CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

zolbetuximab (TBC)

(Astellas Pharma Canada, Inc. (APCA))

Indication: Zolbetuximab, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive as determined by a validated test.

July 8, 2024

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

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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 group and all conflicts of interest information from individuals who contributed to the content are included in the posted submission.

Patient Group Input

Name of Drug: Zolbetuximab

Indication: As first-line treatment combination with chemotherapy for patients with locally advanced unresectable or metastatic HER2 -negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive

Name of Patient Group: My Gut Feeling - Stomach Cancer Foundation of Canada

Author of Submission: Teresa Tiano & Ekaterina Kosyachkova

1. About Your Patient Group

My Gut Feeling – Stomach Cancer Foundation of Canada is the first non-profit organization in Canada, dedicated to providing support, awareness, education, information and advocacy to stomach cancer patients, survivors and caregivers. My Gut Feeling was founded by two stomach cancer survivors; although the organization was initially developed to help people affected by stomach cancer, people with gastroesophageal (GEJ) and esophageal cancer are included in our service programs and receive ongoing support. Our mission is to improve the quality of life for people affected by GEJ cancers and to make systemic changes to reduce incidence and mortality of GEJ cancers. We strive to give a voice to patients and caregivers, and provide peer mentorship based on lived experience with cancer.

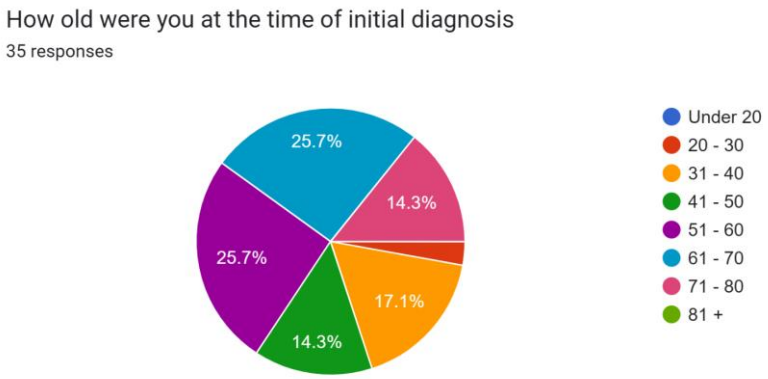
Website: https://mygutfeeling.ca

2. Information Gathering

In order to represent the patient and caregiver voice, My Gut Feeling - Stomach Cancer Foundation of Canada conducted an international online survey to understand the perspective of patients and caregivers affected by gastric, esophageal and/or gastroesophageal (GEJ) cancer including experiences with current treatment and the novel immunotherapy under review. My Gut Feeling launched this survey between June 21st and July 2nd, 2024. The survey link was posted on My Gut Feelings's social media platforms (including Facebook, Instagram and Twitter) as well as the email distribution list for all members. The survey was also shared with patients through additional organizations including: Gastrointestinal Society, Colorectal Cancer Resource & Action Network (CCRAN) and Colorectal Cancer Canada (CCC) through email and their social media channels.

In total, thirty-five people completed the survey, of those, 85.7% identified as a patient and 14.3% identified as a caregiver. Specifically, 68.6% identified as a patient who completed treatment and 17.1% as a patient in current treatment. The majority, 68.6% of respondents identified as female and 31.4% identified as male.

As per the pie-chart below (**Figure 1**), respondents were diagnosed across all ages ranging from 20 to 80 years old.



