Canada's Drug and
Health Technology Agency

CADTH Reimbursement Recommendation

Panitumumab Solution for IV Infusion

Reimbursement request: For the treatment of previously untreated patients with nonmutated (wild-type) *RAS* left-sided metastatic colorectal carcinoma in combination with chemotherapy

Final recommendation: Reimburse with conditions.

Summary of CADTH Recommendation

The Formulary Management Expert Committee (FMEC) reviewed the PARADIGM and CAIRO5 trials. Evidence from the PARADIGM trial showed that panitumumab lengthened overall survival in patients with wild-type *RAS* left-sided metastatic colorectal cancer compared to bevacizumab (both drugs used in combination with chemotherapy). Evidence from the CAIRO5 trial, which only included a subpopulation of patients with liver-only metastatic disease, yielded inconclusive results regarding survival outcomes with substantial uncertainty surrounding the findings. Although panitumumab showed at least similar efficacy to bevacizumab, the magnitude of the comparative benefits could not be quantified due to uncertainty. FMEC highlighted that panitumumab is associated with manageable toxicities.

The expected cost of panitumumab is higher than that of bevacizumab based on publicly available prices.

FMEC recommends that panitumumab, in combination with chemotherapy, be reimbursed for previously untreated patients with wild-type *RAS* left-sided metastatic colorectal cancer if conditions are met. Reimbursement should be restricted to those patients whose disease characteristics are consistent with those of the patients included in the PARADIGM trial.

Therapeutic Landscape

What Is Metastatic Colorectal Cancer?

Colorectal cancer is among the leading causes of cancer among people in Canada, with metastatic colorectal cancer representing a significant burden of disease. Although a minority of patients may be suitable for upfront curative resection, palliative systemic chemotherapy is the primary treatment modality for most patients with unresectable disease, with the goal of extending survival, reducing disease-related symptoms, and improving quality of life.

Why Did CADTH Conduct This Review?

Publicly funded drug plans requested this nonsponsored Reimbursement Review because it met the eligibility criteria outlined in the Procedures for CADTH Non-Sponsored Reimbursement Reviews.

Person With Lived Experience

A 50-year-old from Ontario shared their journey after being diagnosed with stage 4 colon cancer in 2021 and receiving a 3-year life expectancy. They began treatment with chemotherapy and panitumumab and had a positive response. Over the course of their treatment, the number of liver lesions on were reduced from 23 to 1, which gave them the opportunity to enrol in a clinical trial for a liver transplant. They are now recovering from surgery with the hope of now being cancer free.

They highlighted that having an effective treatment was of utmost importance, even if it meant enduring skin reactions, as it provided reassurance that therapy was working. They stressed the importance of being able to maintain quality of life during treatment, emphasizing being able to be present for their family and to witness major milestones. They highlighted that they had public drug coverage for panitumumab and noted that the cost of treating the skin reactions were low. Despite this, they brought attention to the financial burden that many people in Canada living with colon cancer endure, especially if they have to pay for panitumumab out of pocket. They underscored that following treatment, the greatest gift is hope for the future.

Stakeholder Feedback

What Did We Hear From Patients?

Colorectal cancer has a profound and multifaceted impact on patients and their families. Despite advancements in treatment options, disease recurrence, often with a fatal course, remains a reality for many. Fatigue, abdominal pain, limitations to lifestyle, and emotional exhaustion were highlighted as negatively impacting patients' and caregivers' quality of life. Access to affordable, targeted treatments that extend overall survival and improve quality of life was also a significant concern.

What Did We Hear From Clinicians?

Clinician groups emphasized the unmet need in the first-line treatment of left-sided *RAS* wild-type metastatic colorectal cancer, when patients should have access to an epidermal growth factor receptor (EGFR) inhibitor, such as panitumumab, as recommended by international treatment guidelines.

What Did We Hear From the Pharmaceutical Industry?

Industry supported the research protocol, highlighting that it was reflective of the treatment landscape, and noted the same concern as clinician groups regarding the need to access an EGFR inhibitor in the first-line setting.

What Did We Hear From Public Drug Programs?

