CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

DOSTARLIMAB (Jemperli)

(GlaxoSmithKline Inc.)

Indication: Dostarlimab in combination with carboplatin and paclitaxel for the treatment of adult patients with primary advanced or recurrent mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer who are candidates for systemic therapy.

October 30, 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.

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. 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 received.

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.

Stakeholder 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.

Patient Input

Name of Drug: Dostarlimab

Indication: in combination with platinum-containing chemotherapy for the treatment of adult patients with primary advanced or recurrent mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer.

Name of Patient Group: Canadian Cancer Survivor Network

Author of Submission: Lindsay Timm

1. About Your Patient Group

Describe the purpose of your organization. Include a link to your website.

The Canadian Cancer Survivor Network (CCSN) is a national network of patients, families, survivors, friends, community partners, funders, and sponsors who have come together to take action to promote the very best standard of care, whether it be it be early diagnosis, timely treatment and follow-up care, support for cancer patients, or issues related to survivorship or quality of end-of-life care. **https://survivornet.ca/**

2. Information Gathering

CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include **when** the data were gathered; if data were gathered **in Canada** or elsewhere; demographics of the respondents; and **how many** patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.

The Canadian Cancer Survivor Network utilized SurveyMonkey to create and collect all data for the survey on Dostarlimab. The survey was reviewed and commented on by both the Colorectal Cancer Resource & Action Network (CCRAN) and the Canadian Cancer Society (CCS). The survey was disseminated through all the organizations' social media platforms, CCSN's newsletter list, as well as reaching out to the lead clinicians to collect responses. The survey was conducted from October 26, 2023, to November 8, 2023, to obtain responses. All of the respondents to the survey are from Canada. All respondents are patients. All respondents to the survey identify as female. When the survey data was analyzed, it was identified that all the patients who responded did not have experience with Dostarlimab.

3. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

With there still not being a specific screening protocol for the general public, there are still many people being diagnosed with late stage disease who have similar stories to this patient from the previous submission on Keytruda for endometrial cancer done by the Colorectal Cancer Resource and Action Network (CCRAN), ***"I had been symptomatic for years….whose cause couldn't be understood or identified. I just kept bleeding and bleeding. The ultrasounds couldn't pick anything up and then I had a CT scan that sorta picked up something so I went on to have a D&C which picked up my cancer…I was then scheduled for my surgery.. And I have to tell you that 10 minutes before I went into my surgery, I found out that I had metastatic disease to my lungs. It was so shocking and disappointing. How awful for me."*** **Patient D**

When asked what stage of endometrial cancer they had been diagnosed with, the following responses were received from the respondents:

- Stage 1b: 1

- Stage 2: 1
- Stage 3b: 1
- Stage 4a: 1
- Other: 2 (1 Mine was breast cancer, 1 Do not have this type of cancer)

Current treatments that were identified include:

- Radiation: 2
- Surgical Therapy: 4
- Targeted Therapy: 1
- Hormonal Therapy: 1
- Immunotherapy: 1
- Chemotherapy: 4
- Other: 2 (1 I took a pill, don't know the name of it, for 5 years., 1 Acupuncture and massage therapy.)

When asked if there was an aspect of their disease that is most important to them to control, two respondents replied:

- "Recurrence prevention."
- "Kicked out of cancer centre after treatment finished. Should have been assigned a nurse for communication. Had to do all on my own research to get better. Needed better after care."

Respondents were asked if they have had any issues accessing any therapies. The following issues were highlighted by their responses:

- Limited availability in my community: 1
- Other: 3 (1 Any clinical trial using Dostarlimab with niraparib was never mentioned by the clinician., 1 Had difficulty getting a biopsy at my local hospital, it was cancelled twice., 1 Driving from home to Clinic in winter weather.)

When asked if there was anything that they would like to share about their cancer journey, three respondents shared these comments:

- "I was blessed to have unlimited support through the Cancer foundation of Canada. My radiation went very well. Everyone one was so helpful. I just felt very well cared for everywhere."
- "Cancer treatment care was great. Big drop of in care between my GP and gynecologist doctors. No help for after care."
- "I was referred for genetic testing because of family colorectal cancer history. However, my tumour test was not MSI-High. A wise genetic counsellor encouraged me to have the DNA test regardless which I did. Results were positive for Lynch Syndrome. Subsequently my surviving brother and one of my 2 daughters have also tested positive. A second MSI Tumour test requested by the genetic counsellor confirmed the original test results. This was not the first time in my now 35-year long cancer journey that I have had a "false negative" on a test. This can be disconcerting knowledge to have lived with as a now 80-year-old."

4. Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

From CCRAN's previous submission, the following still rings true of the landscape for the treatment of endometrial cancer, for the most part.

“Patients with advanced endometrial carcinoma have limited treatment options. If diagnosed with an early stage of the disease, patients will undergo surgery to remove the uterus (and perhaps the cervix), fallopian tubes and regional lymph nodes. Radiation therapy may also be indicated to kill cancer cells in addition to hormonal therapy to block cancer growth. Carboplatin in combination with paclitaxel are standard chemotherapy treatments indicated for endometrial cancer in both the adjuvant setting and first line treatment of metastatic endometrial cancer. These therapies, particularly the latter, are associated with treatment induced toxicities that compromise patients’ quality of life and fail to extend patients’ longevity in a meaningful way.”

