CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

pembrolizumab (Keytruda)

(Merck Canada)

Indication: Keytruda in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma, whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by a validated test.

December 1, 2023

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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Patient Group Input

Name of the Drug and Indication	Keytruda in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2 positive gastric or gastroesophageal junction (GEJ) adenocarcinoma, whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by a validated test.
Name of the Patient Group	My Gut Feeling - Stomach Cancer Foundation of Canada
Author of the Submission	Ekaterina Kosyachkova and Teresa Tiano
Name of the Primary Contact for This Submission	Ekaterina Kosyachkova
Email	[redacted]
Telephone Number	[redacted]

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 November 10 to November 24, 2023. 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 two additional organizations: Colorectal Cancer Resource & Action Network (CCRAN) and GI Cancers Alliance through email and their social media channels.

In total, forty people completed the survey, of those, 77.5% identified as a patient and 22.5% identified as a caregiver. Specifically, 40.0% identified as a patient who completed treatment and 37.5% as a patient in current treatment. The majority, 80% of respondents identified as female and 20% identified as male. Respondents were diagnosed across all ages ranging from 20 to 80 years old: 20-30 years (5%), 31-40 years (15%), 41-50 years (25%), 51 to 70 years (20%), 61 to 70 years (30%), and 71-80 years (5%). Data was gathered internationally with 72.5% of respondents residing in Canada, 27.5% in the United States and 8.1% 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, esophageal and/or gastroesophageal (GEJ) cancer. The majority of respondents (74.2%) had gastric cancer and the remainder had either esophageal and/or GEJ cancer. Of the respondents, 10% were diagnosed with stage one, 20% with stage two, 27.5% with stage three, 25% with stage four and the remainder of respondents were not given or were not aware of their cancer stage. When the cancer metastasized, in 22.5% it had spread to lymph nodes, 22.5% to peritoneum, 10% to liver and the remainder to other locations including the lungs, bowel and pelvic structures. Most patients (75%) had adenocarcinoma; the remainder had squamous cell carcinoma. When asked about other cancer factors, 15.5% of respondents were told they had HER-2 positive and 20% had HER-2 negative disease but the majority (35%) were not aware of their HER-2 and other biomarker (such as PD-L1) status.

3. Disease Experience

Most respondents (95%), felt that the cancer diagnosis had a *significant* impact on their quality of life, whereas (5%) felt it had a *minimal* impact and no patients (0%) felt it had *no* impact on their quality of life. Areas affected were physical health, mental health, ability to eat, work, finances, social life, identity, and personal image. We received an overwhelming 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. Symptoms of weight loss and fatigue were mentioned most by respondents. For example, one patient describes their experience with chemotherapy resulting in “drastic weight loss, chemo brain, neuropathy, fatigue, [and feeling] weaker than before. [They became] unable to work because of treatment and [their] physical condition”. The physical impact of cancer and its treatment were felt by the entire family unit. For example one caregiver wrote “The whole family’s life and dynamic changed as a result of [the] diagnosis…My dad was unable to keep his food down. He was also extremely exhausted. When it came back it unfortunately wasn't curable, so his body was affected in the typical way that metastatic cancer affects the body (pleural effusion, excessive weight loss, lymphedema, dry heaving/vomiting from exhaustion)...I wish chemotherapy was not so toxic”.

In addition to physical implications, mental health was significantly affected. Both patient and caregiver respondents (especially those with metastatic disease) felt hopeless regarding their prognosis. For example, several patients commented that psychosocially they experienced “anxiety, sleep loss, frequent crying due to anticipatory grief, depression, loss of control, no appetite, [and] feeling crippled” by their disease. These were experienced in relation to the patient and their family structure. One patient wrote that she experiences “constant worry, fear, stress, [and] fatigue [since] starting chemotherapy. The side effects from drugs, lack of sleep, anxiety [and] chemo side effects created stress on other family members”. Another mother explained that “ both of [her] kids have begun doing counseling and [she now has] guilt around that. [She] want[s] them to just have a normal childhood and not have to deal with this”. Cancer impacted patients' ability to work and maintain relationships. One patient was “worr[ied] about being able to afford [the] family lifestyle when expensive drugs [were] not covered by OHIP especially if [they] lose [their] job”. Another patient described a lack of support during their cancer treatment explaining that…”Although [they] have worked hard to stay positive, [they] chose to try to continue working through chemo remotely…now [they] rarely leave [their] home and starting to feel isolated. Friends and neighbors seem to avoid contact because they don’t know what to say/how to act”. Lastly, pre-existing mental health issues became amplified during diagnosis and treatment. For example one person disclosed that they “have always struggled with depression and anxiety…Getting cancer and going through treatment caused [them] to have extreme depression. I truly did not want to be alive anymore.”