Public drug plans inquired about considerations for initiation, continuation, and renewal of therapy. Questions were asked regarding the selection of concomitant chemotherapy, requirements for imaging testing, dosing frequency, and re-treatment or subsequent-line treatment with panitumumab.

Refer to the Stakeholder Input section of the CADTH report.

Deliberation

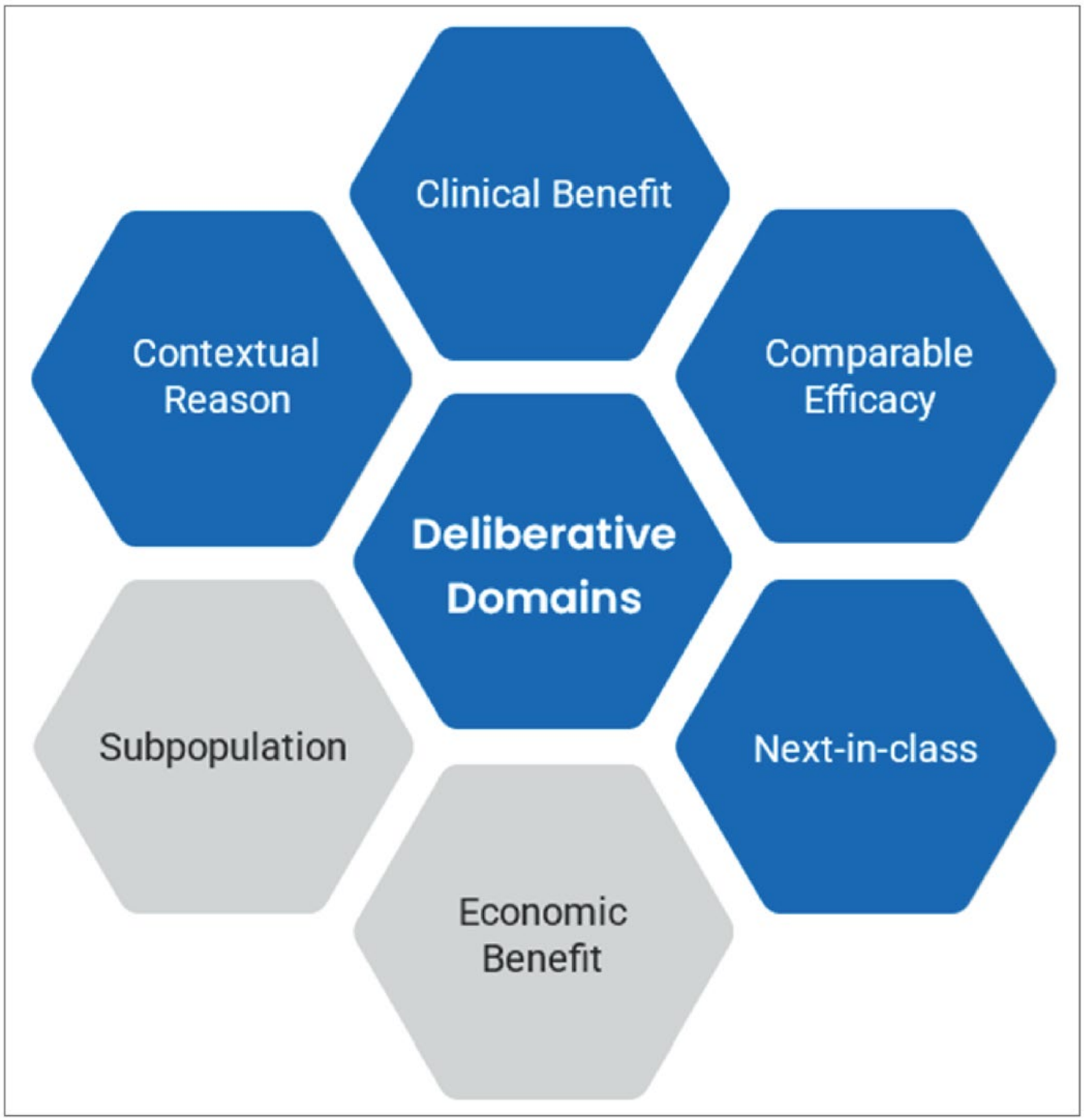
With a vote of 7 to 0 (with 1 member absent), the Formulary Management Expert Committee (FMEC) concluded that panitumumab is a next-in-class drug that shows at least similar efficacy to relevant comparators. However, there are incremental drug acquisition costs for panitumumab compared to bevacizumab, which was identified as the most relevant comparator. The cost-effectiveness of panitumumab relative to bevacizumab remains unknown.

