Stakeholder Input

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Stakeholder Input - Patient Input

Colorectal Cancer Resource & Action Network (CCRAN)

About Colorectal Cancer Resource & Action Network (CCRAN)

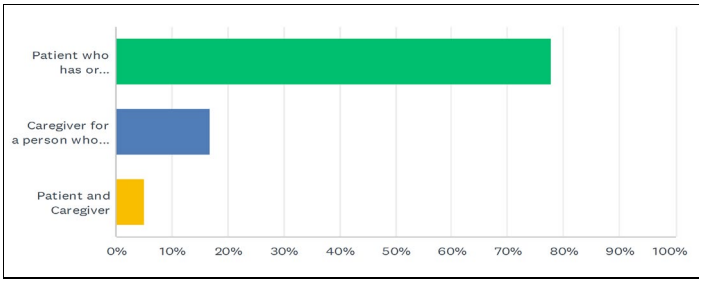
CCRAN is a national, not for profit patient advocacy group championing the health and wellbeing of Canadians touched by colorectal cancer and those at risk of developing the disease, by providing support, education and advocacy to help improve patient outcomes by way of longevity and quality of life. We have an expanded mandate to serve cancer patients outside of the colorectal cancer space through HTA patient evidence submissions, educational events and advocacy initiatives. Our mission is to reduce the burden of cancer in Canada.

Information Gathering

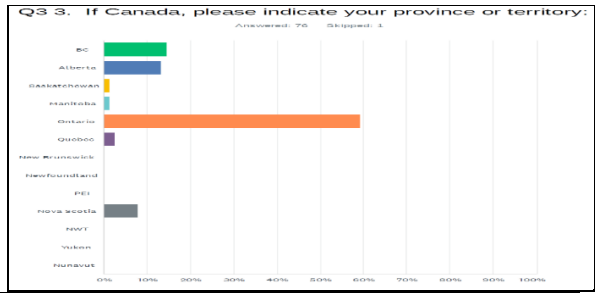
To ensure the metastatic colorectal cancer patient perspective was captured for this therapeutic under review, CCRAN employed a multi-faceted outreach approach. An online survey had been previously developed and administered with respect to another therapy under review (Lonsurf + Bevacizumab) to help capture the **metastatic colorectal cancer patient's**:

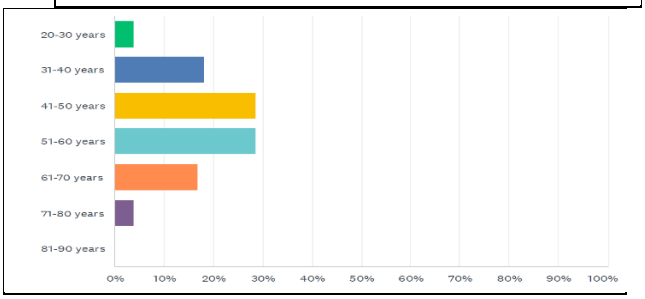
- Experience with respect to the diagnosis of their cancer, cancer journey and drug therapies administered.

The online survey (targeting metastatic colorectal cancer patients **only**) was administered from **June 13 – August 5, 2023** and was promoted through CCRAN's email blasts, social media channels and support groups, surveying registered colorectal cancer patients and caregivers residing in Canada. **77 metastatic survey respondents** replied to the outreach by providing input



77 Survey respondents consisted of **60** patients, **13** caregivers and **4** patients who were also caregivers.





Survey respondents resided in **BC, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, and Nova Scotia.**

Adults between the ages of 20 and 80 are well represented in the survey sample (**Q7**).
69% of the respondents were female (**Q6**).

The survey findings will be referenced throughout this submission for they reflect the perspectives, values and priorities of the advanced colorectal cancer patients whose experiences will inform this submission.

Secondly, an outreach campaign to our registered patients and caregivers was made via email blasts and social media requesting their assistance with this submission from patients who had first hand experience with the therapy under review. We requested these patients or their caregivers contact us if interested in participating in a telephone interview to share their experiential treatment journey. Telephone interviews were conducted by CCRAN between **July 25th and August 3rd 2023 inclusive**, with each patient or caregiver providing first hand, compelling, relevant and high quality input regarding their:

- Experience with respect to the diagnosis of their cancer
- Disease experience
- Experience with respect to administered therapies prior to or post therapy under review and
- Experience with respect to Panitumumab in combination with chemotherapy (Pani + chemotherapy)

The mean age of the interviewed patients is **52** years and median age of the patients at the time of their diagnosis is **50** years. The qualitative data from the interviews is summarized and represented entirely in **APPENDIX 1,** which is attached, and will serve for the most part, as the basis for this qualitative submission, in addition to the objective survey findings.

Finally, a focus group was conducted via zoom on **Friday, August 4th , 2023** between 7:30 and 9:00 p.m. ET with nine metastatic colorectal cancer patients (**Patients H-P**) across Canada to ensure CCRAN captured their perspectives on the disease journey, specifically, relating to metastatic disease-induced symptoms. The patients who participated were tasked with answering the question: "***What symptoms, if any, did you experience from your metastatic colorectal cancer?***" Their thoughtful replies were captured and entered into **TABLE 1** appearing within the second part of the document entitled **APPENDIX 1** and will be referenced herein in **Section 3** of this submission.

Disease Experience

Colorectal cancer is the third most common cancer and the second leading cause of cancer related death in Canada. Despite optimized surgical procedures and adjuvant combination chemotherapy, many of our patients will experience a disease recurrence, often with a fatal course. And when relapsed, the prognosis is quite poor, with a median overall survival of approximately 30 months from initiation of first line systemic therapy. While treatments have improved over the past ten years, more effective therapeutic approaches are required for our metastatic colorectal cancer patients that will help target their disease on a molecular level that will improve not only their survival but quality of life as well.

The online survey results identified **fatigue, bloody stools and diarrhea** as the most prevalent colorectal cancer-induced symptoms as per **Question 9** (**Q9**). **Fatigue** resulting from the cancer was reported to be the most important symptom to control according to patients and caregivers (**Q10**) because it prohibits them from performing every day tasks. In **Q11**, patients relayed that their colorectal cancer-induced symptoms most certainly reduces their quality of life (**QoL**) and interferes with the ability to participate in ordinary daily activities. They are unable to function "*normally*" in their family or work setting: **87%** are unable to work and **60%** are unable to exercise, while **27%** are unable to concentrate and **25%** are no longer able to drive. These are daily functions or tasks that prevent our patients from leading a normal, everyday life. Patients cited limitations that are imposed upon them resulting directly from their cancer. Limitations such as:

- "***Mental well-being: depression, anxiety, frustration and scared of what is to come***."
- "***Not knowing when I can leave my house due to bowel irregularity***"

The top three limitations that had a psychological impact from patients' colorectal cancer (**Q12**) were:

- ***An inability to experience joy (72%)***
- ***Chemo brain making me feel forgetful (46%)***
- ***Constant fatigue makes it difficult to function normally – can't think straight*** (43%)

And some of the open-ended replies to this question included:

- "***Anxiety, flashbacks***"
- "***Tired having cancer on my mind all the time and worry about it…"***
- ***"Want more children but can't"***

It is important to note that not all metastatic patients experience cancer-induced symptoms: 13% of the survey respondents did not experience any symptoms at all prior to their diagnosis: their diagnosis was a result of an incidental finding.

Our seven interviewed patients, however, did experience cancer-induced symptoms prior to their diagnosis (**Patients A-G**). Interviewed patients reported the following symptoms which became troublesome and required immediate attention:"***Bloody stools, weight loss, pencil thin stools, abdominal pain, daily rectal bleeding, back pain, and constipation***."

Patient A is a 50 year old male who had been experiencing bloody stools for well over a year. A colonoscopy eventually ensued which discovered a large rectal tumour which was treated with chemoradiation, surgical resection and adjuvant FOLFOX therapy. Metastatic disease was unfortunately detected nine months post-op in the para-aortic lymph nodes for which he received the therapy under review. He maintains: ***"I guess I had blood thinking it wasn't anything so I didn't really do much hoping it would go away and if it didn't, I would eventually do something. But then I had a colonoscopy and found a tumor in the left side of my colon which was a rectal tumour…"***

Patient B is a 39 year old male who experienced several cancer induced symptoms pre-diagnosis for one year as he tried repeatedly to access diagnostics to account for his symptoms, which included: an ultrasound, mri and colonoscopy. He was finally diagnosed with metastatic disease to his liver. He painfully recalls his journey: "***I was kinda devastated but, initially, I kinda thought that colon cancer was easy just by removing the tumour and then do chemo. But then I learned it wasn't going to be so easy. That's when I got devastated.***"

Respondent C is a caregiver representing his 69 year old father who was originally diagnosed in China but was flown to Canada to be with his son who was happy to care for him during this trying time. The patient was quite symptomatic prior to his diagnosis of metastatic disease (liver and lungs). He immediately started the therapy under review upon accessing Canadian healthcare. In **Caregiver C's** words: "***He had blood in his stools and at the time was not concerned and then in May 2022 he lost weight, over 10kg in 3 weeks, which was concerning him and my mom and went to the hospital. Went through different tests…This is what caught the cancer."***

Respondent D is a caregiver to his 57 year old wife whose cancer-induced symptoms necessitated a trip to the Emergency Room (ER) but her symptoms were attributed to hemorrhoids and, therefore, dismissed, despite having relayed the significant family history to the ER staff. As her symptoms persisted, the patient accessed a FIT one year later, which came back positive. Testing followed which eventually identified and diagnosed her cancer as a stage IV colorectal cancer with metastases to liver and lungs. However, her husband clearly relays: ***"…..the ER doc performed a rectal exam and saw hemorrhoids and accounted for the blood through hemorrhoids. So we trusted them. After one year we accessed a FIT in September 2021 and found blood in her stool. She was in the screening program because of her father who had cancer."***

