costs of panitumumab, bevacizumab, or cetuximab. Costs are based on publicly available list prices and may not reflect actual prices paid by public drug plans in Canada.

Conclusions

Improving survival in patients with cancer remains the primary goal of therapy. As such, evidence from the PARADIGM study suggests that panitumumab may result in a clinically meaningful benefit for overall survival compared with bevacizumab in the first-line treatment of mCRC in patients with left-sided tumours expressing wild-type *RAS*; however, there is uncertainty surrounding the magnitude of those findings due in part to issues with redefinition of the primary population, confounding factors, and imprecision. Findings from the PARADIGM and CAIRO5 studies suggest potential benefits from panitumumab on the secondary outcomes of objective response rate and curative resection rate, compared with bevacizumab, in the first-line treatment of mCRC in patients with left-sided tumours expressing wild-type *RAS*, and potentially in a subset of patients who have liver-only disease. These findings would be particularly relevant in patients for whom curative resection may be considered and in patients with symptomatic disease. However, the interpretation regarding clinical meaningfulness of the results is limited by imprecision because the CIs also include the possibility of little to no clinically meaningful difference between treatments and by limited reporting of statistical analyses. In the 2 studies, panitumumab did not seem to have a significant impact on progression-free survival and duration of response compared with bevacizumab. The evidence did not inform on HRQoL because no data were reported in the publications. The populations in the studies were deemed to be younger and with a better performance status than patients routinely seen in clinical practice in Canada. Two NMAs were reviewed to inform a comparison between panitumumab and cetuximab, and to mitigate the limited reporting of SAEs for the comparison of panitumumab and bevacizumab in the RCTs; however, substantial imprecision for nearly all comparison outcomes precluded any strong conclusion regarding the comparative effects of the drugs, as CIs included the potential for no important difference between treatments, or the possibility that either treatment could be favoured.

In the PARADIGM and CAIRO5 studies, high proportions of patients experienced harms events, of which dermatologic and soft tissue toxicities, as well as hypomagnesemia electrolyte disturbance, were reported more frequently in patients who received panitumumab compared with patients who received bevacizumab. SAEs and WDAEs were numerically higher with panitumumab than with bevacizumab. The harms profile reported in the PARADIGM and CAIRO5 studies appeared consistent with what is currently seen in clinical

practice in Canada according to the clinical experts we consulted. There were too few events to draw a strong conclusion regarding mortality due to AEs; however, numerically more deaths were reported in patients receiving panitumumab for reasons that included known but rare toxicities from the drug, such as interstitial lung disease and other various infections and noninfectious pulmonary disorders. As such, tolerability should be weighed against any potential gain in overall survival expected from treatment.

Results of the cost comparison of drug acquisition costs demonstrate that, when compared to bevacizumab (and used in combination with FOLFOX, FOLFIRI, or XELOX), the reimbursement of panitumumab is expected to increase treatment costs (incremental costs: $2,992 per patient per 28 days). Alternatively, when compared to cetuximab (and used in combination with FOLFOX or FOLFIRI), the reimbursement of panitumumab is anticipated to decrease treatment costs (incremental cost savings: $2,438 per patient per 28 days).

Based on the clinical review conclusions, panitumumab likely results in improved overall survival, improved objective response rate, and improved curative resection rate compared with bevacizumab. Given that panitumumab is associated with incremental costs and incremental benefit compared with bevacizumab, a cost-effectiveness analysis would be required to determine the cost-effectiveness of panitumumab relative to bevacizumab. Because this was not available, the cost-effectiveness of panitumumab relative to bevacizumab for the treatment of patients with mCRC that expresses wild-type *RAS* could not be determined. The clinical review further concluded that cetuximab may result in improved overall survival and improved progression-free survival relative to panitumumab; however, CIs were wide and often included the potential for no important difference between treatments. As such, it is uncertain whether differences between treatments exist. If it is expected that the clinical effects of panitumumab and cetuximab are similar, a comparison of drug acquisition costs may be appropriate.

Because bevacizumab is less costly than panitumumab, a price reduction of 55% would be required for the drug acquisition cost of panitumumab to be equal to bevacizumab. Costs associated with *RAS* and *BRAF* diagnostic testing, as well as administration costs, were not considered in this cost comparison. To adequately consider these alongside the health care resource implications associated with the comparative clinical benefits, a cost-effectiveness analysis of panitumumab in combination with standard first-line therapy compared with all current standard-of-care treatments would be required.

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Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946 to present)
- Embase (1974 to present)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: August 1, 2023

Alerts: Biweekly search updates until project completion

Search filters applied: Randomized controlled trials; controlled clinical trials.