We often forget how difficult of an experience that treatment can be for the caregiver as well. I think that this quote from the previous CCRAN submission depicts both the struggle of the caregiver and the patient, ***“…her life started to deteriorate. So, when she started Nexavar, her quality of life got worse. She could no longer socialize or travel. And Carbotaxol was the worst of them all. Horrible side effects. Her outlook even became negative. She even stopped working. And it was so difficult to watch from a caregiver’s perspective.” Caregiver A***

When asked if any needs in their current therapy are not yet being met, three respondents indicated that it was not applicable. One respondent indicated that mental health support was not being met in their current treatment.

Respondents were asked to select what adverse effects they are currently dealing with while on their treatments. Four respondents selected the following:

- Fatigue: 2
- Neuropathy: 3
- Fluid retention: 1
- Nausea: 1
- Constipation: 1
- Dryness, itching, tightening, and burning in the vagina: 2
- Changes in sexual functioning: 2
- Other: 1 (1 Chemo brain)

When asked if their adverse effects were tolerated, two respondents answered. One said, “half dosage; nausea occasionally; prochlorperazine.” The second respondent stated that it was not applicable to them.

We asked respondents to respond with how they are managing on their current treatment as if they were talking to a friend and what they would tell them. These are their responses:

- How are you managing with surgery: 3 (1 managed well, 1 ok, 1 some bowel pain)
- How are you managing with radiation: 1 (1 ok)
- How are you managing with hormone therapy: 1 (1 ok)
- How are you managing with chemotherapy: 2 (1 Was tough; much nausea and constipation, 1 Affects my thinking, loss of stamina, fatigue)

5. Improved Outcomes

CADTH is interested in patients’ views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

When asked about the following issues that they would hope to see a new drug address to manage their disease, five respondents rated each item as follows (results are weighted averages):

- Maintain quality of life: 4.20
- Delay onset of symptoms: 4.50
- Access to a new option of treatment: 2.75
- Reduce side effects from current medications or treatments: 3.40
- Ease of use: 5.00
- Prolong life: 3.40
- Provide a cure: 3.60

Patients were asked, on a scale of 1-10, with 1 being “no side effects” and 10 being “significant side effects”, if you were to consider taking a new therapy for your cancer, what severity of side effects would you be willing to tolerate in order to extend survival by 2 months, after having been told there is no other available treatment? For example, side effects such as: nausea, fatigue, vomiting, diarrhea. Five respondents gave the following ratings: two, three, four, seven, and ten.

Patients were asked, on a scale of 1-10, with 1 being “no side effects” and 10 being “significant side effects”, if you were to consider taking a new therapy for your cancer, what severity of side effects would you be willing to tolerate in order to extend survival by 6 months, after having been told there is no other available treatment? For example, side effects such as: nausea, fatigue, vomiting, diarrhea. Five respondents gave the following ratings: two respondents selected four, one selected six, one selected eight, and one selected ten.

Patients were asked, on a scale of 1-10, with 1 being “no side effects” and 10 being “significant side effects”, if you were to consider taking a new therapy for your cancer, what severity of side effects would you be willing to tolerate in order to extend survival by 1 year, after having been told there is no other available treatment? For example, side effects such as: nausea, fatigue, vomiting, diarrhea. Five respondents gave the following ratings: four, five, six, nine, and ten.

When asked about the considerations that they make as patients when it comes to balancing the advantages and disadvantages of a treatment, three respondents had these comments to relay:

- “Quality of life and energy,”
- “Longevity and how severe the other side effects are.”
- “Quality of life and extending my life.”

6. Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways? If applicable, please provide the sequencing of therapies that patients would have used prior to and after in relation to the new drug under review. Please also include a summary statement of the key values that are important to patients and caregivers with respect to the drug under review.

Unfortunately, the survey did not capture any respondents who have had experience with the drug under review. However, from the answers in the survey it is clear that the people affected by endometrial cancer are looking for a therapy that will provide them with a better quality of life and are willing to experience some greater side effects if the treatment will extend survival for a longer period of time. Having another option that could provide a more comfortable experience for the patient and allow them to lead a more normal life should be considered a key value.

7. Companion Diagnostic Test

If the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies, or monitor clinical responses to optimally guide treatment adjustments.

What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?

Consider:

- Access to testing: for example, proximity to testing facility, availability of appointment.
- Testing: for example, how was the test done? Did testing delay the treatment from beginning? Were there any adverse effects associated with testing?

- Cost of testing: Who paid for testing? If the cost was out of pocket, what was the impact of having to pay? Were there travel costs involved?
- How patients and caregivers feel about testing: for example, understanding why the test happened, coping with anxiety while waiting for the test result, uncertainty about making a decision given the test result.

N/A

8. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

In addition to the findings in the current survey, we thought it important to reference the submission made by the Colorectal Cancer Resource and Action Network (CCRAN) on Keytruda for endometrial cancer when addressing the unmet need for this community.

“The standard of care for patients with advanced or recurrent endometrial cancer is multiagent systemic chemotherapy, which includes Carbotaxol in the first line setting. In addition to being quite toxic, this combination therapy has, according to our patient input, low response rates which creates **an urgent, unmet need** to provide treatment options that yield better outcomes for this patient population: outcomes that include fewer side effects contributing to an improved quality of life, an extension in progression free survival and overall survival.”

This submission was made approximately two years ago, and the standard of care is still the same, resulting in the same issues of quality of life, toxicity, and low response rate leading to a great unmet need for this population.