Patient E is an early age onset patient who desperately tried to address his over two years in duration symptoms with his primary care physician but was unsuccessful, due to the physician's preconceived demographic of a colorectal cancer patient. The patient had been dismissed repeatedly, but, when he could no longer tolerate his symptoms because they were significantly impacting his quality of life, he demanded a colonoscopy. The patient was diagnosed with a large sigmoid tumour and multiple liver metastases which required immediate initiation of systemic treatment. He had much to say about clinicians dismissing symptoms consistent with colorectal cancer simply based on the patient's age, a sentiment shared by **Patient F as well**, who was also a young onset patient and experienced much the same journey: ***".. I was terrified... I was very angry at myself because I thought what have I done to do this to myself and mad at myself to trust my family doctor so blindly. I should have gone back to my family doctor sooner. He should have been more curious about my symptoms, which were really crc symptoms and done something about them. Maybe it would not have progressed to stage 4."***

Patient G is also a young onset patient (38 years old) and relayed a similar journey to **Patients E and F**, though the covid pandemic had a significant impact as she tried to secure a timely diagnosis which is why she relentlessly continued to advocate for herself. Her cancer-induced symptoms, such as abdominal discomfort and back pain would not permit her to ease up on her relentless pursuit to gain access to diagnostics that could potentially identify the cause of her daily painful symptoms. It took months of being rudely dismissed but she was eventually diagnosed with metastatic disease to the spine, liver, lungs, abdomen, and left clavicle. **Patient G** shares: ***"I had abdominal discomfort and back pain for about 2 months. In may 2021 I felt back pain first. During covid, I tried to make an appointment with my doctor but was ignored so had to make an appointment on the phone and my symptoms were ignored and attributed to constipation and put me on 10 days of laxatives and told me to see how I feel after 10 days…On the same phone call, I had lumps in my neck which were concerning me. She asked if I had my covid vaccine which I had 2 weeks prior, so she said they were a side effect of the vaccine and should reduce or shrink soon. She gave me a requisition form for an ultrasound of my neck which was done and also gave me an ultrasound of my abdomen… The pandemic was presenting too many challenges… then on sept 10 the crc surgeon who saw the reports said there were lesions on my liver….. and picked up left sided primary sigmoid cancer."***

Metastatic colorectal cancer patients who participated in the focus group, **Patients H-P (TABLE 1)** identified the following colorectal cancer-induced symptoms:

- Anemia, bloody stools, abdominal and low back pain
- Difficulty breathing, poor appetite, fatigue
- Abdominal cramping, migraines, dizziness, vomiting, all of which were due to a brain metastasis
- Gas, bloating, occasional diarrhea, daily multiple bowel movements, and the feeling as though bowels had not been completely emptied.

One focus group member (**Patient O**) articulately described the daily toll his cancer induced symptoms imposed upon his life for well over two years before receiving that ultimate diagnosis of metastatic colorectal cancer which identified a "***massive tumour in my sigmoid colon that had almost completely blocked my colon***" and then "***discovered 23 tumours in both lobes of my liver***". **Patient O** describes how devastated he was to receive the diagnosis but he cites "***how much I suffered for many, many months – 2 years actually – with those symptoms and it's symptoms that were due to an advanced case of colorectal cancer – Stage 4. My family doctor really should have listened to me but failed to do so, I think because of my young age***."

As for the toll the disease has taken on caregivers, caregivers who responded to the online survey identified the following as the top four difficulties when caring for colorectal cancer patients (**Q34**):

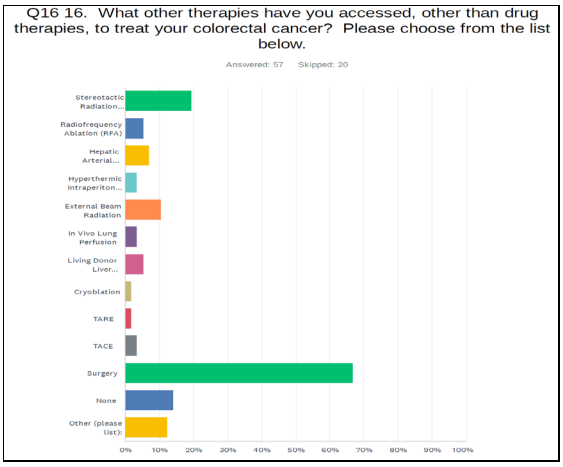
- Loss of lifestyle (70.6%)
- Difficulty managing treatment-induced side effects (54.9%)
- Loss of income (45.1%)
- Inability to cope with the diagnosis (41.9%)

These difficulties merely underscore the impact of the disease on the caregiver as they struggle with the emotional turmoil of the diagnosis, but as one survey respondent states, "***try to run the household on their own while also working, and being a full time caregiver***" is a considerable ongoing challenge imposed upon the caregiver from which there is little to no reprieve. (**Q34**)

Experiences With Currently Available Treatments

Patients with metastatic disease who completed the online survey generally received treatment with fluorouracil-based chemotherapy (with oxaliplatin and irinotecan – **65%**), vascular endothelial growth factor (VEGF)-based therapy (mainly bevacizumab – **50%**), and epidermal growth factor receptor (EGFR)-targeted therapies in confirmed RAS wild type disease (either Cetuximab or Panitumumab – **8%** and **17%** respectively). For patients whose disease was identified to be Microsatellite Instability-High (MSI-High), Pembrolizumab was accessed by **3.4%** of the survey respondents and in patients identified to have a BRAF V600E mutation, Encorafenib in combination with an anti-EGFR therapy was accessed by **5.1%** of respondents. One patient accessed Regorafenib. Open ended replies revealed additional systemic therapies were also accessed: Opdivo in combination with Yervoy for the treatment of a patient's metastatic disease; and Raltitrexed in combination with Oxaliplatin was also identified as a prescribed treatment for a patient (**Q15**).

Q16 highlighted the additional non-systemic therapies utilized in the management of the patients' metastatic disease:



Additional non-systemic therapies included Surgery, SBRT, External Beam Radiation, HAIP, Living Donor Liver Transplant, and In Vivo Lung Perfusion, to mention a few. Complimentary Therapies were included in the open ended replies. Survey respondents cited **fatigue, peripheral neuropathy, hair loss, diarrhea and nausea as the most commonly induced side effects** from their colorectal cancer treatments (**Q17**). The three treatment induced side effects that were most difficult to tolerate as identified in the survey findings were ***fatigue*** (52%), ***neuropathy*** (48%), and ***nausea*** (40%) (**Q19**). In **Question 20**, patients were asked to rate those three side effects across a scale of "***No impact***" to "***Significantly impacting***" their daily life, the results of which appear below:

	NO IMPACT	SMALL IMPACT	MODERATE IMPACT	SIGNIFICANT IMPACT	TOTAL	WEIGHTED AVERAGE
Side Effect #1:	3.77% 2	5.66% 3	33.96% 18	56.60% 30	53	3.43
Side Effect #2:	4.00% 2	8.00% 4	42.00% 21	46.00% 23	50	3.30
Side Effect #3:	4.35% 2	4.35% 2	43.48% 20	47.83% 22	46	3.35

The three weighted averages of ***3.43, 3.30 and 3.35*** each reflect the profound impact the treatment-induced side effects had/have on the patients' daily lives, regardless of the side effects selected: the majority of the respondents selected "***significant impact***" for **Side Effect #1** and the majority then proceeded to select either "***significant impact***" and/or "***moderate impact***" for **Side Effect #2** and **Side Effect #3**.

Medications were prescribed to help address the treatment-induced side effects which included (**Q21**):
"***Emend and Zofran for vomiting, iron for anemia, ondansetron for nausea/fatigue, and CBD, acupuncture and physiotherapy for neuropathy***".

Survey respondents relayed they were required to pay out of pocket for some of the medications prescribed to help address the treatment-induced side effects (**Q22**):
"***Mouthwash was $50, not covered, required 4x."***
"I paid a lot prior to trillium kicking in."
***"Hundreds, in* the deductibles**."
"$500 per year."

The online survey asked if patient needs' were not being met by the current drugs accessible to treat their colorectal cancer (**Q33**)? Over 53% replied "yes" and several open ended replies were furnished by patients:
"***We need access to as many drugs as possible and to know the ones that will work for our cancer beforehand (i.e. biomarker testing***)".
"***Very limited lines of treatment available for us as colon cancer patients***."
"***Quality of life. So many side effects that don't always have answers. Understand each patient is different and have different reactions to different meds, however after 6 years nothing has ever really gotten better or if it has, it's only for a short time. I feel sorry for the oncologist who has patients living longer with treatment but experiencing side effects."***

Five patients and two caregivers participated in the telephone interviews that allowed CCRAN to capture a significant amount of qualitative data with respect to the treatment journeys. Interviewees provided thoughtful and at times heart-wrenching input regarding those journeys, describing the treatments accessed, the impact on their quality of life and the amount of time to disease progression. By way of summary, all patients accessed the protocol under review in the first line setting, with either **FOLFOX** (Patients **C, F, G**) or **FOLFIRI** (Patients **A, B, D, E**). **Patient A** underwent chemoradiation, surgical resection and adjuvant FOLFOX therapy for his stage 3B rectal cancer which he cites as having been "*horrible*". He cites severe neuropathy while having undergone adjuvant FOLFOX therapy as well as debilitating fatigue with which he could not contend. At the time he still had his ostomy, so his life-altering ostomy coupled with debilitating treatment-induced fatigue and neuropathy had diminished his quality of life considerably, preventing him from engaging in life in any meaningful way. **Patients B, C, D and E** have accessed the protocol under review in first line and have had no other systemic therapy. **Patient F** accessed panitumumab + FOLFOX in first line (9 cycles), followed by an extensive and challenging surgery, Xeloda as part of post-op treatment, Panitumumab + FOLFIRI in second line (27 cycles), FOLFOX (9 cycles) in third line; and Avastin + Olaparib + Irinotecan + 5FU in the fourth line setting. Her greatest challenges were in respect of the Xeloda and FOLFOX. **Patient F** explains:
"***I would rate that (Xeloda) as extremely harsh. I had horrible mouth sores, diarrhea, fatigue, and lost 18 pounds because I couldn't eat… Your finger nails come right off. I would rate my quality of***

life a 3 because I couldn't even walk." And ***"…mouth sores, horrible rash, diarrhea, terrible chills, infections with nails on hands and feet. Really weird eyelashes growing out of control and hair loss and neuropathy. I would rate my quality of life a 5 (FOLFOX)***."