Many respondents had concerns over finances due to inability to maintain work due to the diagnosis and/or treatment for cancer. The cancer treatment, the physical and mental symptoms, the time commitment to treatment and the additional costs to treatment created financial strain for patients and caregivers. For example, one patient wrote that they are “unable to work, have been on disability for two years now. It has impacted every aspect of [their] life. Finances are a concern with a fixed income only making about 1/3 of what [they] used to earn. Treatment is easy, but every other week is an inconvenience”. The pressure to work is experienced by patients pre-retirement age; a patient describes that their “cancer diagnosis has completely changed [their] life. Balancing treatment and work has been a challenge. [They] need to work as long as [they] can to maintain [their] group insurance but tracking and meeting [their] nutritional and hydration requirements feels like a part-time job in itself leaving [them] with very little personal time”. The impact went well beyond loss of finances. One patient explained that “cancer took so much from [them]. Having cancer is a full time job affecting finances (impossible to keep working during chemo and during recovery from surgery), and as I was the primary breadwinner in my relationship, it affected us greatly. Loss of identity, who am I besides cancer? Body image; I don’t recognize my body anymore. Loss of intimacy; no libido. My life has been on pause for basically over a year and still going. The need to request help from friends to basic chores. Loss of fertility so no longer possible to have kids.”

Objectively when asked to rank symptom burden, respondents commented that both the cancer itself and the treatments to control the cancer played a major impact on their daily living. Patients and caregivers were asked if any esophageal/GEJ cancer-induced symptoms were experienced *prior* to diagnosis. All (100%) of respondents had experienced at least one symptom *prior* to being diagnosed.

Changes in appetite (50%), weight loss (57.5%), reflux (55%), pain (47.5%), nausea/vomiting (37.5%) and difficulty swallowing (25%) were the most reported symptoms. Other symptoms including bleeding, changes in lab work, ascites and jaundice were also reported by respondents (figure 1). Respondents commented that these symptoms impacted their day to day life.