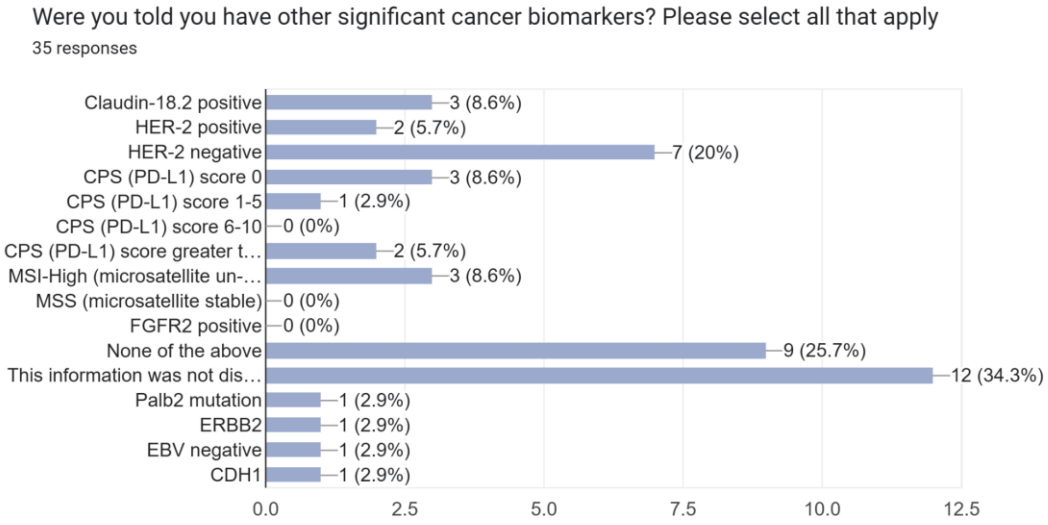
Data was gathered internationally, with 71.4% of respondents residing in Canada, 25.7% in the United States and 2.9% residing outside of North America. To ensure unbiased data collection, respondents were asked to refrain from using personal identifiers to preserve anonymity.

Respondents included in this survey had a diagnosis of gastric, or gastroesophageal (GEJ) cancer. The majority of respondents (88.6%) had gastric cancer and the remainder (11.4%) had GEJ cancer. Of the respondents, 17.1% were diagnosed with stage one, 25.7% with stage two, 28.6% with stage three, 25.7% with stage four, and 2.9% were not given a stage. When the cancer metastasized, in 25.7% it had spread to lymph nodes, 20% to peritoneum, 5.7% to liver and the remainder to other locations including the lungs, brain, bowel and pelvic structures. Most patients (71.4%) had adenocarcinoma; squamous cell carcinoma, diffuse and signet ring cell each had 2.9%. Interestingly, 20% of respondents did not know the type of stomach cancer they had.

When asked about biomarkers and biomarker testing, 51% responded yes to being tested; 22.9% responded no and 25.7% did not know whether they had been tested for biomarkers.Of those that were tested, no one had to pay out of pocket.

The graph below indicates the various types of biomarkers that patients were tested for:

Figure 2 (Biomarker Testing Responses)



Of note, 34.3% responded that the results were not shared with them and 25.7% were told that they had none of the indicated biomarkers. 20% of respondents were HER-2 negative and 5.7% were HER-2 positive, and 8.6% were MSI-High. As well, 8.6% were told that they were tested and were Claudin-18.2 positive.