Patient G accessed the therapy under review in first line (11 cycles and an additional 12 cycles). Her second line therapy consisted of FOLFIRI + Bevacizumab (12 cycles) and upon progression, she accessed Lonsurf (2 cycles) which provided no therapeutic benefit. At that point, she then sought a rechallenge with Panitumumab + FOLFOX as part of fourth line, wherein she is experiencing what she believes to be a clinical response due to improvement in her breathing and a reduction in her cough. Initially in her journey, she required immediate radiotherapy to help bring the spinal metastases under control for she was in a considerable amount of pain: ***"While I was on the radiation and after, I was in a lot of pain. Nerve impingement and I was feeling referral pain and spent most of the time in bed. But the doctor did indicate it was a side effect…. the quality of life wasn't well during or shortly thereafter. Pain was the real side effect from the radiation. I took pain meds to try to help with the pain, hydromorphone which did help."***

Patients A, E, F and G underwent other systemic therapies to which they could compare their therapy under review. Patients report debilitating side effects while undergoing treatments such as neoadjuvant Xeloda, and adjuvant FOLFOX, HAIP (local therapy), palliative FOLFOX, Irinotecan, Avastin, and Olaparib. Patients relayed having derived a clinical benefit in terms of a response, but that response was accompanied by incapacitating side effects such as fatigue, mouth sores, nausea, lack of energy, diarrhea, neuropathy and pain that prevented them from functioning on any reasonable level. Their quality of life was poor to the point where normal daily activities could not be resumed nor could quality time with friends and family be spent, prohibiting them the freedom to "*live life*" as they once did.

Improved Outcomes

Patients treated for their advanced stage colorectal cancer, along with their families, are faced with an ongoing challenge: the prognosis for these patients continues to be poor and, as such, the goal is to provide these patients with therapeutics to manage their disease ensuring improved longevity and quality of life is achieved. Hence, when asked "***What improvements would you like to see in new treatments that are not available in current treatments***?", online survey respondents clearly highlighted their desire to access therapies that will effectively control their disease with respect to improvements in their physical condition (for example, tumour shrinkage, tumour stability, reduction of pain and improved breathing – **Q38**). Patients found these improvements to be of utmost importance, as reflected in the weighted average score of **9.78** out of a possible 10.

The survey results also revealed therapies that provide improvements in a patient's quality of life (i.e. improvement in mobility, sense of wellness, relief from side effects) are important to patients and caregivers and scored equally as high, with a weighted score of **9.50** (**Q39**).

87.1% of patients would take a therapy that could provide better quality of life during their lifetime even if it does not extend survival (**Q41**). And after being told there is no other available treatment for their cancer, patients would be prepared to access a toxic therapy provided an appropriate survival benefit is realized for them: the greater the survival benefit (**2 months, 6 months, 1 year**), the more likely the patient was willing to access a toxic therapy and endure the treatment's toxic side effects (**Qs 42, 43 and 44**), generating the following weighted scores: **5.02 (2 months), 6.59 (6 months) and 7.53 (1 year)** respectively. Patients provided the following open-ended replies;

- "***Oral drugs… and we need access to as many drugs as possible and we need to know the ones that will work for our cancer before hand (i.e. biomarker testing)***
- ***Meaningful improvement in survival time***
- ***Develop a drug that does not involve hair loss. Give me something to treat metal mouth other than sucking on lemon drops or rinsing with salt water – avoid these…***
- ***The chemos available will not cure me. There needs to be more options."***

The interviewed patients provided their perspective on the improvements they would like to see in a drug therapy. They maintain a therapy should regress disease with minimal to no side effects. They prefer a therapy that is designed to cure a patient's cancer. And while the therapy is destroying the cancer, it

should not be destroying the balance of the body's healthy cells, rendering the patient debilitated and unwell. The patient's quality of life should be maintained at all times to ensure they are living their best life **and not a former glimpse of what used to be their life**. If a therapy cannot provide a cure, it should indeed provide a significant extension in survival. A drug therapy should also be conveniently administered: it should be an **orally administered therapy** in the comfort of a patient's home. This would eliminate considerable travel and stress for the patient, their caregiver and the entire family, such that travel costs are avoided and precious time spent away from home is spared. And if the therapy must be infused at a cancer centre, then it should be infused in the shortest amount of time possible with minimal chair time for the patient. Additionally, they emphasized the need for treatments that could provide a durable, longstanding response. One patient actually recommended that a vaccine be formulated and administered to help prevent or treat cancer. **Caregiver D** summarized it nicely:
"***Actually, if an oral therapy can be available, that would be ideal. Infusions need to be eliminated. That would be powerful. We need to stop going to cancer centres as often as we do. It can save us money and time. And a lot of effort. And of course my wife wants to see the reduction in toxicity because she suffers those side effects. And more types of medications to keep patients going as long as possible if a cure is not possible. But a cure is what we are after here.***"

Six of the interviewed patients maintained that Panitumumab + Chemotherapy possesses most of the desired improvements. According to the patients and caregivers, it is capable of regressing disease, prolonging life, and in some, providing a no evidence of disease status, as well as providing minimal to moderate side effects. This is a protocol that can allow patients to resume daily activities, some of whom were able to become gainfully employed again, engage in life by spending time with family and friends, raise their young children, and permit them the freedom to appreciate life despite the horror of having received a diagnosis of metastatic colorectal cancer.

Experience With Drug Under Review

The therapy under review is being recommended for the first line treatment of metastatic colorectal cancer in patients confirmed to have left sided, RAS wild-type (WT) disease. There is evidence to support the use of Panitumumab + Chemotherapy in the first line setting (Paradigm Study) to help improve patient outcomes for this subset of the patient population based on tumour sidedness and RAS mutational status. Panitumumab targets the patient's tumour's molecular characteristics, thereby, improving response which we observed in the qualitative data secured from the telephone interviews CCRAN conducted. We strongly support the incorporation of Panitumumab in combination with chemotherapy in the front line treatment of RAS WT, left sided metastatic colorectal cancer, based on the qualitative data obtained, for the following reasons:

As a result of the therapy, **Patient A** acquired a 'No Evidence of Disease' (NED) status after 12 cycles of Panitumumab + Chemotherapy and has continued to maintain that status after 3 years. **Patients B and D** qualified for a liver resection and in **Patient E's** case, he is now a candidate for the Living Donor Liver Transplant Study because his 23 tumours have reduced to merely one! And **Patient D** has also qualified for the In Vivo Lung Perfusion Study allowing for both lungs to be resected. Hence, these patients are being treated with curative intent as a result of the extraordinary results experienced from their first line treatment involving Panitumumab + Chemotherapy. The balance of the patients (**Patients C, F and G**) all experienced a remarkable response while on the therapy under review, as high as an 80% objective response permitting treatment breaks (**Patient C**) and periods of disease remission lasting in excess of two years (**Patient F**); and maintain they have achieved disease regression with a good quality of life. Our seven interviewed patients each accessed the treatment under review in first line therapy. Panitumumab treatment may result in skin-related toxicities, as well as other toxicities, and as such, can affect a patient's quality of life. All patients experienced the skin-related toxicity: the rash on their face and upper body, which they cited was typically moderate in severity. However, while patients did experience times of difficulty with respect to the facial or upper body rash, they did express a certain level of comfort knowing they were experiencing the "Pani-induced rash", for they had come to learn that it was considered to be a strong predictive biomarker of clinical benefit in patients treated with this anti-EGFR therapy. It, therefore, provided some degree of reassurance knowing they were not undergoing discomfort needlessly. Fatigue was also a common side effect of the therapy reported by our interviewed patients, followed by itchiness, constipation (chemotherapy), hair loss, neuropathy (oxaliplatin-induced),

mouth sores (chemotherapy), nausea (chemotherapy), and overgrown eyelashes/eyebrows (panitumumab). While undergoing the therapy under review, interviewed patients scored their quality of life on a scale of **1-10**, with 1 representing very poor and 10 representing very good quality of life. They provided the following scores respectively: **4, 7, 7, 7, 7, 8, 7.** While **Patient A** provided a low QoL score (4), he did admit that the therapy under review was better tolerated than the adjuvant therapy he endured: "***I tolerated this treatment better than folfox. …Even though the rash was wicked, it was just temporary in comparison to the long-term symptoms of the folfox, ie the ongoing neuropathy from the folfox. I can't say enough about this treatment that has saved my life."***

For those patients who were experiencing cancer-induced symptoms prior to starting the therapy (**Patients C, D, F and G**), patients report complete symptom resolution: "***Yes, I had abdominal discomfort, and lumps in my neck reduced completely after 2-3 cycles.***" And only **Patient E** was required to stop the therapy due to treatment-induced toxicity (facial rash) whose treatment cessation lasted a brief two weeks; the balance of the patients complied with the treatment schedule and maintained it was well worth accessing the therapy under review for it provided what they believed to be: ***a cure, improved quality of life, prolonged life, achieving surgical candidacy (not once but three times for one patient), amelioration in symptoms***; and **Patient G** is now undergoing a rechallenge with the therapy under review wherein she is reporting to derive a clinical benefit once again. In **Caregiver D's** words: "***It managed to get her to surgery 3 times. Her liver lesion was 10 cm and then it went down so significantly such that it was resectable. It was amazing. So ya, it sure was worth it. Where would she be today if it wasn't for Pani? It even surprised her oncologist. Even he opposed surgery, every time. But he is now a believer. Pani plus chemo changed his mind***."