For every review, FMEC deliberated on the following 6 domains as illustrated in the Deliberative Framework (Figure 1):

- Clinical benefit: Whether there is sufficient clinical evidence to support the population under consideration for reimbursement.
- Comparable efficacy: Whether there is evidence to support at least comparable efficacy between the drug under review and relevant comparator(s).
- Next-in class drug (drug using an already known molecular mechanism): Whether there are other therapies currently available or whether the drug under review has a novel mechanism of action.
- Economic benefit: Whether the drug under review represents potential cost savings compared to appropriate comparator(s).
- Subpopulation: Whether there is a subpopulation that would benefit from the drug under review if there is too much uncertainty in the broader population studied.
- Contextual reasons: Whether there are contextual reasons for reimbursing the drug under review that are not captured in the clinical or economic evidence.

For this review, the 4 domains of clinical benefit, contextual reason, comparable efficacy, and next-in class were the focus of FMEC's deliberation and reimbursement recommendation (Figure 1). The other 2 domains (subpopulation and economic benefit), while discussed, were less of a focus of the deliberation.

Figure 1: Deliberative Framework



Note: The darker shaded deliberative domains were considered most relevant and contributed the most to the reimbursement recommendation by the committee. The lighter shaded domains were less of a focus in the deliberation.

Decision Summary

Table 1: Why Did FMEC Make This Recommendation?

Decision node	Reason
Does the drug demonstrate sufficient evidence for clinical benefit? Is the benefit of the drug at least comparable to the rest of the class?	• FMEC clinical experts identified survival improvement as a significant unmet need. • Overall survival is widely recognized as the gold-standard goal of therapy in the treatment of cancer and is considered the most relevant outcome in clinical practice according to the FMEC guest specialists. FMEC noted that this was also highlighted by the clinician group input and input by 2 patient groups and an individual with lived experience. • FMEC reviewed the evidence from the PARADIGM trial and concluded that panitumumab lengthened overall survival in patients with wild-type *RAS* left-sided mCRC compared to bevacizumab (both drugs being used in combination with chemotherapy). • FMEC acknowledged that there is uncertainty in the evidence in the PARADIGM trial because the wide confidence intervals may also include the possibility of no clinically meaningful difference between treatments. Therefore, the magnitude of the benefits of panitumumab compared with bevacizumab could not be quantified. • FMEC also noted that findings for progression-free survival and key secondary outcomes (i.e., objective response rate and curative resection rate) in PARADIGM and CAIRO5 were inconclusive, contributing to the uncertainty in the evidence. • • FMEC discussed toxicities associated with panitumumab, considering the feedback from patient groups, FMEC clinical experts, and the person with lived experience. FMEC concluded that panitumumab is associated with manageable toxicities.
Is the drug a next-in-class medication?	• FMEC clinical experts identified panitumumab as a next-in-class drug as they considered cetuximab a comparator to panitumumab given their similar mechanism of action. • However, panitumumab is preferred clinically because cetuximab is associated with substantial infusion reactions due to its chimeric nature and with increased adverse events. • Based on the clinical experts' experience, FMEC concluded that panitumumab presented with a favourable safety profile compared with cetuximab.
Is there an economic benefit?	• Based on publicly available prices, panitumumab is more costly than bevacizumab (resulting in incremental costs) and less costly than cetuximab (resulting in incremental cost savings). • Given that panitumumab is associated with incremental costs and potential incremental benefit compared with bevacizumab, a cost-effectiveness analysis would be needed to determine the value of panitumumab relative to bevacizumab.