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

1. 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

2. 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
GSK-2022			X	
GSK-2023			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: Lindsay Timm
Position: Community Engagement Manager
Patient Group: Canadian Cancer Survivor Network
Date: **November 8, 2023**

Clinician Input

CADTH Project Number: PC0325
Generic Drug Name (Brand Name): Dostarlimab (Jemperli)
Indication: in combination with platinum-containing chemotherapy for the treatment of adult patients with primary advanced or recurrent mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer
Name of Clinician Group: Ontario Health (CCO) Gynecology Cancer Drug Advisory Committee
Author of Submission: Dr Sarah Ferguson, Dr. Tiffany Zigras, Dr. Orit Freedman, Dr. Julie Ann Francis, Dr. Julie My Van Nguyen

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

This information was gathered at a DAC meeting.

3. Current Treatments and Treatment Goals

For primary advanced: standard of care is chemotherapy (carboplatin/paclitaxel)

For recurrent: If disease free interval >6 months would retreat with carboplatin. Now for dMMR can treat with single agent pembrolizumab after progression on platinum-based chemotherapy.

Goals of therapy: Prolong life, delay disease progression, reduce severity of symptoms, improve QoL, reduce burden on caregivers, maintain independence, minimize toxicities.

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 is a treatment gap as there is no molecular directed therapy for these patients. The response to chemotherapy is moderate and not sustained. There is a high recurrence rate with advanced stage disease (stage 3 or 4). If it is recurrent then it is not curable.

5. Place in Therapy

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

As per the indication, however, for patients with primary advanced endometrial cancer, if patients are responding well to this treatment, it might be clinically indicated to interrupt treatment to have other modalities (ie surgery or radiation).

It is also reasonable for patients to have a treatment break if they have maintained a good response and then resume treatment before any disease progression occurred or if disease progression occurred during a break.

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?

The Gyne DAC believes there is a benefit for all patients (dMMR and pMMR) based on the primary outcome for the overall population. The Gyne DAC recognize that the benefit is greater for the dMMR/MSI-H population, however the benefit is still greater than what is obtained with the current standard of care.

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?

Clinical assessment with physical exam, imaging as per clinical standard of practice.

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

Disease progression, toxicity, intolerability, patient preference.

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]?

Outpatient clinic in hospitals

6. Additional Information

This trial was powered to assess both MMR-proficient and MMR-deficient patients, and the overall patient population demonstrated a PFS benefit with dostarlimab. Given the limited treatment options and high mortality rate in this patient population, the Gyne DAC advocates for extending the use of dostarlimab to all patients, aligning with the trial's framework.

If a patient has an allergy or intolerance to one of the chemotherapy drugs (such as carboplatin, paclitaxel) within the dostarlimab regimen, they can continue using dostarlimab in combination with the other chemotherapy drug alone or use dostarlimab as a standalone treatment.

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.

3. 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.

4. 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.

5. 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. Sarah Ferguson
Position: Lead, OH-CCO Gynecology Cancer Drug Advisory Committee
Date: 19-10-2023

☒ **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
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. Tiffany Zigras
Position: Member, OH-CCO Gynecology Cancer Drug Advisory Committee
Date: 19-10-2023

☒ 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				
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. Orit Freedman

Position: Member, OH-CCO Gynecology Cancer Drug Advisory Committee
Date: 19-10-2023

☒ 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

	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 4

Name: Dr. Julie Ann Francis
Position: Member, OH-CCO Gynecology Cancer Drug Advisory Committee
Date: 19-10-2023

☒ 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
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 5

Name: Dr. Julie My Van Nguyen
Position: Member, OH-CCO Gynecology Cancer Drug Advisory Committee
Date: 24-10-2023

☒ 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
GSK (funds JHCC Gyne Onc Division Journal clubs)		X		
Add company name				

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

CADTH Project Number	
Generic Drug Name (Brand Name)	Dostarlimab
Indication	Dostarlimab in combination with chemotherapy for primary treatment of endometrial cancer
Name of the Clinician Group	The Society of Gynecologic Oncology of Canada (GOC)
Author of the Submission	Dr. Alon Altman

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

The Society of Gynecologic Oncology of Canada (GOC) is a non-profit multidisciplinary organization. It is the national society representing health care professionals including physicians, nurses, and scientists involved in the treatment and prevention of gynecologic cancer. GOC strives to improve the care of

women with, or who are at risk of, gynecologic cancer by raising standards of practice, encouraging ongoing research, promoting innovation in prevention, care and discovery and advancing awareness.

2. Information Gathering

Please describe how you gathered the information included in the submission.

The information in this submission represents data from completed and presented/published clinical trials as outlined in references. References are of peer-reviewed manuscripts or presentations at international, academic meetings, both of which are well-accepted approaches to the rapid dissemination of new clinical data to the global oncology community.

1. ENGOT – EN6-NSGO/GOG3031/RUBY trial: Dostarlimab in combination with chemotherapy for treatment of primary advanced or recurrence endometrial cancer: a placebo-controlled randomized phase 3 trial

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

Endometrial carcinoma is 4th most common cancer and the 6th cause of cancer-related deaths in Canadian women. In 2021, approximately 7985 women were diagnosed, and 1400 women died of this disease (Canadian Cancer Statistics, 2021). It is one of the few cancers in which both the incidence and death rates have been increasing steadily. Data from Ontario Cancer Registry, 2018, show that the age-adjusted death rates have been rising by 1.9% each year from 2009–2018.