When asked "***What has the therapy allowed you to do***?", patients provided plenty of evocative and thoughtful replies, abounding in heartfelt, emotional and tearful exchanges, which included the author of this submission as well. Patients were able to travel, both close to home and far distances, some as far as Europe, renting a villa with her siblings in the beautiful region of Tuscany, Italy. Seeing that a number of our interviewed patients were early age onset, most cited being able to spend time raising their children which is a responsibility of paramount importance to these patients, who were prepared to resume with vigor and enthusiasm. Walking their children to school or taking their children to swimming lessons, soccer, baseball, or just watching them grow, was one of the most fulfilling and greatest privileges awarded to them, courtesy of the therapy under review. Patients were also provided with the opportunity to undergo surgical resection which was happily welcomed by patients because, according to patients, it provided them with greater longevity and the will to live with hope. One patient was able to celebrate his son's high school graduation and his 25th wedding anniversary with his wife, milestones he believed were not destined to be in his future. Another was able to continue to work as a psychologist because of the remarkable extension in her longevity provided by the therapy under review. She was then subsequently provided with the opportunity to finally retire on her own terms at the normal retirement age, and was not forced to do so by her cancer. Patients were/are able to spend quality time with friends, family colleagues and the community celebrating life, because they are well enough to do so. One patient is able to take the bus on a daily basis to perform normal, everyday tasks such as grocery shopping. And finally in the words of **Caregiver D**: "***Ya, this therapy allowed her to get surgery and live. Live longer, so she can continue to raise our children. Our children mean the world to us. They are why we live in this country. For a better life for our children. That's what this treatment has allowed – it has allowed time with our children. More time. That's what treating cancer is all about***."

And **Caregiver C** describes his father's journey: "***This treatment didn't impact a lot of his life. He can go out, he socializes with people, he is able to take his daily walks, he has been able to vacation and we plan to take a trip to Banff early August as a family and we can't wait. All this has been courtesy of this treatment that has regressed his disease. He goes shopping at the supermarket with my mom. He takes the bus on his own. He socializes in the community park from China because he doesn't feel sick. His life is normal. Not bed ridden, not couch ridden. He is out and about. A good quality of life."***

Companion Diagnostic Test

Metastatic CRC patients with confirmed left-sided primaries have their tumour samples analyzed for mutations in KRAS and NRAS genes (extended RAS) to help inform treatment decisions regarding anti-EGFR monoclonal antibodies, such as Panitumumab therapy, in combination with chemotherapy in the first line setting. These tests, [molecular testing or Next Generation Sequencing (NGS testing)], are ordered by the medical oncologist upon receipt of patient referral and it is the oncologist's hope that the biomarker testing results are reported to them by the time the first patient consultation takes place to help inform first line treatment decisions. These tests are typically performed within the regional cancer center or are sent out and performed by an accredited laboratory that conforms to quality guidelines and routinely participate in proficiency testing.

Our seven interviewed patients each underwent biomarker testing prior to initiating Panitumumab therapy, and all, except for **Patient E**, had their tumour's RAS mutation status determined prior to the incorporation of panitumumab into their treatment protocol. **Patient E** introduced Panitumumab into their third cycle of therapy because biomarker testing results had not been generated in a timely manner to help inform treatment decisions. No patient was required to pay out of pocket for testing, nor were they required to travel for testing, nor was there any inconvenience imposed upon them with respect to testing and the necessity for the test was nicely explained to them by their respective oncologists. There was no anxiety seeing that the results for the most part were reported in a timely manner. Some of the patients did go on to have additional genomic testing performed to help identify any additional mutations or alterations that could be actioned: ***"Yes, a handful of genes that were tested but no mutations. I did do the Foundation One testing later and pretty much nothing came back from that. TMB was zero. No actionable mutations came back actually."***

Our qualitative data underscores the following: If gene testing shows that a tumour is RAS wild type, then initial treatment with panitumumab plus chemotherapy on a left sided colorectal primary suggests some rather impressive long term benefits of early use of this anti-EGFR therapy.

Anything Else?

Survey respondents expressed a desire to have their cancer treated with precision medicines through their open-ended replies. ***"…Personally, I need a treatment that would allow me to address my actionable mutation…"*** . We look to precision oncology to individualize the therapeutic management of cancer patients according to their tumour's genetic profile. The use of high-throughput techniques, such as molecular testing and NGS testing, has certainly paved the way for the implementation of precision oncology for our metastatic colorectal cancer patients, through treatments such as panitumumab + chemotherapy in the first line setting, as clinicians work to extend survival and improve quality of life for this vulnerable cancer population. And primary tumour location is also considered an established and crucial prognostic and predictive factor in the first line treatment of mCRC when considering panitumumab + chemotherapy.

Our interviewed patients were asked to provide some final thoughts about their experience with the therapy under review, which they did quite generously and happily. Patients admitted that the therapy provided them with the best chance of extending overall survival, and in **Patient A**, achieving an NED status. It is one of the few CRC therapies that are biomarker driven, which is highly sought after by patients when seeking a targeted therapy for metastatic disease, because it not only targets a particular molecular pathway, but, it also is administered based on the location of the patient's primary tumour. Patients emphasized the therapy's ability to convert the patient from inoperable to operable by significantly regressing disease, thereby, extending their lifespan. One patient cited their experience with the therapy as having enhanced her treatment journey because this biomarker driven treatment extended her life from 2 to 7 years (**Patient F**). And finally, **Patient E** shared his experience as having achieved not only significant regression but the opportunity to now enter a study that may ultimately declare him cured: "***Give us effective treatments that provide hope and pani provides that to us. It got me to the point where I am a candidate for the living donor liver transplant program. And this will hopefully make me curative once and for all. This could be the case for other Canadians too. So this treatment will provide hope for others too in Canada."***

Lastly, for RAS WT, left sided mCRC patients who have not accessed Pani in the first line setting since making this submission, kindly permit these patients to access the therapy in later lines to ensure the maintenance of distributive justice. If publicly reimbursed, Panitumumab + Chemotherapy would be an extremely important first line therapy in patients identified with RAS WT, left sided colorectal cancer. Funding this therapy aligns well with the patient perspectives captured within this submission. We, therefore, strongly support and urge that a positive funding recommendation be issued for this therapy for the first-line treatment of mCRC patients with left-sided primary tumours that express wild-type (WT) RAS.

Appendix: Patient Group Conflict of Interest Declaration - Colorectal Cancer Resource & Action Network (CCRAN)

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Amgen			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Colorectal Cancer Canada

About Colorectal Cancer Canada

Colorectal Cancer Canada is the nation's not for profit colorectal cancer patient organization dedicated to colorectal cancer awareness and education, supporting patients and their caregivers and advocating on their behalf.

Colorectal Cancer Canada is registered with CADTH.

www.colorectalcancercanada.com

Information Gathering

To capture the patient and caregiver perspective on the drug under review, Colorectal Cancer Canada (CCC) launched an online survey in English and French from August 1, 2023 to August 17, 2023 that was completed by a total of 16 respondents. 15 respondents were patients and 1 was a caregiver. Four patients (Patient 1, 8, 9, 15) had experience with the drug under review. Data was gathered from respondents across Canada. The survey was disseminated through CCC's monthly newsletter and posted on CCC's social media platforms (Twitter, Linkedin, Instagram and Facebook) as well as on those of international colorectal cancer organizations. CCC's patient support specialists also reached out to patients in CCC's monthly support groups to complete the survey. Three patients who completed the survey agreed to participate in a qualitative interview by telephone/Zoom to expand on their experience with the drug under review. A copy of the survey questions as well as the survey results by section are attached in this submission.

Table 1: Demographics of Patients and Caregiver Surveyed

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Country and Region	Quebec, Canada	British Columbia, Canada	Ontario, Canada	Quebec, Canada	Newfoundland & Labrador, Canada	Quebec, Canada
Gender, Age	Female, 51-60 years	Female, 61-70 years	Female, 31-40 years	Female, 31-40 years	Male, 61-70 years	Female, 41-50 years
Stage at Dx, sidedness, RAS status	IV, left-sided, RAS wild-type	III	IV, left-sided, RAS wild-type	IV	IV	III, left-sided, RAS mutated
	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	
Country and Region	Nova Scotia, Canada	Nova Scotia, Canada	Quebec, Canada	Quebec, Canada	British Columbia, Canada	

Gender, Age	Female, 31-40 years	Female, 61-70 years	Male, 41-50 years	Gender unspecified, 61-70 years	Female, 61-70 years	
Stage at Dx, sidedness, RAS status	IV	IV, left-sided, RAS wild-type	IV, left-sided, RAS wild-type	Unsure	IV, right-sided	
	Patient 12	Patient 13	Patient 14	Patient 15	Caregiver 1	
Country and Region	Alberta, Canada	Prince Edward Island, Canada	Quebec, Canada	Quebec, Canada	British Columbia, Canada	
Gender, Age	Female, 51-60 years	Female, 51-60 years	Male, 61-70 years	Male, 51-60 years	Female, 51-60 years	
Stage at Dx, sidedness, RAS status	IV, left-sided	III, left-sided	IV, left-sided	IV, left-sided, RAS wild-type	IV, right-sided, RAS mutated	

Disease Experience

Survey data regarding disease experience is summarized in the PDF attached, entitled: "Summary graphs – Disease Experience".