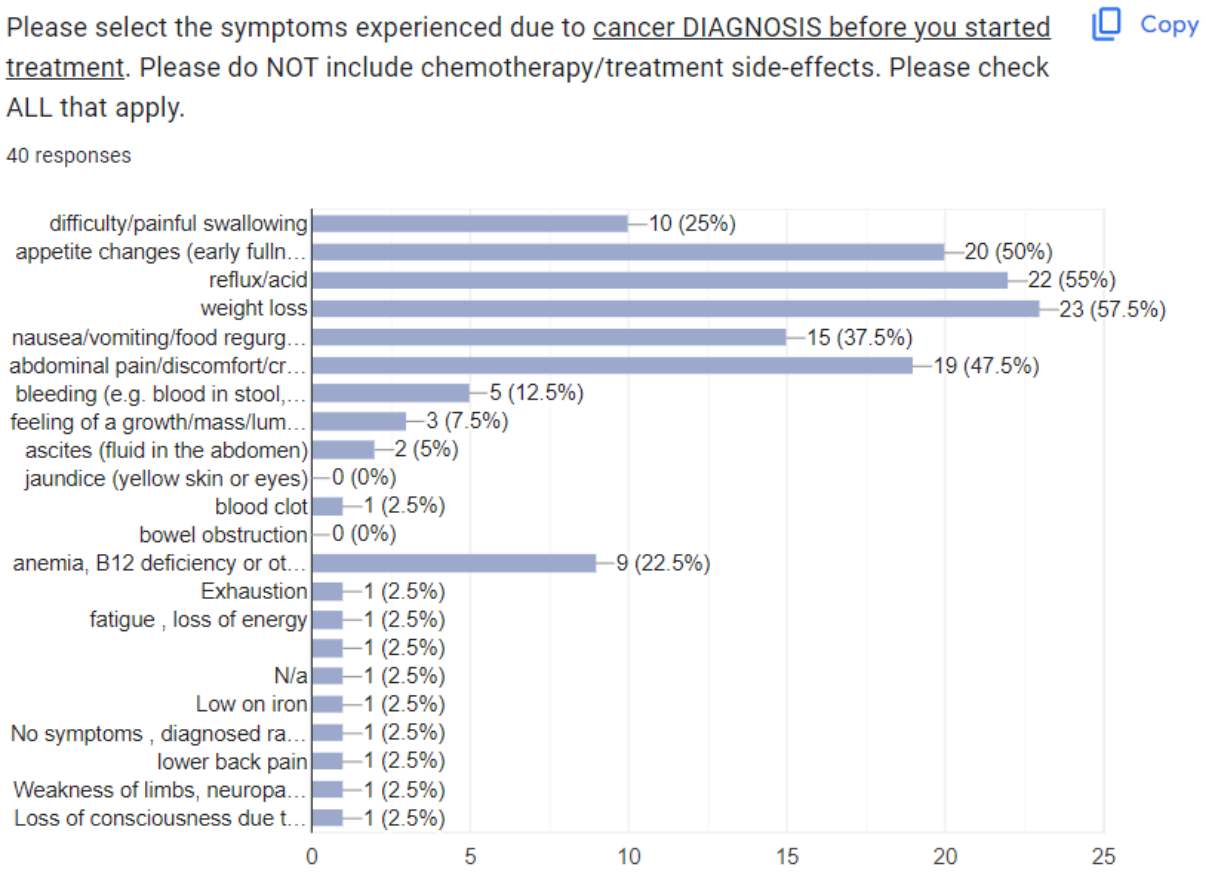

Figure 1. Patient and caregiver reported symptoms prior to diagnosis with gastric, esophageal or gastroesophageal cancer.

4. Experiences With Currently Available Treatments

Respondents reported that they had experience with a variety of treatment modalities. Of those that pursued treatment: 87.5% had chemotherapy, 40% had immunotherapy, 40% received surgery and 25% received radiation. Only 15% of patients were offered a clinical trial and 85% received standard of care treatments. Participants were asked to evaluate the effectiveness of their treatment on a scale of 1 to 10 (1 = “not effective”, 10 = “very effective”). Figure 2 demonstrates that responses were split. Respondents were able to comment on why they gave the specific ranking. Those that ranked their care as five and below cited recurrence, tumor progression, side effects and lack of alternatives as the reason for finding the treatment less effective. For example one patient stated they provided this ranking “In May of 2022, I was given the good news that my last CT was clear and it seems that right after that, a tumour started to grow in my abdomen. I ask myself, would this have happened if I had been able to continue/tolerate the chemo”. Some respondents felt that despite disease stability, the quality of life implications lead to dissatisfaction with current therapies, for example, one patient wrote that “chemotherapy controlled initially but after 5 cycles, there was some progression, now immunotherapy only because too many adverse side effects…We need more targeted treatments”.. The respondents that replied with a rating of greater than 5 cited that they were satisfied with their treatment because it caused the cancer to shrink, caused a reduction of symptom burden or resulted in remission.

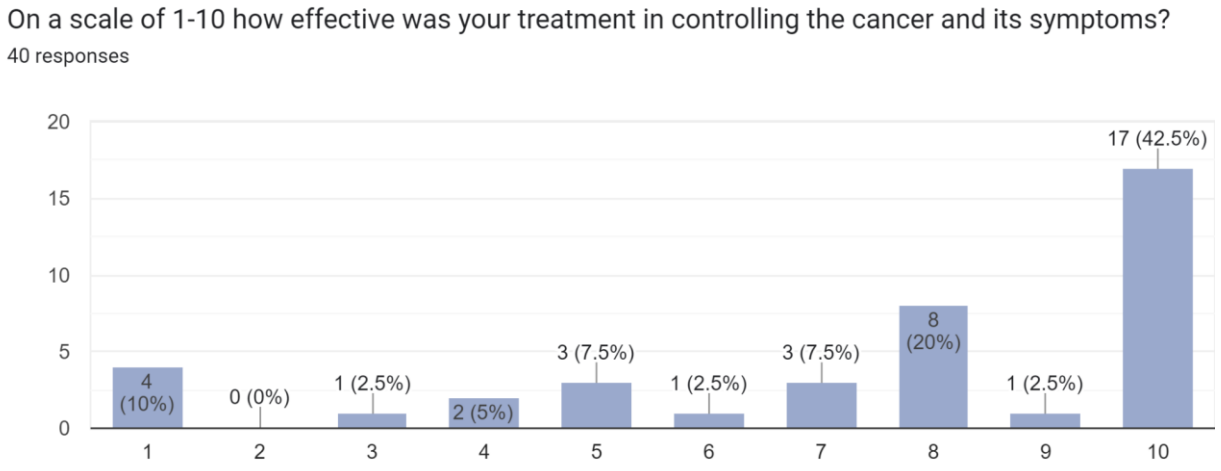

Figure 2. Respondents were given an opportunity to evaluate the efficacy of their cancer treatment