Although the majority of patients diagnosed with endometrial cancer present with early-stage disease and are cured with a combination of surgery with or without adjuvant chemotherapy and radiotherapy, approximately 20% of these patients, remain at a high risk of recurrence. These patients, including an additional 15 to 20% of patients who are diagnosed with advanced stage disease at initial presentation, are not candidates for curative treatment. Their mainstay of treatment is systemic therapy, but options are limited and responses short-lived. Radiotherapy remains an option for palliation of cancer-related symptoms and managing localized disease but is very rarely curative. The average life-expectancy of a patient with recurrent/metastatic endometrial cancer is 2 years.

Standard treatment options for patients with advanced or metastatic endometrial cancer include endocrine therapy with aromatase inhibitors and progestins, and cytotoxic chemotherapy. Unfortunately, responses are not very durable. In the1st-line setting, carboplatin/paclitaxel, the gold standard chemotherapy regimen for advanced or recurrent endometrial cancer (NRG Oncology/GOG0209 trial), has a response rate of 45 to 65%, with a progression-free-survival of 13 to 14 months (GOG209 final analysis, Miller D, Filiaci V, Mannel R et al, JCO 2020; 38).

An improved understanding of the molecular background of endometrial cancer, including the ability to characterize specific molecular subgroups, has allowed the introduction of new treatment options for patients with endometrial cancer (Kandoth, C., et al., *Integrated genomic characterization of endometrial carcinoma.* Nature, 2013. **497**(7447): p. 67-73.). These include molecularly targeted agents, including anti-angiogenic agents, and immunomodulatory approaches such as the immune checkpoint inhibitors. Approximately 30% of endometrial cancers harbour defects in mismatch repair genes (dMMR), leading to microsatellite instability and high tumour mutational burden (TMB). In these patients, DNA repair deficiency and the high neoantigen load potentially render the cancer cells more susceptible to immunotherapy with anti–programmed death 1 (PD-1) inhibitors. Several studies have shown that in patients with dMMR endometrial cancer, who have recurred or progressed on platinum based chemotherapy, pembrolizumab, an anti–PD-1 monoclonal antibody achieves meaningful and durable responses (KEYNOTE-158 study). Dostarlimab has also shown durable activiety in previously treated dMMR and pMMR endometrial cancers (Oaknin A et al. 2022). It is important to highlight that in the 70% of endometrial cancers that do not harbour defects in

MMR pathway, or are MMR-proficient (pMMR), responses to immune checkpoint inhibitor monotherapy remain low. In these patients, the combination of pembrolizumab and Lenvatinib has demonstrated meaningful benefit (Phase 3 KEYNOTE-775 -SGO 2021)

In the first line treatment setting very little treatment changes have occurred. The ENGOT-EN6-NSGO/GOG-3031/RUBY trial is the first trial examining a new treatment strategy in the first line setting. This trialwas a phase 3 randomized double blind multicentered controlled trial of Dostarlimab (500 mg IV) with Carboplatin and Taxol with 3 years maintenance compared to Carbo/Taxol with placebo. Overall 494 patients were randomized to the trial with equal baseline characteristics. The RUBY trial also included multiple histologies including carcinosarcoma, endometriod, mixed, serous, clear cell and other. Final results showed an improvement in PFS in dMMR(Placebo 7.7 months vs Dostarlimab Not reached) and overall population (placebo 7.9 months vs Dostarlimab 11.8 months). Overall survival also was trending to improvement for Dostarlimab with a HR of 0.64 in the overall population and 0.30 in the dMMR population. Overall the Dostarlimab was well tolerated and similar to the cytotoxic chemotherapy arm.

Canadian women affected by endometrial cancer do not have a national advocacy organization to represent them. They need urgent access to these novel treatment options that have demonstrated vastly superior efficacy over standard of care chemotherapy. Thus, the GOC members are advocating for them.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

An ideal treatment would provide more durable disease control (PFS is an acceptable surrogate of disease control), with an acceptable tolerability profile leading to minimal adverse effects on patients' quality of life. Ideally, an agent should also lead to improved overall survival in comparison with an accepted standard of care. Dostarlimab combined with cytotoxic chemotherapy in advanced stage or metastatic dMMR endometrial cancer meets these criteria. Its toxicity is low with durable prolongation of good quality life.

As this patient population is being treated with curative intent, the most important goals that an ideal treatment would address includes prolongation of response and survival, optimizing quality of life, minimizing toxicity and adverse effects

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

1. *Not all patients respond to available treatments*
2. *Patients become refractory to current treatment options*
3. *No treatments are available to reverse the course of disease*
4. *No treatments are available to address key outcomes*
5. *Treatments are needed that are better tolerated*
6. *Treatment are needed to improve compliance*
7. *Formulations are needed to improve convenience*

Response: Chemotherapy alone in the first line setting has been the standard for many years with poor outcomes. Improvement in PFS and OS in advanced endometrial cancers with a combined immuno agent is critical for patient outcome.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

With respect to the request for Dostarlimab combined with cytotoxic chemotherapy in advanced stage or metastatic dMMR endometrial cancer, MMR status can be assessed indirectly by IHC staining to determine the presence of four MMR proteins: MLH1, MSH2, MSH6, and PMS2. dMMR is defined as the loss of at least one of these proteins. IHC is an inexpensive, automatable method that can offer quick results and can be performed in-house by any specialized clinical pathology laboratory. This test lends itself to reliable interpretation by trained pathologists based on standardized parameters such as identifying preserved or lost nuclear expression of one or two of these within the tumor cells, with a binary result without the need for an additional threshold (Le Flahec et al. 2017). This test has been widely adapted in Canada by most centres and readily used. Currently dMMR vs pMMR is helping guide treatment in the second line setting.