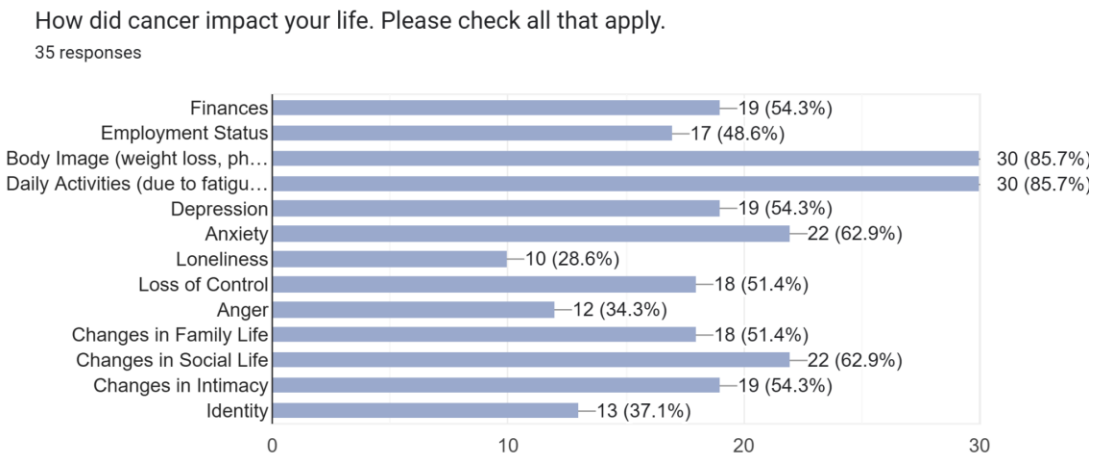
3. Disease Experience

Almost all respondents (97.2%), felt that the cancer diagnosis had a significant impact on their quality of life, whereas (2.9%) felt it had a minimal impact and (0%) felt it had no impact on their quality of life. The areas affected were physical health, mental health, ability to eat, work, finances, social life, identity, and personal image. We received a number of direct quotes from patients and caregivers describing their disease experience; we attempted to select direct quotes that best exemplified these challenges. Respondents commented on the physical implications of cancer and its treatment. Dealing with weight loss/weight gain and the toll it takes on patients was noted by many respondents. For example, one patient describes their experience: “I struggle without focus in my life. My focus used to be my job. Now it has to be food and eating. I measure and track everything I eat and drink to be sure I'm meeting my daily calorie and protein requirements. I have to be careful not to burn too many calories because making up calorie deficits is difficult. Daily nutrition management is exhausting.”

Both patient and caregiver respondents and especially those with metastatic disease, reported a significant decline in their mental health and anxiety about finances due to the cancer diagnosis and its treatment.Patients are often unable to work during treatment, so income is affected. The situation is made worse with additional expenses such as traveling back and forth for treatment, parking expenses, and spending more on groceries for a specialized diet. In many cases, patients can never return to work; one patient described how difficult staying positive was: “I worry about our retirement plans...will we have enough money to retire, will we be able to travel as we planned, or at all? I also worry that my aggressive cancer will recur. All this makes staying positive and getting well incredibly difficult.”

One patient simply said, “Cancer changes everything.” This is reflected in the graph below. A majority of the respondents (85.7%) indicated that their body image was impacted due to weight loss and physical transformation, and that due to fatigue their daily activities were greatly affected. Cancer impacted mental health for many respondents. Patients suffered from anxiety (62.9%), depression (54.3%), and even anger (34.3%).

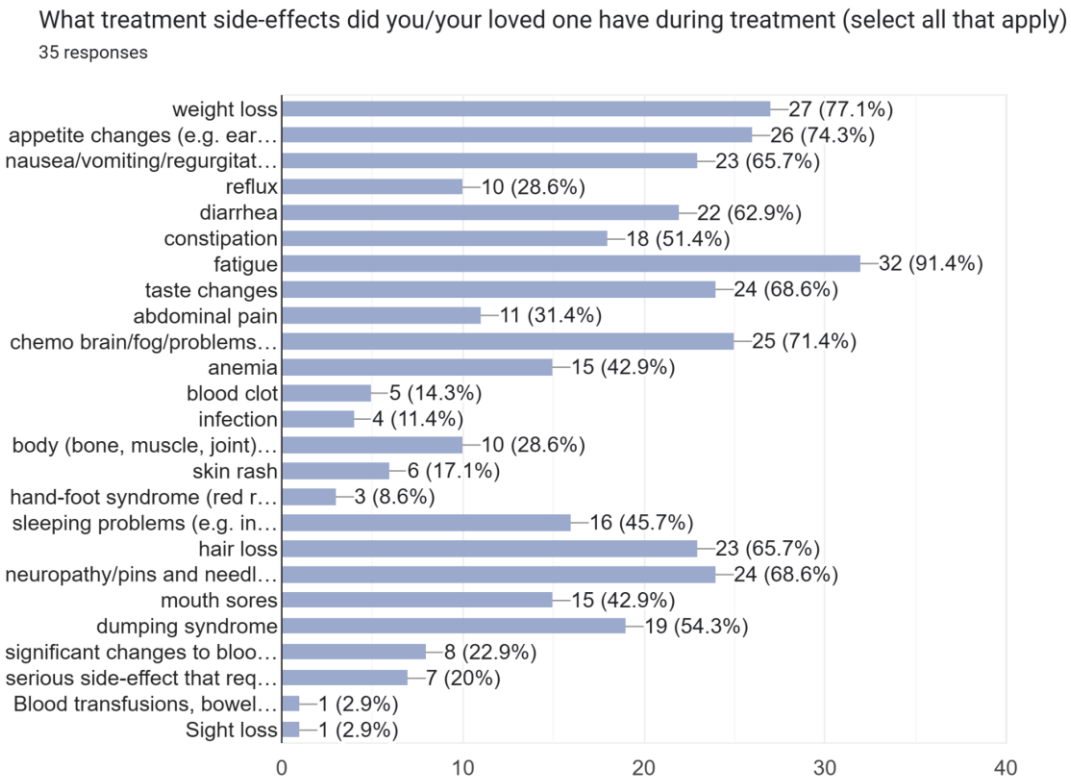
Figure 3 (Impact of Cancer on Life)