Patients and caregivers were asked about which symptoms of colorectal cancer (CRC) they experienced (Q9). 94% of respondents experienced CRC symptoms (Q8), with bloody stools, abdominal pain, fatigue and weakness cited as the most common symptoms. When asked what the top CRC symptoms were the most important to control (Q10), respondents selected fatigue and weakness, abdominal pain, anemia, and diarrhea. 13 out of 16 patients/caregivers indicated that their CRC symptoms directly and/or indirectly limited their quality of life (Q11). Respondents were asked to select the three most important ways the CRC symptoms they experienced impacted their quality of life, with ability to work, ability to exercise, and ability to participate in social activities cited as the most important.

When asked about the psychological impact of CRC (Q12), patients cited persistent fear of [the] cancer getting worse or recurring (coming back); feeling consistently worried, nervous or uneasy; persistent fear of hopelessness about [the] future; and inability to concentrate or perform activities that require mental acuity as the most common impacts. One patient expanded on the impact of CRC in their interview: "*The part that impacts my life more is not the question of whether I will die, but rather, how my life at the moment is limited. I can't travel, I can't plan more than 3 weeks ahead. I feel like I am wearing handcuffs".*

Caregivers were uniquely questioned on the difficulties they faced while caring for the individual living with CRC (Q36-39). The one caregiver who responded to the survey indicated that the main difficulties they faced were: inability to plan for the future, time spent at medical appointments, difficulty managing treatment-induced side effects or symptoms of the cancer, feeling helpless or inadequate, and physical/emotional exhaustion (caregiver burnout). They indicated that an average of 0-10 hours were dedicated per week to managing the patient's side effects, and an average of 0-10 hours a week were dedicated to managing the patient's treatment including taking them to appointments, administration of medication, and hospital/clinic visits.

Caregivers who were interviewed for a previous submission by CCC for panitumumab provided the following open-ended responses regarding the difficulties they faced:

- "*Managing time to attend appts and treatments, feeling helpless when the patient cannot eat or is unable to do her regular activities, so I have to take over those activities along with managing my daily chores. "*
- *"Had to go part time. Financial challenges. Worry, anxiety, depression*."

Experiences With Currently Available Treatments

Survey data regarding experience with currently available treatments is summarized in the PDF attached, entitled: "Summary graphs – Experiences with Currently Available Treatments".

Patients and caregivers were asked to indicate which drug therapies they have accessed to treat their CRC (Q19). FOLFOX, FOLFIRI, capecitabine, and panitumumab were cited most frequently. Fatigue, diarrhea, hair loss and nausea were cited as the most common side effects experienced with drug therapies (Q24), while the most difficult side effects to tolerate were neuropathy, nausea and fatigue (Q26). Patients/caregivers were asked whether they experienced any difficulties during the administration of a treatment (Q20). 8 patients responded, with 4 patients indicating that they experienced no difficulties. From the 4 other respondents, the following open-ended responses were provided:

- *"Yes. Difficulties swallowing, difficulties with Port-o-cath installation. Problems with displacement of Port-o-cath in heart. Hepatic Arterial Infusion challenges with dosage and abdominal pain; pain in my hands"*
- *"Vomiting during infusion, chemo delays due to blood parameters being too low."*
- *"First port-o-cath blocked with fibrin clot three weeks after implantation. A second one had to be placed."*
- *"Mechanical issues with 5-FU pump*"

When asked whether these drug therapies have been effective at controlling the symptoms of the cancer, such as pain (Q21), 15% of patients/caregivers said "no", 31% said "somewhat", and 54% said "yes". When asked whether these drug therapies have been effective at controlling the progression of the disease (Q22), 8% said "no", 25% said "somewhat", and 67% said "yes", with the following open-ended responses:

- *"They allowed me to reduce tumour burden and have the cancer removed from the colon, liver and lungs"*
- *"Was able to proceed with surgery since I had a response to chemo, therefore I became a surgical candidate"*

Respondents also indicated (Q23) that they accessed other therapies such surgery and radiofrequency ablation to treat their cancer. Patients/caregivers were asked if they experienced any difficulties accessing drugs for their colorectal cancer (Q28), to which the following open-ended responses were provided:

- *"Had to leave the country for some of the treatments. (HAI)"*
- *"My Avastin has now been defunded by BC Cancer and I don't have extended coverage and so far no one has been able to tell me the cost so I can know if I can afford it"*
- *"Panitumumab outside the formulary, had to apply for a special exception"*

Patients/caregivers were asked to rate on a scale of 1-10 (1 being "not important", 10 being "very important") the importance of access to new, effective therapies for CRC (Q14). 93% of respondents indicated that access to such therapies was very important to them. When patients/caregivers were asked whether they believed their needs are not being met by current drugs available to treat their cancer (Q35), 39% replied "yes", with the following open-ended responses:

- *"Options seem more diversified in the U.S."*
- *"Need options beyond FOLFOX and FOLFIRI"*
- *"Need more information about what is available I am only told there is a protocol for my stage of cancer, and treatment is determined by BC Cancer*".

Improved Outcomes

Survey data regarding improved outcomes is summarized in the PDF attached, entitled: "Summary graphs – Improved Outcomes".

Patients/caregivers were asked to rate how important it is to them for a new therapy to bring about improvement to their physical condition and quality of life (Q40 and Q41). 67% of respondents replied that it is very important for a new therapy to bring about improvement to their physical condition (e.g. tumour shrinkage, tumour stability, reduction of pain) and 64% of respondents indicated that it was very important for a new therapy to bring about improvement in their quality of life. 100% of respondents indicated that they would be willing to take a drug that has been proven to provide better quality of life even if it does not extend overall survival (Q42).

The series of questions Q43-46 aimed to understand patient and caregiver trade-offs with respect to tolerating significant side effects associated with the drug under review (skin reaction, anemia, mouth sores) if overall survival was 10 months; 8 months; 6 months and 4 months:

- 100% of respondents replied that tolerating significant side effects would be acceptable if overall survival was 10 months;
- 100% of respondents replied that significant side effects would be tolerable if overall survival was 8 months;
- 100% of respondents replied that significant side effects would be tolerable if overall survival was 6 months;
- 75% of respondents replied that significant side effects would be tolerable if overall survival was 4 months;

These results are significant because even when overall survival is modest, at 4 months, three quarters of patients/caregivers are willing to tolerate significant side effects.

Experience With Drug Under Review

Survey data regarding experience with drug under review is summarized in the PDF attached, entitled: "Summary graphs – Experience with Drug Under Review".

Four patients with left-sided, RAS wild-type mCRC who completed the online survey had experience with the drug under review as first-line treatment in combination with chemotherapy. Three of the four patients agreed to participate in a qualitative interview to expand on their experience with the drug under review. The therapy was funded through their provincial health plans. All 4 patients indicated that panitumumab plus chemotherapy was able to shrink/control their CRC and/or metastasis (Q56). One patient replied, *"Left-sided WT with liver mets. The treatment successfully reduced liver lesions and is now used for maintenance therapy."* From the qualitative interviews, one patient indicated that they *"started treatment [with panitumumab and chemotherapy] in August. By December, the 4 targeted liver mets had reduced in size by 31%".* Another patient indicated that *"after 6 months on panitumumab and chemotherapy, all traces of the cancer disappeared".* Another patient replied, "*"This combination had the longitudinal force of getting through to NED, improvement of QoL and enabled me to undergo surgery for the basic functional repair of my pelvic region".*

The most common side effects experienced by the patients were skin reaction (rash, dryness, itching), mouth sores, sore eyes, fatigue, and diarrhea (Q57). Skin reaction was cited by all 4 patients as the most

difficult side effect to tolerate, with one patient rating their side effects a 10 out of 10, indicating that they experienced “debilitating side effects that impact daily living”.

1 out of the 4 patients indicated that they experienced difficulty receiving panitumumab and chemotherapy, indicating that they had problems with their port due to severe skin rash from the treatment. While management of side effects and lifestyle changes due to treatment were cited as the most difficult aspects of panitumumab and chemotherapy (Q64), all four patients rated their quality of life (Q62) a 7 out of 10 (1 being “low/severely impacted and 10 being “high/normal living”). 2 out of 4 patients indicated that they were still able to continue their daily activities or work while undergoing treatment (Q63), while the other 2 patients could not:

- *“I could not work due to the side effects, and I was unable to participate in social activities due to the pain.”*
- *“Exercise was hard because I was trying to figure out what I could do when my energy levels were so low.”*

Patients who participated in additional interviews with CCC were asked to expand on their experience with skin toxicity, as it was a significant side effect with the drug under review:

- *I saw a dermatologist and they increased the dose of the medications to treat my rash which improved significantly from there on.”*
- *“I was at my lowest when I had my skin toxicity. Between that and my neuropathy. I could not do anything. I was so cranky, depressed and full of rage. But after I was connected with the dermatologist, things improved very quickly. I was taken off the antibiotics and put on zinc supplements. Then I began Accutane. It improved significantly”*
- “*The skin rash was the absolute worst for my morale. It was painful, embarrassing, made me lose my privacy and limited my QOL. However, under the care of dermatology, this resolved and I'm more hopeful.”*
- *“The first time on panitumumab, the skin problems were really awful. I received some prescriptions for antibiotics and creams, but when my skin got worse they sent me to a dermatologist. To be honest, the skin problems did not improve much until I finished treatment. I am on panitumumab again and my skin problems only get bad at certain moments in the cycle now.”*

When asked if there is a particular unmet patient need with current therapies that panitumumab as first-line therapy could help alleviate, one patient responded that it has a “*better response, better cancer control than FOLFOX or FOLFIRI alone”.* In one qualitative interview, the patient commented that *“overall, I don’t think that chemo alone could have had the same impact. My cancer completely disappeared for a year and a half, so for me, [panitumumab and chemotherapy] was really worth it.”*

Q65 asked patients to explain whether accessing the drug under review allowed them to fulfill or accomplish anything that they would not have other been able to had they not accessed the therapy. The patients replied:

- *“Yes, my metastasis completely disappeared. I was able to stop chemo for 1,5 year allowing me to travel with my family and resume works for a while.”*
- *“Yes, allowed for breaks during which I could travel, visit family. Life extension due to panitumumab enabled me to work full time and to retire on time.”*

Two patients expanded further in their qualitative interview:

- *“As bad as the side effects were, panitumumab brought a huge reduction of tumour volume and extended my life. I was able to see my son graduate from his Masters program, return to work and retire on time. Because of this combination, I was NED for a period of a time during which I*

was able to undergo pelvic reconstruction surgery to repair the damage that was done to my kidney and bladder as a result of the ureter stent I had put in because my tumour was pressing on it. I was able to get the surgery done and hugely improve my quality of life…it has been the most comfortable I have been in all my years living with CRC. After this surgery I was able to travel across Canada for a 3-month holiday and enjoy my life."