The drugs under review will address the unmet need in this patient population.

6. Place in therapy

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

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

Immunotherapy has a different mechanism of action when compared to chemotherapy. Dostarlimab binds to the PD-1 receptor, blocking both immune-suppressing ligands, to help restore T-cell response and immune response.

Dostarlimab combined with cytotoxic chemotherapy in advanced stage or metastatic dMMR endometrial cancer will address the disease process, and is vastly superior to any currently available chemotherapy alone.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

Not applicable in this case. For Dostarlimab combined with cytotoxic chemotherapy in advanced stage or metastatic dMMR endometrial cancer this would be the first line treatment for advanced cancers and would not need to try other treatment first.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

This treatment would be given first line. Currently recurrent use of PD-1 inhibitors is unclear. Some evidence in other cancers support retreatment but within endometrial cancer is currently unclear.

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the 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)?

Response:

The population that was studied in the above trials:

Dostarlimab for patients with dMMR endometrial cancer that have advanced or metastatic endometrial cancers.

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

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

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

MMR IHC can be done on all endometrial cancer tissue specimen throughout Canada at a low cost.

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Patients that are not suitable candidates for systemic treatment based on performance status, co-morbidities (including poorly controlled hypertension, uncontrolled auto-immune disease etc).

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

If so, how would these patients be identified?

Response:

For dostarlimab, those patients will be identified by the reflective MMR IHC that is performed on all endometrial cancer patients in Canada. dMMR patients would be eligible.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

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

Response:

. Response to therapy would be based on (1) patient symptoms (2) tumour markers where applicable and (3) tumour assessment by CT or MR completed every 2 to 3 cycles of therapy (i.e. every 6 to 9 wks)

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*

- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

A clinically meaningful response would be maintaining radiographic disease control (i.e. tumour response or stabilization on CT/MR) with good tolerance of treatment (i.e. </= grade 2 treatment-related adverse effects) and stable or improving symptoms of disease. Assessment of radiographic response is objective, however determination of clinical benefit will have an element of subjectivity.

6.10. How often should treatment response be assessed?

Response:

Response to therapy would be based on cross-sectional tumour assessment by CT or MR completed every 2 to 3 cycles of therapy (i.e. every 6 to 9 wks). Tolerability of regimen would be assessed every cycle and more often as needed depending on patients' symptoms with clinical assessment (including close blood pressure monitoring) and laboratory investigations (standard hematology, chemistry, thyroid function etc).

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

Disease response: Patients would continue on treatment for 6 cycles followed by Dostarlimab for up to 3 years.

Adverse events: Treatment should be held for moderate-severe immune-related toxicity and managed as per standard guidelines

Patient preference: Patients can and may decide to discontinue treatment at any time.

6.12. What settings are appropriate for treatment with the drug under review?

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

Response:

Patients being managed at a cancer centre by oncologists with expertise in (1) systemic therapy for gynecologic cancers and (2) managing immune-related adverse events

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant?

Response:

n/a

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

Response:

n/a

8. 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.

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 <u>each clinician</u> that 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

Clinician Information	
Name	*Alon Altman*
Position	*GYNECOLOGY ONCOLOGIST/Professor University of Manitoba*
Date	*14/09/2023*
☒	**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.

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**
GSK	☒	☐	☐	☐
Merck	☒	☐	☐	☐
Pfizer	☒	☐	☐	☐
Clovis	☒	☐	☐	☐
Novasure	☒	☐	☐	☐
Array	☒	☐	☐	☐
AstraZeneca	☒	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Danielle Vicus*
Position	*Gynecologic Oncologist, Sunnybrook Health Centre, Toronto*
Date	*21-09-2023*
☒	**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.

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

Declaration for Clinician 3

Clinician Information	
Name	*Mark Carey*
Position	*Clinical Professor, University of British Columbia*
Date	*Please add the date form was completed (26-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.

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**
Verastem Oncology	☒	☐	☐	☐
Hexamer Therapeutics	☒	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Shannon Salvador*
Position	*GYNECOLOGY ONCOLOGIST/Associate Professor McGill University*
Date	*14/09/2023*
☒	**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.

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**
GSK	☒	☐	☐	☐
Merck	☒	☐	☐	☐
AstraZeneca	☒	☐	☐	☐
EISAI	☒			

Declaration for Clinician 5

Clinician Information	
Name	*Lesley Roberts*
Position	*Gyncologic Oncologist, University of Manitoba*
Date	*26-09-2023*
☒	**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.