4. Experiences With Currently Available Treatments

When asked what treatments patients had or were having, almost half (45.7%) had FLOT, 8.6% had chemotherapy (FOLFOX or FOLFIRI alone), 8.6% had chemotherapy and immunotherapy combined. The remainder of respondents (37.1%) had a combination of various treatments, including 5FU + radiation, surgery, and Xeloda and Keytruda, to name a few. As shown in the graph below, patients experienced many side effects with fatigue (91.4%) and weight loss (77.1%) being the highest.

Figure 4 (Side Effects During Treatment)



When asked if they felt their treatment was effective at controlling their cancer and the symptoms, 62.9% responded that it was very effective, 31.5% felt it was moderately effective, and 5.6% felt the treatment had little or no efficacy whatsoever. In retrospect, some patients felt they weren't provided all the possible options. One patient responded: "I wasn't given treatment options. A combo of FLOT and surgery was the only option given. I was understandably concerned when the pathology came back after surgery showing no signs that my 4 cycles of FLOT had any effect on my disease, and it had spread outside the stomach wall while chemo was delivered. I also received no options for a change to my chemotherapy for my post-surgery chemo, even after asking. I was told that FLOT was the "best" option they had to give me. Going through post-op chemotherapy with the knowledge that pre-op chemotherapy had no effect was incredibly difficult mentally, and I believe my mental state slowed my healing once post-op chemotherapy was complete."

5. Improved Outcomes

When evaluating their treatment options, patients and caregivers considered multiple factors such as quality of life, treatment side effects, convenience of treatment, duration of treatment and the survival benefits. Respondents recognized that treatments had trade-offs and each respondent placed a different value on these considerations based on their preferences.

A majority of respondents (82.9%) would choose a treatment that offers a longer life and survival rate despite the side effects. 8.6% felt that having more treatment options with the least amount of side effects would result in a better quality of life. One caregiver wrote: "Find a treatment that keeps our loved ones with us longer."

Convenience of treatment was another consideration for patients and caregivers. 8.6% chose the option that was most convenient with the least amount of hospital visits. For example patients preferred oral chemotherapy taken at home to an IV chemotherapy administered in a hospital setting, favouring less frequent visits to the hospital .

6. Experience With Drug Under Review

None of the 35 respondents of our survey had experience with the drug under review.

7. Companion Diagnostic Test

We did not ask questions related to companion diagnostic testing.

8. Anything Else?

Gastric, gastroesophageal cancers are rare in Canada with few treatment options. Biomarker testing is becoming routine in Canada. Novel biomarker targets are being tested rapidly in this cancer site. Personalized medicine based on biomarkers is on the rise. Drug combinations that attack multiple targets should be studied and the combinations that improve overall survival (OS) should be rapidly expedited by CDA as potential therapeutic options to fill the urgent and unmet need for gastro-esophageal cancers. For those patients and caregivers impacted by this diagnosis, having options brings about a sense of control and hope at a time when cancer strips the patient and family of their identity. This survey administered by My Gut Feeling shows that there is an unmet patient and caregiver need to receive equitable access to therapies that may prolong life, improve symptoms, reduce risk of recurrence and improve treatment tolerability. My Gut Feeling strongly supports the use of Zolbetuximab (Vyloy) in combination with chemotherapy as first-line treatment for patients with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive

From our survey results we also drew the following conclusions:

1) Patients need to be informed about their biomarkers and eligible treatment options without barriers before starting first line therapy. Treatment options should include information about standard of care options, clinical trials and self-pay options for novel therapies

2) Biomarker testing should be accessible to all Canadians at the onset of their disease

3) New targeted drug combinations improve both survival and quality of life. Patients and caregivers should have a choice in treatment options based on their own personal values and preferences. Treatment options should be available barrier free for all Canadians, covered under the universal healthcare system to benefit the subset of cancer patients that would benefit from this therapy.