While current therapies lead to mixed satisfaction from respondents in terms of perceived efficacy and cancer control, current treatments have a variety of side effects impacting quality of life. All respondents identified at least one treatment related side effect with 87.5% reporting fatigue. Other common symptoms included weight loss (70%), appetite changes (77.5%), nausea/vomiting (65%), diarrhea (52.5%), taste changes (75%), alopecia (75%), chemo brain (67.5%), insomnia (58.1%), neuropathy (70%) and abdominal pain (42.5%). Less commonly reported symptoms included reflux, constipation, anemia, blood clots, infection, body aches, skin rash, hand-foot syndrome, insomnia, mucositis, dumping syndrome and blood-work abnormalities (figure 3). Respondents were able to leave additional comments regarding their treatment experiences. We asked respondents to identify the top 3 “worst” symptoms from treatment. While fatigue and appetite changes leading to weight loss were reported as some of the worst side effects of treatment, there was no overall consensus regarding the functionally impairing side-effects of treatment, thus demonstrating how participants vary in evaluating perceived side-effects. While most were able to tolerate treatment as prescribed, 15.5% had to stop treatment because of being hospitalized for an adverse event, 20% received a dose reduction in treatment and 7.5% had to delay or skip a treatment cycle of systemic therapy. It is apparent from these survey results that for the majority of respondents the currently available treatments had significant implications on quality of life.

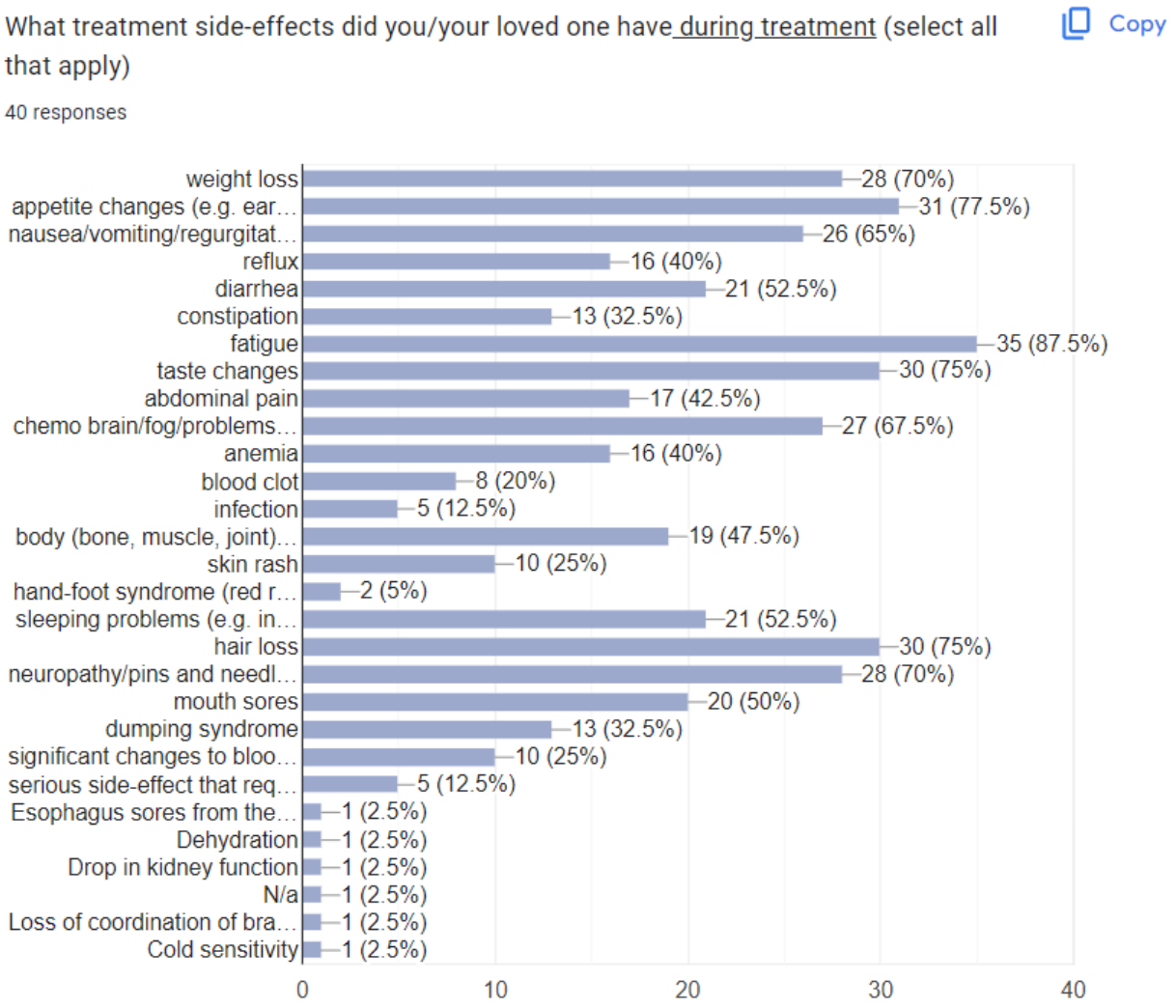

Figure 3. Patient and caregiver reported side effects while on treatment for gastric, esophageal or gastroesophageal cancer.