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

CADTH Reimbursement Review
Clinician Group Input Template

CADTH Project Number	**PC0325-000**
Generic Drug Name (Brand Name)	**Dostarlimab (Jemperli)**
Indication	**In combination with platinum-containing chemotherapy for the treatment of adult patients with primary advanced or recurrent mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer**
Name of the Clinician Group	**Canadian Clinician Group with expertise in treating women with advanced and recurrent endometrial cancer, coordinated by the Canadian Cancer Society**
Author of the Submission	**Dr. Lucy Gilbert, with review and input from all clinicians who signed a COI declaration**

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

We are a Canadian Clinician Group made up of gynecologic oncologists and medical oncologists from across Canada, with expertise in treating women with advanced endometrial cancer. We are responding to this call for clinician input on the use of dostarlimab in combination with platinum-based chemotherapy (standard-of-care), for the treatment of patients with advanced and recurrent mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer. Our input is coordinated by the Canadian Cancer Society. As I have been nominated as the head of this Clinician Group, I shall provide some context.
I am a Professor in the Department of Obstetrics & Gynecology and in the Department of Oncology, at McGill University. I hold the Robert Kinch Chair in Women's Health in the Department of Obstetrics and Gynecology. As from 1st January 2024, I shall assume the post of Gerald Bronfman Chair of Oncology, McGill University. I have been the Chief of Service and Director of Gynecologic Oncology, as well as the Gynecologic Cancer Multi-disciplinary Team (comprising surgeons, medical oncologists, radiation oncologists, site specialized pathologists and radiologist, palliative care specialists, etc.) at McGill University Health Centre (MUHC) for two decades, and chair a 2.5 hour tumour board every week. I operate on and give systemic treatment (chemotherapy, immunotherapy, targeted therapy) to patients with gynecologic cancers. Thus, patients remain within my service for the entire trajectory of their care, from diagnosis till death, giving me a good insight into effective sequencing of treatments and when to transition stopping active treatment. I am a member of the Steering Committee of the Ruby Trial (relevant to this application), and also serve in the Steering Committee of other landmark trials of immune checkpoint inhibitors for advanced or recurrent endometrial cancer.

2. Information Gathering

Please describe how you gathered the information included in the submission. The group of clinicians who have contributed to this report includes leading experts specialized in the treatment of advanced endometrial cancer from different parts of the country. The number of patients who present with primary advanced or recurrent endometrial cancer is relatively small compared to breast, lung or colorectal cancer. Thus, oncologists practicing in tertiary care oncology centres have the critical volume of patients

that is needed to get a true sense of the relative value of various treatment options. Under the purview of the Canadian Cancer Society's Advocacy Division, I prepared the draft report and sought input from the members of the group. The draft was reworked to incorporate the collective input. As this group includes gynecologic oncologists and medical oncologists who treat the disease exclusively with systemic treatments, attitudes towards sequencing of treatments and the number of regimens used differed. Furthermore, there are region-specific challenges, which influence attitudes toward a specific treatment. I have incorporated the perspectives of the group to provide CADTH with a full sense of how the use of this product may impact clinical practice across the provinces.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Background and current treatment landscape for Endometrial cancer as a whole

Endometrial Cancer (EC), which is the 4th most common cancer in Canadian women, was traditionally viewed as a 'nice' cancer with a good prognosis and received little attention because of its low casemortality-ratio of 18% (in 2023, estimated 8,500 new cases of EC and 1,550 deaths, in Canada[1]). The overall mortality is low because most cases of EC are diagnosed in early stages and are effectively cured by surgery with or without adjuvant treatment. Gynecologic oncologists have made great strides in the surgical management of early endometrial cancer by adopting robotic and laparoscopic surgery and sentinel lymph node mapping. These minimally invasive procedures have substantially reduced the post operative morbidity associated with laparotomy and surgical staging in overweight women, without compromising survival.

Current treatment landscape for advanced or recurrent Endometrial cancer

However, when EC presents in advanced Stages, or recurs after primary treatment, the outcome is very poor. Prior to 2012, we used triplet chemotherapy- Adriamycin, Cisplatin and Taxol - to treat advanced endometrial cancer. It was a toxic regimen. Following GOG 209[2] a Randomized controlled trial (RCT) in which we took part, this triplet regimen was compared to a doublet of carboplatin and paclitaxel (Taxol). The doublet was shown to be 'non-inferior' to the triplet regimen with similar survival and significantly less toxicity. Thus, carboplatin and Taxol has been the standard of care for primary advanced and recurrent EC since 2012. The median progression free survival (PFS) of 13 months and median overall survival of 3 years, achieved with this doublet, highlights the unmet need for patients with advanced and recurrent EC[2].

Figure 1

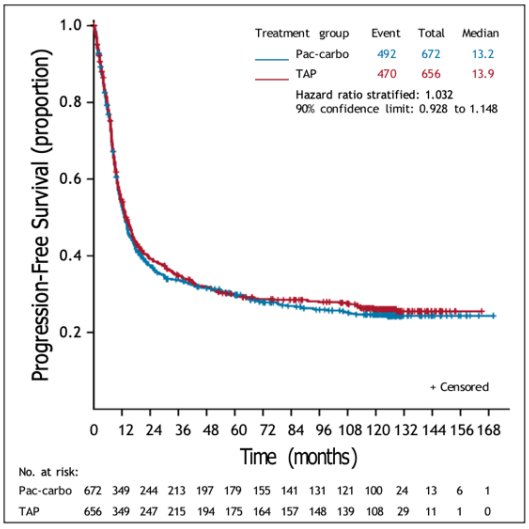
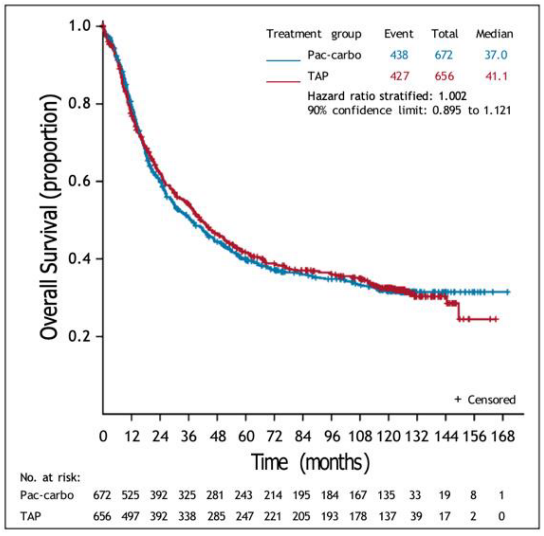