- *"The treatments were really not easy due to the side effects, especially fatigue and skin problems. It was worth the dealing with them to stabilize the metastases and take a break from treatment, which allowed me to visit my family in France over the summer and spend time with my children on family vacation down south. Something I hadn't been able to do since before my diagnosis 2 years prior."*

When asked whether they believe the drug under review should be funded for the treatment of mCRC, patients replied with the following open-ended responses:

- *"Yes. It gives patients an option that improves survival and extends life."*
- *"Yes. In my case, it was proven to have reduced liver mets in size. Skin toxicity resolved under the care of a dermatologist and with the reduced frequency of treatment (every three weeks rather than bi-weekly)."*
- *"Yes. It gave such good results for me that I think everybody should have access."*
- *"Absolutely. Just know that there are resources that can help and don't be afraid to ask. Even if it is a little rash, don't be afraid to ask for help! you can get additional help to resolve it and greatly improve your QoL"*
- *"This is an effective treatment for colon cancer so if I was KRAS wildtype I would want to access this treatment due to the additional overall survival benefit."*
- *"Yes, it is very important to provide hope to others in similar circumstances."*
- *"I had a great response to it both times I was on it. An 80% reduction in tumour volume both times."*

In summary, access to panitumumab as first-line treatment for mCRC patients with left-sided, RAS wild-type primary tumours is extremely important because it provides patients in this subgroup with an effective, targeted therapeutic option. Despite the difficult side effects that are associated with the drug under review, patients indicate that the trade-offs are worth it. The drug in combination with chemotherapy is able to reduce tumour burden and extend survival, allowing some mCRC patients to enjoy breaks in treatment, albeit temporary, but nonetheless important to participate in valuable life events that have a significant impact on improving their quality of life. Patients underlined the importance of seeking support early on for the skin toxicity linked to this drug to minimize the negative impact on quality of life during treatment.

Companion Diagnostic Test

RAS mutation status provides actionable information when deciding on a first-line treatment option in mCRC. All four patients who had experience with the drug under review had biomarker testing done after diagnosis and their RAS status was determined to be RAS wild-type.

Based on the survey results, 64% of respondents had biomarker testing done after they were diagnosed with CRC, 14% of respondents stated that biomarker testing was not done, and 21% were unsure. 57% of respondents indicated that the RAS status of their tumour was determined, 7% indicated that the RAS status of their tumour was not determined, and 36% were unsure. These findings suggest that while the majority of respondents did have biomarker testing done and RAS status determined, a proportion of respondents did not or were uncertain about whether biomarker testing was done at all, let alone familiar with the details of their RAS status. Given that the majority of the survey respondents were diagnosed with stage IV CRC, biomarker testing for RAS mutation status ideally should have been completed in *all*

cases. There is a need for greater awareness and education among patients regarding the importance of timely biomarker testing as it is an important determinant in the CRC treatment trajectory.

Anything Else?

Panitumumab is an effective, therapeutic option for the mCRC patient population with left-sided, RAS wild-type primary tumours. Given that this drug is only reimbursed in certain provinces, we believe that there is a strong need for equity of access for all patients with mCRC regardless of where they are located. **We, therefore, strongly support and urge that a positive funding recommendation be issued for panitumumab for the first-line treatment of left-sided, RAS-wild-type metastatic colorectal cancer.** We believe this drug aligns well with the identified patient and caregiver need for an effective treatment option that is capable of prolonging life and maintaining QoL.

Conflict of Interest Declaration - Colorectal Cancer Canada

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No.

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Abbvie Corp.			X	
Amgen Canada Inc.				X
Astra Zeneca Canada Inc.				X
Bayer Inc.				X
Boehringer Ingelheim Ltd.				X
Hoffmann-La Roche				X

Innovative Medicines Canada				X
INCYTE			X	
Janssen Inc.				X
Pfizer Canada Inc.				X
Taiho Pharma Canada			X	
GlaxoSmithKline				X
Novartis			X	
Merck Canada Inc.				X
Bristol Myers Squibb Canada				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Stakeholder Input – Clinician Input

Disclaimer: The views expressed in each submission are those of the submitting organization or individual and not necessarily the views of CADTH or of other organizations. As such, they are independent of CADTH and do not necessarily represent or reflect the views of CADTH. No endorsement by CADTH is intended or should be inferred.

By filing with CADTH, the submitting organization or individual agrees to the full disclosure of the information. CADTH does not edit the content of the submissions.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting organization or individual and all conflict of interest information are included in the submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

CADTH is committed to treating people with disabilities in a way that respects their dignity and independence, supports them in accessing material in a timely manner, and provides a robust feedback process to support continuous improvement. All materials prepared by CADTH are available in an accessible format. If materials provided to CADTH by a submitting organization or individual are not available in an accessible format, CADTH will provide a summary document upon request. More details can be found within CADTH's accessibility policies.

Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee ("GI DAC")

About CCO Gastrointestinal Cancer Drug Advisory Committee ("GI DAC")

OH-CCO's Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

Information Gathering

Information was gathered via videoconferencing.

Current Treatments and Treatment Goals

For mCRC patients with left-sided primary tumors that express *RAS* wild-type, with those who have MSI-L/MSS/pMMR status, the first line treatment includes multiagent chemotherapy with or without a biologic (i.e. bevacizumab). For patients with MSI-H/dMMR status, the first line treatment option is pembrolizumab.

The treatment goals are to prolong life, delay disease progression and improve symptoms.

Treatment Gaps (unmet needs)

Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

There is a lack of routine availability of anti-EGFR treatment in the first line setting.

Place in Therapy

How would the drug under review fit into the current treatment paradigm?

This treatment would be used for first line RAS wild-type, left sided mCRC.

If panitumumab is given in the first line setting, patients should have access to bevacizumab in the second line setting.

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Patients best suited are those with RAS wild type tumors that are left-sided, and patients who would otherwise be eligible for systemic chemotherapy. The definition of left-sided tumors is heterogeneous due to the differing inclusion criteria of the major trial. Therefore, the designation of the left-sided tumors should be left to the discretion of the treating physician and presentation to the MCC.

Patients least suited would be those with a right-sided tumor, *RAS* mutant tumor, or patients not fit for multi-agent chemotherapy.

This treatment should not be used in the neoadjuvant setting for patients with resectable metastases (i.e., liver, lung, etc.).

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Patient outcomes are determined using CEA values and cross-sectional imaging as per standard clinical practice.

What factors should be considered when deciding to discontinue treatment with the drug under review?

Disease progression, unacceptable toxicity and patient preference are factors to consider.

However, if patients are intolerant to chemotherapy, they should have the option to continue with panitumumab alone.

What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

This treatment can be administered in the outpatient setting.

Additional Information

With respect to RAS testing, there are variations across sites with having access to testing as well as the turnaround time for results. So, there needs to be equitable access to RAS testing and a reasonable turnaround time for the results, across the province.

Conflict of Interest Declarations - CCO Gastrointestinal Cancer Drug Advisory Committee ("GI DAC")

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

4. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   Yes, OH-CCO provided a secretariat function to the group.

5. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

6. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Erin Kennedy

Position: Lead, OH-CCO GI DAC

Date: 30-08-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
No COI				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Michael Raphael

Position: Member, OH-CCO GI DAC

Date: 18-08-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
No COI				

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Suneil Khanna

Position: Member, OH-CCO GI DAC

Date: 18-08-2023

☐ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Dr. Yoo-Joung Ko

Position: Member, OH-CCO GI DAC

Date: 18-08-2023

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Amgen	X			

* Place an X in the appropriate dollar range cells for each company.

Canadian Gastrointestinal Oncology Evidence Network (CGOEN)

About Canadian Gastrointestinal Oncology Evidence Network (CGOEN)

The Canadian GI Oncology Evidence Network (CGOEN) is a virtual and inclusive network of Canadian GI Oncology clinicians who contribute to the knowledge of GI cancer and its treatments, including participating in clinical trials, conducting observational research, and involvement in local/provincial and national clinical guideline developments and health technology assessment.

Information Gathering

Data is from a Phase 3 trial of Panitumumab vs. Bevacizumab with standard first line chemotherapy for patient with RAS-wild type, left sided metastatic colorectal cancer. Data supporting the use of upfront EGFR monoclonal antibody therapy with chemotherapy in this population is largely from retrospective analysis of Phase 3 trials. This is the first prospective trial looking at this specific population. There is an improvement in overall survival of 37.9 months vs 34.3 months (HR 0.82, P=0.03) panitumumab vs bevacizumab. There is an increased response rate of 74.9% vs. 67.3% leading to increased curative resection rates of 18.3% vs. 11.6% panitumumab vs. bevacizumab respectively.