Limits:

- Conference abstracts: excluded

Table 14: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary

Syntax	Description
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word (MEDLINE)

Database Strategy

Database(s): Ovid MEDLINE(R) ALL

Search Strategy:

1. Panitumumab/
2. (Vectibix* or Vectibex* or panitumumab* or ABX-EGF or Abenix* or Panitumab or panitunumab or AMG 954 or AMG954 or 6A901E312A).ti,ab,ot,kf,rn,nm.
3. or/1-2
4. exp Colorectal neoplasms/
5. ((colorectal or colo-rectal or rectocolonic or recto-colonic or colon or colonic* or rectal or rectum or sigmoid or rectosigmoid* or anal or anus or perianal or circumanal) and (cancer* or neoplas* or tumo?r* or carcinoma* or CRC or mCRC or malignan* or sarcoma* or adenocarcinoma* or adenoma* or metastatic* or metastas*)).ti,ab,kf.
6. or/4-5
7. 3 and 6
8. (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
9. Randomized Controlled Trial/
10. exp Randomized Controlled Trials as Topic/
11. “Randomized Controlled Trial (topic)”/
12. Controlled Clinical Trial/
13. exp Controlled Clinical Trials as Topic/
14. “Controlled Clinical Trial (topic)”/
15. Randomization/
16. Random Allocation/
17. Double-Blind Method/
18. Double Blind Procedure/
19. Double-Blind Studies/
20. Single-Blind Method/

21. Single Blind Procedure/
22. Single-Blind Studies/
23. Placebos/
24. Placebo/
25. Control Groups/
26. Control Group/
27. (random* or sham or placebo*).ti,ab,hw,kf.
28. ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
29. ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
30. (control* adj3 (study or studies or trial* or group*)).ti,ab,kf.
31. (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
32. allocated.ti,ab,hw.
33. ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
34. ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
35. (pragmatic study or pragmatic studies).ti,ab,hw,kf.
36. ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
37. ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
38. (phase adj3 (III or “3”) adj3 (study or studies or trial*)).ti,hw,kf.
39. or/8-38
40. 7 and 39

Database(s): Embase Search Strategy:

1. *panitumumab/
2. (Vectibix* or Vectibex* or panitumumab* or ABX-EGF or Abenix* or Panitumab or panitunumab or AMG 954 or AMG954).ti,ab,kf,dq.
3. or/1-2
4. exp colorectal cancer/ or exp Colorectal tumor/
5. ((colorectal or colo-rectal or rectocolonic or recto-colonic or colon or colonic* or rectal or rectum or sigmoid or rectosigmoid* or anal or anus or perianal or circumanal) and (cancer* or neoplas* or tumo?r* or carcinoma* or CRC or mCRC or malignan* or sarcoma* or adenocarcinoma* or adenoma* or metastatic* or metastas*)).ti,ab,kf,dq.
6. or/4-5
7. 3 and 6

8. (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
9. Randomized Controlled Trial/
10. exp Randomized Controlled Trials as Topic/
11. "Randomized Controlled Trial (topic)"/
12. Controlled Clinical Trial/
13. exp Controlled Clinical Trials as Topic/
14. "Controlled Clinical Trial (topic)"/
15. Randomization/
16. Random Allocation/
17. Double-Blind Method/
18. Double Blind Procedure/
19. Double-Blind Studies/
20. Single-Blind Method/
21. Single Blind Procedure/
22. Single-Blind Studies/
23. Placebos/
24. Placebo/
25. Control Groups/
26. Control Group/
27. (random* or sham or placebo*).ti,ab,hw,kf.
28. ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
29. ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
30. (control* adj3 (study or studies or trial* or group*)).ti,ab,kf.
31. (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
32. allocated.ti,ab,hw.
33. ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
34. ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
35. (pragmatic study or pragmatic studies).ti,ab,hw,kf.
36. ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
37. ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
38. (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.
39. or/8-38

40. 7 and 39
41. 40 not (conference abstract or conference review).pt.

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search terms -- Vectibix OR Vectibex OR panitumumab OR "ABX-EGF" OR Abenix OR Panitumab OR panitunumab OR "AMG 954" OR AMG954]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the WHO. Targeted search used to capture registered clinical trials.