5. Improved Outcomes

When evaluating their treatment options, patients and caregivers considered multiple factors such as quality of life, treatment side effects, cost of treatment, 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. For example, when asked *"how important is it for you that new therapies bring about improvement in quality of life"*. Almost all respondents (75%) replied with a 10 or "extremely important". While cancer control was an important consideration, treatment came at a cost to quality of life which may not be tolerable to all patients. For example, one patient wrote "I could not tolerate chemotherapy... too many side effects to continue and I was told there is no cure…I stopped chemo so I could spend more time with family instead of feeling sick from chemo". In contrast another patient wrote that she had "3 years of chemo, multiple surgeries, many hospital stays but it give 3 years". Convenience of treatment was another consideration for patients and caregivers. For example patients preferred an oral chemotherapy taken at home to an IV chemotherapy administered in a hospital setting, favouring less frequent visits to the hospital and shorter time in the chemo chair. Patient satisfaction also depended on the medical team. Patients wished to have frequent discussions with their oncologist to discuss options and preferred to be a part of the decision making process. A patient wrote that "[she] had to rely totally and put trust in the medical and surgical oncologists to build the appropriate

treatment plan for [her]. The appropriate treatment plan in my case was relatively straightforward. However with a different initial diagnosis [she] would not have known where to go to get information so that [she] might have an informed discussion with [her] doctors"

We asked respondents if they would pay out of pocket for additional therapies. The majority of respondents were interested in discussing treatment options even if they were not covered by their current healthcare plan or universal healthcare. Most, 32.5%, replied with a “yes”. The remainder of respondents stated they would “maybe” pay for these treatments if the treatment improved survival (12.5%), maybe - depending on cost (25.0%) and maybe - depending on impact on quality of life (17%). This once again demonstrates that while survival is important, respondents place different values on quality versus quantity of life. While our survey found that most people (75%) did not have to pay directly out of pocket for specific treatments, the remainder of respondents (25%) paid for either some targeted therapy or adjunct medications either through private pay or insurance. One patient disclosed that immunotherapy cost “over $52,000 for one year and [he] had to file for bankruptcy”. Another patient mentioned the financial implications of getting treatment in a hospital “pa[ying] deductible of insurance $2500.00 for meds, parking $500.00, tolls $200.00 and prescription co-pays $250.00.” Certain combinations of targeted therapies including HER-2 and anti-PD-L1 therapies can cost the patients ranging from $6,000 to $10,000 per month through private pay. Another avenue to improve patient outcomes may be achieved through providing equal access to treatment access. Respondents received access to treatment through publicly funded healthcare, private insurance, drug access programs, Access to Hope, personal savings or donations. With the onset of biomarker testing in GEJ cancers, the universal healthcare system and private insurance lags behind, leaving Canadians with the bill for targeted therapies.

Our survey findings revealed that treatment access varied by geographic location. Standard of care treatments such as surgery or chemotherapy were more accessible than novel therapies such as immunotherapy. Barriers to access identified included institutional and health care system barriers, limited availability of treatment and how quickly treatment could be accessed. Respondents had many great suggestions in terms of how to better access treatment. For example, one patient wrote that “there has to be more Canadian information available on the internet about treatment options available or forthcoming. Much of the information is U.S. based and patients are left wondering if this might be available to them. I don't advocate getting your treatment plan from the internet but it does empower you to have an informed discussion with your doctor..”. Unanimously, 98% of respondents felt it was “extremely important” to have access to more treatment and 96.5% felt that these cancers needed to have more advocacy to have funded treatment options. One patient wrote simply that we need “increased approval of treatment options, pharmacare and universal coverage for treatments and more overall funding”. While current treatments options may improve patient survival, there are clear limitations in available treatment options, access to new therapies and patient centred discussion regarding options. Patients and caregivers want more options from which to choose so that they can make informed decisions based on their values and preferences.

6. Experience With Drug Under Review

Based on our survey, eleven respondents had experience with Pembrolizumab (Keytruda), the drug under review. Two respondents received Pembrolizumab with chemotherapy and one respondent received it with Trastuzumab and chemotherapy. In these respondents, 28.5% received the drug through a clinical trial, 28.5% received the drug through private insurance, 19.1% through a drug access program, 9.2% received the therapy as standard of care for their disease. At the time of the survey, 75% were actively on this drug and had been on it for at least one month. Participants commented that they were satisfied with this drug primarily because it had fever side-effects and was more convenient than their standard of care treatment such as chemotherapy or surgery. Fatigue continued to be the most reported symptom (37.5%), however overall the side effect profile appeared to be much less relative to standard of care treatment.