Appendix: Patient Group Conflict of Interest Declaration

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.

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

No, My Gut Feeling - Stomach Cancer Foundation of Canada independently completed this submission

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, My Gut Feeling independently collected and analyzed data used for this submission

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
Eli Lilly Canada Inc.	x			
Taiho Pharma Canada Inc.			x	
Bristol Myers Squibb			x	
Jazz Pharmaceuticals			x	
AstraZeneca Canada Inc.				x
Astellas			x	
Merck Canada Inc.				x
Daiichi Sankyo			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.

Name: Teresa Tiano

Position: Chair & Co-Founder

Patient Group: My Gut Feeling - Stomach Cancer Foundation of Canada

Date: **July 8, 2024**

Clinician Group Input

CADTH Project Number: PC0338-000

Generic Drug Name (Brand Name): zolbetuximab

Indication: In combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive as determined by a validated test.

Name of Clinician Group: Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee

Author of Submission: Dr. Erin Kennedy, Dr. Suneil Khanna, Dr. Michael Raphael, Dr. Rachel Goodwin

1. About Your Clinician Group

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.

2. Information Gathering

Information was gathered by email.

3. Current Treatments and Treatment Goals

Currently, there are no approved treatments specifically targeting tumours which overexpress CLDN18.2 As such, standard first-line chemotherapy for metastatic, Her2 negative gastric cancer consists of chemotherapy (usually FOLFOX) combined with immunotherapy (nivolumab currently funded; pembrolizumab approved but unfunded).

Treatment goals include to prolong life, delay disease progression, maintain quality of life.

4. Treatment Gaps (unmet needs)

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

There currently are no approved drugs that specifically target tumours with CLDN 18.2 overexpression. The SPOTLIGHT study showed that zolbetuximab is an active agent for this population.

5. Place in Therapy

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

The addition of zolbetuximab would give clinicians an alternative option to nivolumab, which is currently approved.

5.2. 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 with HER2-negative, CLDN18.2-positive advanced gastric or GEJ cancer.

Unfortunately, first-line zolbetuximab and first-line nivolumab have not been compared head-to-head for pts with CLDN 18.2 overexpression. We suspect that chemo/zolbetuximab will be the clear first-line choice in patients with CLDN 18.2 overexpression + PD-L1 negative/low. It's unclear whether immunotherapy (nivolumab/pembrolizumab) or zolbetuximab is the best first-line option for patients with CLDN 18.2 overexpression and PD-L1 CPS > 5%.

When patients are CLDN18.2+ and CPS+, it is physician's choice on which agent to add (i.e., zolbetuximab, nivolumab or immunotherapy). This is based on comorbidities and toxicity profile that will still maintain good quality of life of the patient.

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

CT scans should be done regularly as per clinician discretion. As per the SPOTLIGHT trial, the addition of zolbetuximab to chemotherapy should improve both PFS and OS (although there was no difference in objective response rates).

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

Disease response as well as immune-related toxicities, overall functional status.

5.5 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]?

Patients should be under the care of a medical oncologist.

6. Additional Information

Approval of zolbetuximab will require upfront Claudin 18.2 testing in all patients (in addition to Her2 and PD-L1 CPS, which is currently mandated). The testing is inexpensive, but assays will need to be developed/standardized.

7. Conflict of Interest Declarations

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.

   OH (CCO) provided a secretariat function to the group.

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: Dr. Erin Kennedy

Position: Lead, Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee

Date: 26-06-2024

☒ **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**
Add company name				
Add company name				
Add or remove rows as required				

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

Declaration for Clinician 2

Name: Dr. Suneil Khanna

Position: Member, Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee

Date: 17-06-2024

☒ 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
Add company name				
Add company name				
Add or remove rows as required				

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

Declaration for Clinician 3

Name: Dr. Michael Raphael

Position: Member, Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee

Date: 17-06-2024

☒ 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
Add company name				
Add company name				
Add or remove rows as required				

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

Declaration for Clinician 4

Name: Dr. Rachel Goodwin

Position: Member, Ontario Health (Cancer Care Ontario) Gastrointestinal Cancer Drug Advisory Committee

Date: 17-06-2024

☒ 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

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Add company name				
Add company name				
Add or remove rows as required				

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