Figure 2



GOG 209[2] -The median progression free survival (PFS) of 13 months and median overall survival of 3 years with Paclitaxel and Carboplatin vs Taxol, Adriamycin, Cisplatin (TAP)[2]

Relentless increase in death rates associated with Endometrial Cancer

Underestimating EC has done women a grave disservice. Whereas the age specific death rates for most cancers are falling, EC is an outlier in that the death rate has risen relentlessly year on year, in all ages and ethnic groups in Canada[3,4] (figures 3[3] and 4[4]). Stats by Cancer Care Ontario[4] - demonstrate that the Age-adjusted death rates for EC have been rising by 1.9% each year over 2009–2018, with an alarming doubling of incidence of EC in women 30-49 years from 5.7/100,000 in 1997 to 11.3/100000 in 2016.

Figure 3

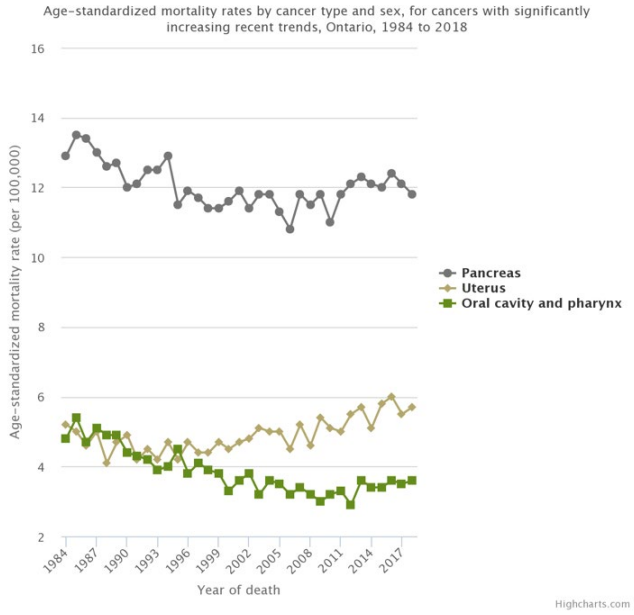
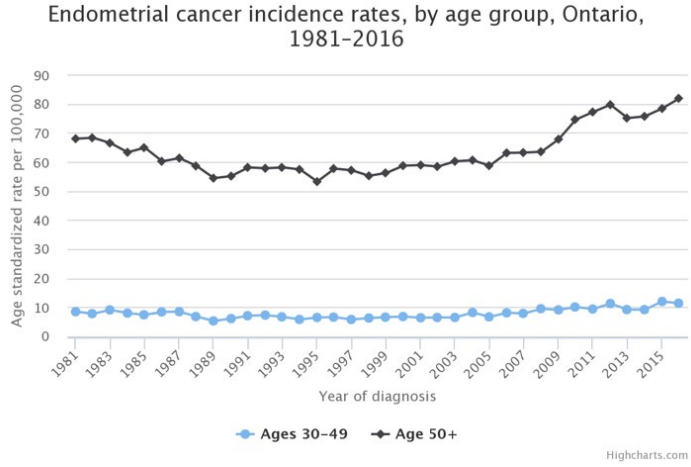
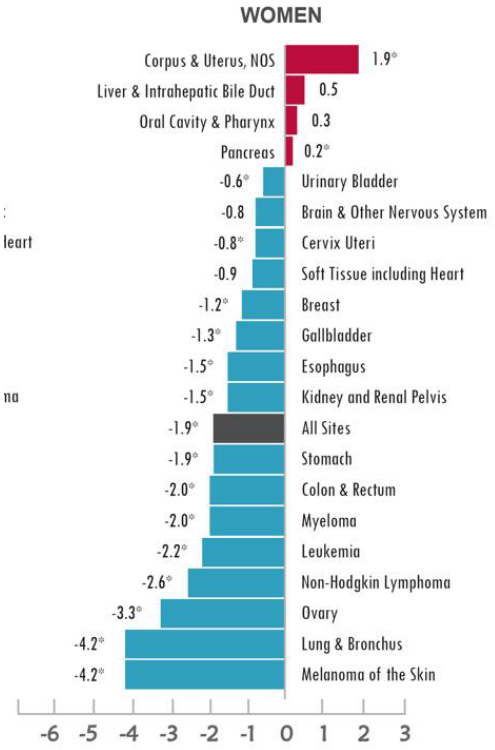


Figure 4



This increase in the age-specific-death rate associated with endometrial cancer is not specific to Canada but seen in all high-income countries, including the US. Figure 5 shows that of the top 20 cancers affecting US women, EC is associated with the steepest age adjusted increase in death rate.