When asked to rate the statement *“compared to other previous treatments Pembrolizumab (Keytruda) was easier to tolerate overall”* (1= “strongly disagree”, 10= “strongly agree”), 100% of respondents ranked it a five or above. When asked to rate the statement *“Pembrolizumab (Keytruda) has improved my quality of life”* on a 1 to 10 scale (1= “strongly disagree”, 10 = “strongly agree”), 80% selected five or greater. Respondents who were satisfied with the drug mentioned disease control, for example one patient stated “cancer went into remission and now my CT reads No Evidence of Disease”. One patient mentioned that their cancer symptoms improved “Pembrolizumab helped me eat and swallow food without pain”. Other patients were satisfied because of the minimal side

effect profile, for example “It has very little side effects, it doesn’t leave me bed ridden like chemo did for me”.

When asked if respondents had additional comments, one patient simply stated that “Targeted drugs like HER-2 and immunotherapy have a place in Canada….access to more treatment options and improving prognoses should be top priority”. Although most patients were not treated directly with Pembrolizumab and Trastuzumab combination, our survey generated additional comments with respondents asking for more access to this combination. This again demonstrates a need for patients and caregivers to have options and information on novel therapies that could improve the length and/or quality of life**.**

7. Companion Diagnostic Test

We did not ask questions related to companion diagnostic testing.

8. Anything Else?

Being diagnosed with any cancer is challenging. Gastric, esophageal and gastroesophageal cancers are rare in Canada with few treatment options. Biomarker testing including HER-2 and CPS testing is becoming routine in Canada. Drug combinations that attack multiple targets should be studied; combinations that improve overall survival (OS) and progression free survival (PFS) should be rapidly expedited as potential therapeutic options to fill the urgent and unmet need in GEJ cancers. For those patients and caregivers impacted by this diagnosis, having options is important since it 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 targeted therapy drugs such as such as Pembrolizumab with Trastuzumab and chemotherapy in first-line treatment of adult patients with locally advanced unresectable or metastatic HER2 positive GEJ cancers when CPS is greater than 1.

Combination targeted therapies are the future of oncology and there are subsets of gastric, esophageal and gastroesophageal cancer patients that can benefit from such drug combos. While most respondents surveyed were on active treatment. Even respondents that had completed treatment continued to struggle years after treatment suggesting that the cost of standard treatment without a personalized approach with lifelong implications on quality of life. Based on the objective research completed over a short time frame, the conclusion of My Gut Feeling - Stomach Cancer Foundation of Canada is to strongly support the funding recommendation of Pembrolizumab in combination with Trastuzumab and chemotherapy in the first line treatment of adult patients with locally advanced unresectable or metastatic HER2 positive GEJ cancers when CPS is greater than 1.

From our survey results we drew the following conclusions:

1. Patients need to be informed of their treatment options without barriers; including standard of care options and 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; drug access and cost should not be barriers.
4. 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 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, My Gut Feeling 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 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**
Eli Lilly Canada Inc.	X			
Taiho Pharma Canada Inc.	X			
Bristol Myers Squibb			X	
Jazz Pharmaceuticals			X	
Astra Zeneca				X
Astelles			X	
Merk			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: Ekaterina Kosyachkova

Position: Vice-Chair and Co-Founder

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

Date: November 30, 2023

Clinician Group Input

Clinician Group Input 1

CADTH Project Number: PC0343

Generic Drug Name (Brand Name): Pembrolizumab (Keytruda)

Indication: In combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma, whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by a validated test.

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

Author of Submission: Dr. Erin Kennedy, Dr. Suneil Khanna

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

In first line treatment, patients receive chemotherapy + trastuzumab (ToGA regimen). Ramucirumab/paclitaxel is given in second line. Single agent irinotecan or regorafenib is used in third line.

There is now some data supporting the use of trastuzumab deruxtecan in Her2+ gastric cancer (third line setting), however this isn't available in Ontario.

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.

Outcomes for patients with Her2+ gastric cancer are poor, with median OS less than 2 years. Preliminary OS results from KEYNOTE-811 suggests a 3 month survival benefit, however those results are not statistically significant (and are immature).

5. Place in Therapy

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

Pembrolizumab would be added to standard first-line therapy. Most patients who get standard therapy (FOLFOX/trastuzumab) would be candidates for pembrolizumab, with the standard contraindications. We have experience giving immunotherapy in the first-line Her2 negative setting, and so don't expect many issues.

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?

Which patients are most likely to respond to treatment with drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

How would patients best suited for treatment with drug under review be identified (e.g., clinician examination/judgement, laboratory tests (specify), diagnostic tools (specify))

Are there any issues related to diagnosis?