Decision node	Reason
Is there a subpopulation that would benefit from the drug or is there sufficient evidence to support a recommendation for the entire population within the reimbursement question?	• FMEC concluded that there is sufficient evidence to support a recommendation for the entire population of patients with wild-type *RAS* left-sided mCRC. • FMEC noted that the PARADIGM trial was performed in the entire population within the reimbursement question. • The FMEC clinical experts considered that patients in the trial were younger with better performance status than those typical of clinical practice in Canada. • As such, treatment with panitumumab, in combination with chemotherapy, should be reimbursed for patients whose disease characteristics are consistent with those of the patients included in the PARADIGM study.
Is there a contextual reason for reimbursing the drug that is not captured in the clinical or economic evidence?	• FMEC noted the following contextual issues in favour of reimbursing panitumumab: the clinical experts discussed the use of panitumumab in subsequent lines of treatment on a case-by-case basis and the differential access for panitumumab across jurisdictions.

EGFR = epidermal growth factor receptor; FMEC = Formulary Management Expert Committee; mCRC = metastatic colorectal carcinoma.

Full Recommendation

With a vote of 6 to 1 (with 1 member absent), FMEC recommends that panitumumab, in combination with chemotherapy, be reimbursed for previously untreated patients with wild-type *RAS* left-sided metastatic colorectal cancer if the conditions presented in Table 2 are met.

Table 2: Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Panitumumab, in combination with chemotherapy, should be reimbursed for the first-line treatment of adult patients with all of the following: 1.1. mCRC that is left-sided and *RAS* wild-type 1.2. good performance status (ECOG 0 to 1) 1.3. no active brain metastases.	Treatment with panitumumab, in combination with chemotherapy, should be reimbursed for patients whose disease characteristics are consistent with those of patients included in the PARADIGM clinical trial.	FMEC highlighted the importance of timely testing that must be done for *KRAS*, *NRAS*, and *BRAF* genes, with *RAS* status known, to access treatment with panitumumab. Reimbursement of panitumumab should also be limited to patients who have *BRAF* wild-type disease.
Discontinuation		
2. Panitumumab, in combination with chemotherapy, should be continued until any of the following: 2.1. evidence of progression of disease 2.2. patient intolerance 2.3. withdrawal of consent.	The PARADIGM and CAIRO5 trials investigated the use of panitumumab, in combination with chemotherapy, until disease progression occurred. The clinical experts also noted that this aligns with clinical practice in Canada.	To assess response to treatment, routine imaging should be performed as per standard of care (e.g., every 2 to 3 months, based on resource availability).
Prescribing		
3. Panitumumab, in combination with chemotherapy, must be initiated by a clinician with expertise in the treatment of mCRC.	Patients with mCRC are expected to be under the care of an experienced clinical team to address the complexity of treatment, maximize potential benefits, and mitigate adverse events.	—
Cost		
4. A price reduction is required.	Based on publicly available list prices, a price reduction may be required for the acquisition costs of panitumumab to equal those of bevacizumab biosimilars.	—

ECOG = Eastern Cooperative Oncology Group; FMEC = Formulary Management Expert Committee; mCRC = metastatic colorectal cancer.

Feedback on Recommendation

The Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee, Colorectal Cancer Resource & Action Network (CCRAN), Amgen Canada Inc., and the drug plans provided feedback on the draft recommendation. All agreed with the committee's recommendation. The stakeholder feedback was reviewed, and editorial revisions on the cost condition were made.

FMEC Information

Members of the committee: Dr. Emily Reynen (Chair), Dr. Alun Edwards, Ms. Valerie McDonald, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, as well as Dr. Rachel Goodwin and Dr. Howard Lim (guest specialists).

Meeting date: February 1, 2024

Conflicts of interest: None

Special thanks: CADTH extends our special thanks to the individual who presented directly to FMEC and to patient organizations representing the community of those living with colorectal cancer, notably Colorectal Cancer Canada (CCC) and the Colorectal Cancer Resource & Action Network (CCRAN), which include Barry Stein, Cassandra Macaulay, Steve Slack, Filomena Servidio-Italiano, Iris Karry, and Carine Legault.

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