Reference:

Panitumumab vs Bevacizumab Added to Standard First-line Chemotherapy and Overall Survival Among Patients With RAS Wild-type, Left-Sided Metastatic Colorectal Cancer: A Randomized Clinical Trial.

Watanabe J, Muro K, Shitara K, Yamazaki K, Shiozawa M, Ohori H, Takashima A, Yokota M, Makiyama A, Akazawa N, Ojima H, Yuasa Y, Miwa K, Yasui H, Oki E, Sato T, Naitoh T, Komatsu Y, Kato T, Hihara M, Soeda J, Misumi T, Yamamoto K, Akagi K, Ochiai A, Uetake H, Tsuchihara K, Yoshino T.

JAMA. 2023 Apr 18;329(15):1271-1282. doi: 10.1001/jama.2023.4428.

PMID: 37071094

Current Treatments and Treatment Goals

The current funding for the treatment of left sided RAS wild type metastatic colorectal is first line chemotherapy (fluoropyrimidine with either irinotecan or oxaliplatin) combined with bevacizumab. EGFR monoclonal antibody can be used in bevacizumab ineligible patients. If EGFR monoclonal antibody therapy is not used in the first line – then it is used in the third line setting after second line chemotherapy. The goals of treatment is improvement in overall survival and quality of life. It should be noted 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 metastatectomy.

Treatment Gaps (unmet needs)

Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

It should be noted that Canada is an exception in this treatment paradigm as EGFR monoclonal antibody therapy is a standard of care option for first line treatment with chemotherapy without the need to ineligible for bevacizumab. These patients are also allowed to receive second line bevacizumab as treatment guidelines.

The current Canadian treatment paradigm leaves oncologists in a difficult position – if they feel the patient should receive first line EGFR therapy with chemotherapy for the survival benefit, they must declare them

bevacizumab ineligible. Consequently, they will be denying patients access to bevacizumab in the second line setting given they have declared the patient ineligible for this treatment.

Place in Therapy

How would the drug under review fit into the current treatment paradigm?

EGFR monoclonal antibody therapy is already approved for use in metastatic colorectal cancer RAS wild type. Currently the main use in third line due to funding and first line eligibility restrictions.

This drug review and if approved would put Canada's treatment paradigm in line in patients with RAS WT mCRC and consistent with the standard of care in other countries.

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Eligible patients:

Metastatic or locally advanced left sided colorectal adenocarcinoma RAS wild type

ECOG 0,1

Able to tolerate systemic therapy

Ineligible patients:

ECOG 2 or greater

Inadequate organ function for treatment

RAS testing is needed which is already used and approved in Canada. This already part of standard of care for colorectal cancer. RAS mutant do not respond to treatment and represent 50% of cases of colorectal cancer.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Clinical practice mirrors that of the PARADIGM clinical trial. The goal of treatment is overall survival and improvement in symptoms/QOL. Patients are currently able to have an excellent quality of life for years maintaining activities of daily living.

Patients are assessed routinely clinically and via imaging. Treatment is changed due to tolerance, progression or patient preference.

What factors should be considered when deciding to discontinue treatment with the drug under review?

Treatment should be discontinued with progression of disease, toxicity of drug (severe rash or diarrhea < 10%) or patient preference.

What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

There is strong clinical familiarity with managing patients on this therapy as EGFR monoclonal antibody therapy is already widely used in metastatic colorectal cancer so can be used in any oncology setting. Tumor testing in the first-line setting to identify patients with RAS WT disease is already an accepted

standard of care. (Ref: Yu etal, Tumour Biomarker Testing in mCRC: Canadian Consensus Guidelines, her Adv Med Oncol 2022 Jul 20;14)

Additional Information

Current access to EGFR monoclonal antibody therapy in Canada is an outlier in the treatment of metastatic colorectal cancer. First line EGFR monoclonal antibody therapy with chemotherapy in left sided RAS wild type metastatic colorectal cancer with subsequent second line bevacizumab with chemotherapy is a standard of care in the majority of countries. This is based on retrospective analysis of several phase 3 upfront EGFR monoclonal antibody therapy with chemotherapy. Approval of this protocol will put us in line with the rest of the world.

Conflict of Interest Declarations - Canadian Gastrointestinal Oncology Evidence Network (CGOEN)

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Brandon Meyers

Position: Medical oncologist

Date: 01-98-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
AstraZeneca	X			

Ipsen		X		
Roche		X		
Incyte	X			
Bayer	X			

*Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Vincent Tam

Position: Medical Oncologist, Tom Baker Cancer Centre, University of Calgary

Date: 01-09-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

Company	**Check appropriate dollar range***			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AstraZeneca			X	
Eisai		X		
Incyte	X			
Ipsen		X		
Merck	X			
Roche		X		

*Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Ravi Ramjeesingh

Position: Medical Oncologist

Date: 01-Sept-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

Company	**Check appropriate dollar range***			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
AstraZeneca		X		

Amgen	X			
Roche	X			
Incyte		X		
Eisai		X		
Ipsen	X			
Merck	X			
Jannsen	X			
Pfizer	X			
Novartis	X			
Knight	X			

*Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 4

Name: Petr Kavan

Position: Medical Oncologist

Date: 22 Aug 2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 4: Conflict of Interest Declaration for Clinician 4

Company	**Check appropriate dollar range***			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Roche	X			
Bayer	X			
Amgen		X		
AstraZeneca	X			
Astellas	X			
BMS	X			
Lilly	X			
Tahio			X	
Eisai	X			
Ipsen	X			

*Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 5

Name: Howard Lim

Position: Medical Oncologist

Date: 22-aug--2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 5: Conflict of Interest Declaration for Clinician 5

Company	**Check appropriate dollar range***			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Roche	X			
Bayer	X			
Amgen	X			
AstraZeneca		X		
Astellas	X			
BMS		X		
Lilly	X			
Tahio	X			
Eisai		X		
Ipsen	X			
Varian	X			

*Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 6

Name: Sharlene Gill

Position: Medical Oncologist, BC Cancer - Vancouver

Date: 22-08-2023

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 6: Conflict of Interest Declaration for Clinician 6

Company	**Check appropriate dollar range***			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Taiho Canada	X			
Roche Canada		X		
Amgen Canada		X		
Viatris	X			

Merck	X			
Pfizer		X		

*Place an X in the appropriate dollar range cells for each company.

Stakeholder Input – Industry Input

Disclaimer: The views expressed in each submission are those of the submitting organization or individual and not necessarily the views of CADTH or of other organizations. As such, they are independent of CADTH and do not necessarily represent or reflect the views of CADTH. No endorsement by CADTH is intended or should be inferred.

By filing with CADTH, the submitting organization or individual agrees to the full disclosure of the information. CADTH does not edit the content of the submissions.

CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting organization or individual and all conflict of interest information are included in the submission; however, the name of the author, including the name of an individual patient or caregiver submitting the patient input, are not posted.

CADTH is committed to treating people with disabilities in a way that respects their dignity and independence, supports them in accessing material in a timely manner, and provides a robust feedback process to support continuous improvement. All materials prepared by CADTH are available in an accessible format. If materials provided to CADTH by a submitting organization or individual are not available in an accessible format, CADTH will provide a summary document upon request. More details can be found within CADTH's accessibility policies.

Amgen Canada Inc.

Does the proposed project scope accurately reflect the treatment landscape?

The proposed project to evaluate whether panitumumab should be publicly reimbursed in combination with chemotherapy for the first-line treatment of mCRC patients with left-sided primary tumours that express wild-type *RAS* is reflective of the treatment landscape.

The American Society of Clinical Oncology strongly recommend the use of an EGFRi, including panitumumab, plus doublet chemotherapy as first line therapy for patients with left-sided MSS or pMMR *RAS* wt mCRC.[1] The European Society of Medical Oncology recommend the use of EGFRi, including panitumumab, with doublet chemotherapy for all mCRC patients with *RAS/BRAF* wt, MSS/MSI-L left-sided mCRC.[2] Previously published Canadian Consensus statements (2017) recommend that in patients with RAS wild-type left-sided mCRC, standard chemotherapy (FOLFOX or FOLFIRI) in combination with an EGFRi (cetuximab or panitumumab) is recommended in the first-line setting.[3] The more recent Canadian Consensus statements on biomarker testing (2022) re-confirmed this with a strong recommendation requiring extended RAS testing in order to inform decision regarding the use of EGFRi in combination with chemotherapy for left-sided mCRC.[4]

Hence, an EGFRi in combination with chemotherapy for patients with *RAS* wild-type MSS/pMMR left-sided mCRC represents evidence- and guideline-backed first-line treatment, and should be considered for public reimbursement for all such eligible patients.

Are you aware of relevant published studies that you would like considered in the clinical review?