[Search terms -- Vectibix OR Vectibex OR panitumumab OR "ABX-EGF" OR Abenix OR Panitumab OR panitunumab OR "AMG 954" OR AMG954]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms -- Vectibix OR Vectibex OR panitumumab OR "ABX-EGF" OR Abenix OR Panitumab OR panitunumab OR "AMG 954" OR AMG954]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- Vectibix OR Vectibex OR panitumumab OR "ABX-EGF" OR Abenix OR Panitumab OR panitunumab OR "AMG 954" OR AMG954]

Grey Literature

Search dates: July 20, 2023, to July 28, 2023

Keywords: Vectibix OR Vectibex OR panitumumab OR "ABX-EGF" OR Abenix OR Panitumab OR panitunumab OR "AMG 954" OR AMG954

Limits: None

Updated: Search updated before the completion of stakeholder feedback period

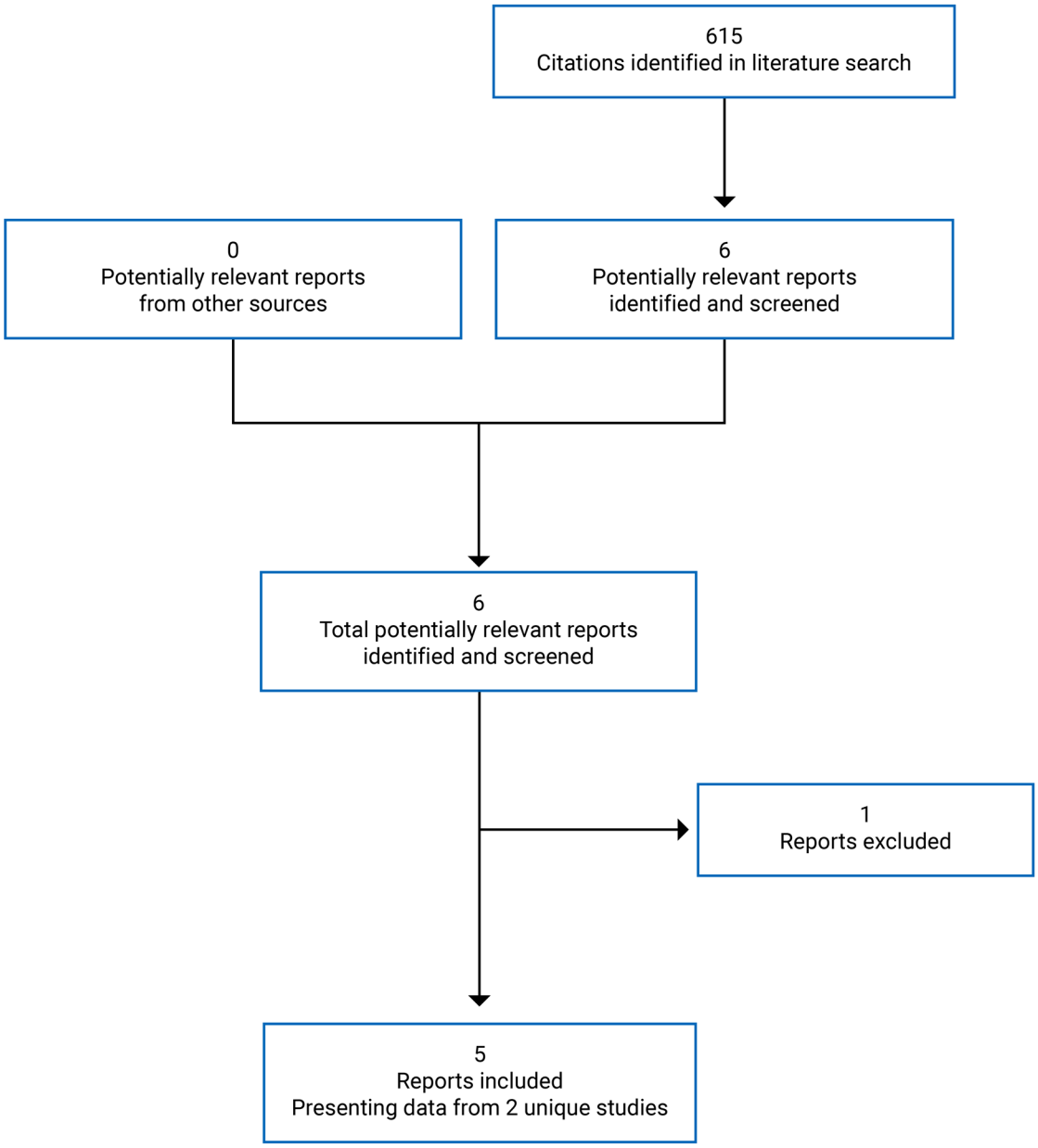
Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Internet Search

Appendix 2: PRISMA Flow Diagram

Note that this appendix was not copy-edited.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies



Appendix 3: Excluded Studies

Note that this appendix has not been copy-edited.

Table 15: Excluded Studies

Reference	Reason for exclusion
Chan, E. 2010. Clinical Advances in Hematology & Oncology 2010 8(1):37-9.	Other design (review article, clinical practice guideline or expert opinion)

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.