Is a companion diagnostic test required?

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Is it possible to identify those patients who are most likely to exhibit a response to treatment with drug under review?

<Enter Response Here>

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?

Are outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

What would be considered a clinically meaningful response to treatment? Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Examples: improved survival; reduction in the frequency/severity of symptoms (provide specifics regarding changes in frequency, severity, etc.); attainment of major motor milestones; ability to perform activities of daily living; improvement of symptoms; and stabilization (no deterioration) of symptoms.

<Enter Response Here>

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

Examples: disease progression (specify, e.g. loss of lower limb mobility); certain adverse events occur (specify type/frequency/severity); or additional treatment becomes necessary (specify).

<Enter Response Here>

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]?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

If a specialist is required, which specialties would be relevant?

<Enter Response Here>

6. Additional Information

It would be good to have Pembrolizumab available as first-line treatment for metastatic gastric cancer, especially considering that there aren't good treatment options for these patients with poor mOS numbers. Preliminary OS data suggests a HR of 0.80, improvement in mOS of 3 months (although this is currently not significant/immature). Preliminary graphs don't show a "flat tail" to the curve, so responses are likely not very durable. This data is very similar to the data from CHECKMATE-649 (FOLFOX/Nivo for Her2 negative).

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 <u>each clinician</u> 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: OH-CCO GI DAC lead

Date: 30-11-2023

☒ **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**
Add company name				

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

Declaration for Clinician 2

Name: Dr. Suneil Khanna

Position: OH-CCO GI DAC member

Date: 27-11-2023

☒ 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
Add company name				

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

Clinician Group Input 2

CADTH Project Number: PC0343-000

Generic Drug Name (Brand Name): pembrolizumab (Keytruda)

Indication: Keytruda in combination with trastuzumab, fluoropyrimidine - and platinum-containing chemotherapy, for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma, whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by a validated test.

Name of Clinician Group: Canadian Gastrointestinal Oncology Evidence Network (CGOEN)

Author of Submission: Dr. Rachel Goodwin, Medical Oncologist, The Ottawa Hospital Cancer Center, Ottawa. Specialty: Gastrointestinal & Neuroendocrine cancers

with

Dr. Vincent Tam, Medical Oncologist, Tom Baker Cancer Centre, Calgary. Disease site specialty: Gastrointestinal cancers.

Dr. Jennifer Knox, Medical Oncologist, Princess Margaret Cancer Centre, Toronto. Disease site Specialty: Gastrointestinal cancers.

Dr. Ravi Ramjeesingh, Medical Oncologist, Dalhousie University, Halifax. Disease site Specialty: Gastrointestinal cancers, particular focus on hepatobiliary cancers

Dr. Sharlene Gill, Medical Oncologist, BC Cancer Agency, Vancouver. Specialty: Gastrointestinal (GI) cancers

Dr. Petr Kavan, Medical Oncologist, McGill University Health Centre. Disease site specialty: gastrointestinal (GI) cancers and neuroendocrine tumors (NETs).

Dr. Eric Chen, Medical Oncologist, Princess Margaret Cancer Centre, Toronto. Disease site specialty: gastrointestinal cancers.

Dr. Jennifer Spratlin, Medical Oncologist, Cross Cancer Institute, Edmonton. Specialty: Gastrointestinal cancers.

1. About Your Clinician Group

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 development and health technology assessment.

2. Information Gathering

Information gathered for this submission was based on personal experience in treating patients with metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma and expert evidence-based review by Canadian gastrointestinal cancer specialists of information presented at the European Society of Medical Oncology international oncology meeting, and simultaneously published in the Lancet:

Pembrolizumab plus trastuzumab and chemotherapy for HER2-positive gastric or gastro-esophageal junction adenocarcinoma: interim analyses from the phase 3 KEYNOTE-811 randomised placebo-controlled trial.

Janjigian YY, Kawazoe A, Bai Y, Xu J, Lonardi S, Metges JP, Yanez P, Wyrwicz LS, Shen L, Ostapenko Y, Bilici M, Chung HC, Shitara K, Qin SK, Van Cutsem E, Tabernero J, Li K, Shih CS, Bhagia P, Rha SY; KEYNOTE-811 Investigators.

Lancet. 2023 Oct 19:S0140-6736(23)02033-0. doi: 10.1016/S0140-6736(23)02033-0. Online ahead of print.

PMID: 37871604

3. Current Treatments and Treatment Goals

The current treatment for HER2 positive metastatic gastro-esophageal cancer is 5FU/platinum with trastuzumab based on the TOGA trial (Bang Y etal Lancet 2010). Data has been extrapolated to the HER2 positive esophageal adenocarcinomas from the gastric and GE junction results. Immunotherapy is currently approved in gastroesophageal adenocarcinomas and squamous cell carcinomas but only in the HER2 negative population.