The Panitumumab and RAS, Diagnostically useful Gene Mutation for mCRC (PARADIGM) study is the first prospective, phase 3, randomized, controlled trial to assess the superiority of panitumumab compared to bevacizumab in combination with chemotherapy in patients with *RAS* wt, left-sided (primary tumours in the descending colon, sigmoid colon, rectosigmoid and rectum) mCRC.[5] To our knowledge, it is the first and largest prospective head-to-head study comparing anti-EGFR and anti-VEGF agents based on tumour-sidedness in patients with *RAS* wt mCRC. The study randomized 823 participants with both left and right sided tumours from 197 centers in Japan and of those 400 participants received panitumumab with mFOLFOX6 and 402 received bevacizumab with mFOLFOX6. Three hundred and twelve participants and 292 participants with left-sided mCRC receiving panitumumab and bevacizumab respectively were included in the analysis for OS.[5]

The study met its primary endpoint of OS with a statistically significant improvement in median survival of 3.6 months with panitumumab plus mFOLFOX6. The median survival time was 37.9 months (95.798% CI, 34.1-42.6 months) for patients in the panitumumab arm vs 34.3 months (95.798% CI, 30.9-40.3 months) with bevacizumab (stratified HR, 0.82; 95.798% CI, 0.68-0.99; P = .03).[5] The median PFS was 13.1 months (95% CI, 11.6-14.5 months) with panitumumab vs 11.9 months (95% CI, 11.3-13.5 months) with bevacizumab (HR, 1.00; 95% CI, 0.83-1.20) in participants with left-sided tumors.[5] Higher response rates, higher curative resection rates, greater depth of response, and rates of early tumour shrinkage were also reported in the panitumumab arm vs the bevacizumab arm.[5] The greater depth of response (-59.4% vs -43.6% in the panitumumab and bevacizumab groups, respectively, in the left-sided population) may be a better predictor of post-progression survival than PFS in this patient population.[6] In addition, there were a greater number of patients who underwent curative resection in the panitumumab arm (18.3%; 95% CI, 14.1%-23.0%) vs the bevacizumab arm (11.6%; 95% CI, 8.2%-15.9%), which may contribute to the lack of difference in PFS while contributing to the OS differences.[5]

A prospective biomarker study of participants included in PARADIGM reported clinical outcomes of those with MSS/MSI-L, *RAS* wt, and *BRAF-V600E* wt left-sided mCRC. These biomarkers were selected based on current guideline recommendations for clinically relevant biomarkers in first-line mCRC. Over 90% of participants from the PARADIGM study were included in the biomarker study including 256 participants in the panitumumab plus mFOLFOX6 arm and 241 participants in the bevacizumab plus mFOLFOX6 arm

with MSS/MSI-L, *RAS* wt, and *BRAF-V600E* wt left-sided mCRC. In this population the overall survival was 40.6 (95% CI, 36.3-44.4) months in the panitumumab arm vs 34.8 (95% CI, 31.3-41.2) months in the bevacizumab arm, a difference of 5.8 months; HR, 0.79 (95% CI, 0.64-0.97).[7]

The results from the PARADIGM study confirmed the results from the previously published ESMO retrospective pooled analysis of six EGFRi studies in first line *RAS* wt mCRC. This analysis demonstrated improved overall survival for patients with *RAS* wt left-sided mCRC when an EGFRi with chemotherapy was used in the first line compared to chemotherapy with or without bevacizumab.[8]

While Canadian participants were not included the PARADIGM study, baseline disease characteristics and outcomes in the bevacizumab group were consistent with studies in other countries.[5] A prior pharmacokinetic analysis of panitumumab across 14 studies in multiple tumour types comparing Japanese to non-Japanese patients has determined that Japanese patients have similar exposure to panitumumab and supported the same dosing regimen when compared to non-Japanese populations.[9] Additionally, a post-marketing surveillance study of Japanese patients with mCRC confirmed that the safety and effectiveness of panitumumab in this population was similar to data reported in the clinical trials with global populations.[10]

No new safety signals were found in the PARADIGM study. Adverse events more common with panitumumab compared to bevacizumab included acne-like dermatitis, paronychia, dry skin, and hypomagnesemia.[5] Skin toxicities like those noted in PARADIGM are known to be common with EGFRi therapy and can be effectively managed through prophylactic regimens as demonstrated by Lacouture and colleagues in the Skin Toxicity Evaluation Protocol with Panitumumab (STEPP) phase 2 study.[11]

In the PARADIGM study 44.6% of patients in the panitumumab arm went on to receive bevacizumab in a later line of therapy and 58.2% of patients in the bevacizumab arm went onto receive an EGFRi. Treatment sequence may affect outcomes on subsequent treatments and survival. An exploratory analysis of OS for patients treated with either first-line panitumumab (EGFRi) and second-line VEGFi therapy, or first-line bevacizumab (VEGFi) and second-line EGFRi, was conducted using data from three prospective randomized panitumumab trials. The median OS was prolonged in patients with left-sided mCRC receiving the panitumumab→VEGFi treatment sequence (43.4 vs 32.4 months in the panitumumab→VEGFi vs bevacizumab→EGFRi groups, respectively; HR 0.61; 95% CI 0.33 to 1.11 and HR 0.56; 95% CI 0.30 to 1.04 in the *RAS* WT and *RAS* WT/*BRAF* WT groups, respectively).[12] It has been proposed that first-line EGFRi use can increase VEGF expression levels sensitizing the tumour to subsequent VEGFi treatment. This contrasts use of VEGFi in the first-line which can lead to resistance to both VEGFi and EGFRi.[13]

Do you have additional comments that you feel are pertinent to this review?

Panitumumab is approved by Health Canada for the treatment of previously untreated patients with non-mutated (wild-type) *RAS* metastatic colorectal carcinoma (mCRC) in combination with FOLFOX (infusional 5-fluorouracil, leucovorin, and oxaliplatin).[14] The proposed project scope of panitumumab in combination with chemotherapy, for the first-line treatment of mCRC patients with left-sided primary tumours that express wild-type *RAS* represents approximately 70-80% of the total *RAS* wt mCRC population that would be eligible for first-line treatment as per the Health Canada label.[5,9]

The prior pERC recommendation for the use of panitumumab with chemotherapy, for the first-line treatment of mCRC patients with left-sided primary tumours that express wild-type *RAS* highlighted several limitations of the available data, which was limited retrospective analyses.[15] The PARADIGM study addresses these limitations. It is a prospective, randomized, controlled, phase 3 study powered to detect a difference in overall survival specifically in patients with *RAS* wt left-sided primary tumours. The study met its primary endpoint demonstrating the superiority of panitumumab with mFOLFOX6 over bevacizumab with mFOLFOX6 based on overall survival.[5]

Abbreviations

CI	confidence interval
EGFRi	epidermal growth factor receptor inhibitor
ESMO	European Society for Medical Oncology
HR	hazard ratio
mCRC	metastatic colorectal cancer/carcinoma
mFOLFOX	modified infusional 5-fluorouracil, leucovorin, and oxaliplatin
MSS/MSI-L	microsatellite stable / microsatellite instability-low
OS	overall survival
PFS	progression-free survival
pMMR	proficient mismatch repair
VEGFi	vascular endothelial growth factor inhibitor
wt	wild-type

References

1. Morris VK, Kennedy EB, Baxter NN, et al. Treatment of Metastatic Colorectal Cancer: ASCO Guideline. *J Clin Oncol*. 2023;41(3):678-700.
2. Cervantes A, Adam R, Roselló S, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34(1):10-32.
3. Abrahao ABK, Karim S, Colwell B, Berry S, Biagi J. The predictive effect of primary tumour location in the treatment of metastatic colorectal cancer: a Canadian consensus statement. *Curr Oncol*. 2017;24(6):390-400.
4. Yu IS, Aubin F, Goodwin R, et al. Tumor Biomarker Testing for Metastatic Colorectal Cancer: a Canadian Consensus Practice Guideline. *Ther Adv Med Oncol*. 2022;14:1-29.
5. Watanabe J, Muro K, Shitara K, et al. Panitumumab vs Bevacizumab Added to Standard First-line Chemotherapy and Overall Survival Among Patients With RAS Wild-type, Left-Sided Metastatic Colorectal Cancer: A Randomized Clinical Trial. *JAMA*. 2023;329(15):1271-1282. Erratum in: *JAMA*. 2023;329(24):2196.
6. Heinemann V, Stintzing S, Modest DP, et al. Early tumour shrinkage (ETS) and depth of response (DpR) in the treatment of patients with metastatic colorectal cancer (mCRC). *Eur J Cancer*. 2015;51(14):1927-1936.
7. Yamazaki K, Muro K, Watanabe J, et al. Efficacy of panitumumab in patients with left-sided disease, MSS/MSI-L, and *RAS/BRAF* WT: A biomarker study of the phase III PARADIGM trial. *J Clin Oncol*. 2023;41:16_suppl, 3508-3508.
8. Arnold D, Lueza B, Douillard JY, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. *Ann Oncol*. 2017;28(8):1713-1729.
9. Ma P, Yang BB, Wang YM, et al. Population pharmacokinetic analysis of panitumumab in patients with advanced solid tumors. *J Clin Pharmacol*. 2009;49(10):1142-1156.
10. Boku N, Sugihara K, Kitagawa Y, et al. Panitumumab in Japanese patients with unresectable colorectal cancer: a post-marketing surveillance study of 3085 patients. *Jpn J Clin Oncol*. 2014;44(3):214-223.

11. Lacouture ME, Mitchell EP, Piperdi B, et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive Skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. *J Clin Oncol*. 2010;28(8):1351-1357.
12. Peeters M, Forget F, Karthaus M, et al. Exploratory pooled analysis evaluating the effect of sequence of biological therapies on overall survival in patients with *RAS* wild-type metastatic colorectal carcinoma. *ESMO Open*. 2018;3(2):e000297.
13. Zaniboni A & Formica V. The Best. First. Anti-EGFR before anti-VEGF, in the first-line treatment of RAS wild-type metastatic colorectal cancer: from bench to bedside. *Cancer Chemother Pharmacol*. 2016;78(2):233-244.
14. Vectibix (panitumumab): 100 mg, 400 mg (20 mg /mL) for injection [product monograph]. Mississauga (ON): Amgen Canada Inc.; 2021.
15. pCODR Expert Review Committee (pERC) final recommendation: Panitumumab (vectibix): submitted reimbursement request in combination with chemotherapy, for the first-line treatment of mCRC patients with left-sided primary tumours that express wild-type (WT) RAS. Ottawa (ON): Pan-Canadian Oncology Drug Review; 2018: https://www.cadth.ca/sites/default/files/pcodr/pcodr_panitumumab_vectibix_ls_mcrc_fn_rec.pdf. Accessed 2023 Sep 5.