The addition of pembrolizumab to 5FU/platinum/trastuzumab based treatment significantly increases median overall survival to 20 months vs 15.7 months in tumors with a PDL1 CPS score > =1. In the CPS <1 the median survival 16.1 months vs 22.3 months respectively. The objective response rate increased to 72.6% vs 59.8%.

Immunotherapy is already funded in Canada for HER2-negative gastroesophageal cancer and the addition of this therapy to a targeted therapy such as trastuzumab in the HER2 positive population demonstrates and improvement in survival and reduction in the tumor burden with the increase in response rate. The additional treatment did not increase toxicities with similar rate of Grade 3 adverse events at 58% vs 51%.

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.

Currently immunotherapy is only available for HER2 negative tumors. The treatment for HER2 positive disease has not improved for the past 13 years. This evidence supports benefit of the addition of immunotherapy in combination with trastuzumab and chemotherapy for the HER2 positive patients.

5. Place in Therapy

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

This combination would introduce access to immunotherapy to a patient population who have previously been excluded due to HER2 biomarkers. The benefit of immunotherapy is considered additive to chemotherapy and trastuzumab.

Pembrolizumab would be used the first-line treatment in addition to the existing treatment protocols for HER2 positive gastro-esophageal cancer. As oncologists are already well familiar with the management of patients on pembrolizumab, this combination does not introduce new concerns regarding toxicity management.

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?

Based on the sub group data – tumors with a CPS score $\geq$1 benefit from treatment with the addition of pembrolizumab. PDL1 CPS testing with a validated test should be performed. While it is not currently a Health Canada requirement for HER2 negative tumors – clinical guidelines recommend CPS testing for gastroesophageal cancers. This is evolving within the Canadian landscape.

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?

Patients would be undergoing clinical evaluations on a regular basis for clinical response and toxicity per current treatment standards. In addition, routine imaging during timed intervals is performed for objective assessments. Similar outcomes to clinical

trials are used to determine benefit to treatment. A meaningful response would be patient preference, tolerability of treatment, quality of life, and response on imaging.

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

Treatment discontinuation is determined by patient preference, adverse events, or disease progression – either radiologic or clinical.

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]?

Immunotherapy and trastuzumab are currently delivered as standard of care in all oncology centres. This would be appropriate for all centres.

6. Additional Information

<Enter Response Here>

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.

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

   NO

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 <u>each clinician</u> 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 Rachel Goodwin

Name: Rachel Goodwin

Position: Medical Oncologist, The Ottawa Hospital

Date: 10-100-2023

☒ **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: Rachel Goodwin

Company	Check appropriate dollar range*

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Merck: Speaker and Ad Board		x		
BMS: Speaker and Ad Board		x		
Astellas: Speaker and Ad Board		x		

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

Declaration Petr Kavan

Name: Petr Kavan MD

Position: Medical Oncologist Dpt of Oncology McGill University, Co-chair GI oncology Rossy Cancer Network McGill, CRP program director, LDI Jewish General Hospital McGill University

Date: 22-Nov-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.

Conflict of Interest Declaration

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

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

Declaration for Ravi Ramjeesingh

Name: <Ravi Ramjeesingh>

Position: <Medical Oncologist>

Date: <28-Nov-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

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 Eric Chen

Name: Eric Chen

Position: staff physician, Division of Medical Oncology and Hematology, Princess Margaret Cancer Center

Date: 30-11-2023

☒ 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

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

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

Declaration for Sharlene Gill

Name: SHARLENE GILL

Position: Medical Oncologist & Professor of Medicine, BC Cancer - Vancouver

Date: 30-11-2023

☒ 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.

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Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Merck	X			

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

Declaration for Jennifer Spratlin

Name: Jennifer Spratlin

Position: Associate Professor, University of Alberta; Medical Oncologist, Cross Cancer Institute

Date: 30-11-2023

☒ 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.

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Incyte advisor	x			
Astrazeneca advisor	x			
Taiho advisor	x			
Ipsen advisor	x			
BMS advisor	x			
Astellas advisor	x			
BOLD advisor	na			

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

Declaration for Vincent Tam

Name: Vincent Tam

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

Date: 30-11-2023

☒ **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.

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AstraZeneca			X	
BMS	X			
Eisai		X		
Incyte	X			
Ipsen		X		
Merck	X			
Roche			X	

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

Declaration Jennifer Knox

Name: <Jennifer Knox>

Position: <Medical Oncologist>

Date: <30-Nov-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.

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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		
Roche	X			
Incyte		X		
Eisai	X			
Ipsen	X			
Merck	X			
Pfizer	X			

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