Figure 5

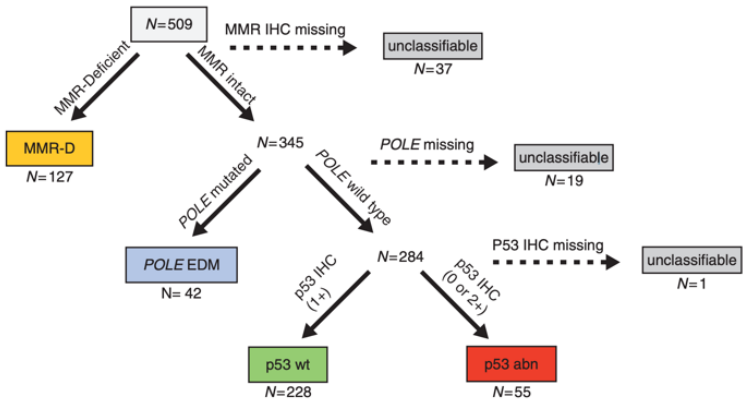


The cancer related deaths associated with EC are almost exclusively from advanced or recurrent disease. Thus, if the increasing death rate is to be reversed, we should aim to be more effective in the treatment of advanced and recurrent endometrial cancer. Clearly, the standard of care doublet chemotherapy for advanced or recurrent cancer has not stemmed this increasing death rate.

Incorporating precision treatment for EC into routine clinical practice to reverse death rates

In 2013, The Cancer Genome Atlas Research Network (TCGA) established that using molecular classification based on integrated genomic, transcriptomic and proteomic characterization using array- and sequencing-based technologies genomic, rather than traditional histopathological classifications can help better guide biomarker driven therapy.

Figure 6 Validation of ProMisE in a final cohort of 452 endometrial carcinomas[6]



However, this was too cumbersome to incorporate into routine clinical practice. Figure 6 demonstrates the pragmatic, molecular classification -ProMisE6-developed by a group from British Columbia, in collaboration with international partners. ProMisE, which uses immunohistochemistry, is accessible to any tertiary care pathology laboratory for the fraction of the cost of the tests used by TCGA.

From Figure 6**,** it is clear women with mismatch repair deficient EC (dMMR EC) is the second largest group of EC (between 25-30% of EC).

Figures 7 A & B, show that dMMR EC account for the 2nd highest group to recur and die of the disease. *It is precisely this group of high-risk women (dMMR) that is the subject of this review.*

Figure 7 A

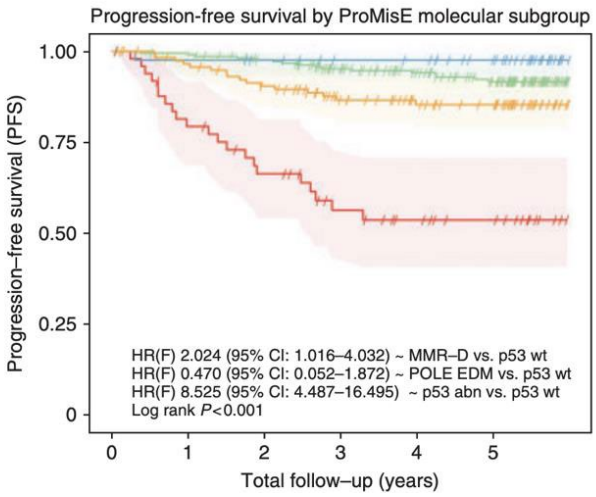


Figure 7 B

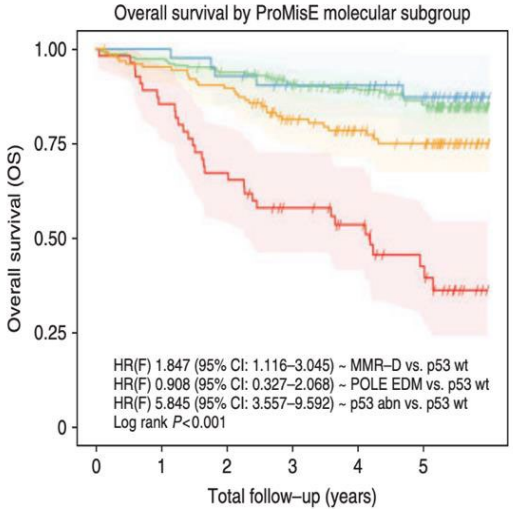


Figure A & B. Kaplan–Meier survival analyses according to ProMisE molecular subgroups, with distribution of events at year of follow-up shown. (A) Progression-free survival (PFS), (B) Overall survival (OS).

Can anything be done to reduce the high failure rate associated with standard of care chemotherapy alone in the primary treatment of advanced and recurrent EC?

The RUBY trial[7], a phase 3, double-blind, RCT was designed to determine whether the addition of dostarlimab to standard of care Carboplatin and Taxol in the front line setting would increase the PFS and OS. The trial included 118 dMMR patients (out of a total 494 patients)

The estimated Kaplan–Meier probability of PFS at 24 months was

61.4% (95% [CI], 46.3 to 73.4) for
dostarlimab + Chemo every 3 weeks for 6 cycles followed by
maintenance dostarlimab every 6 weeks for 3 years
vs
15.7% (95% CI, 7.2 to 27.0) for
carboplatin and paclitaxel every 3 weeks for 6 cycles alone

The addition of dostarlimab to chemo was associated with a **72% lower risk of progression or death** (HR, 0.28; 95% CI, 0.16 to 0.50; P<0.001) among patients with dMMR–MSI-H tumors.
The 72% lower risk of progression or death with quadrupling of the median PFS was not associated with significantly more grade ≥3 adverse events compared to the standard of care chemotherapy arm.

Figure 8[7]

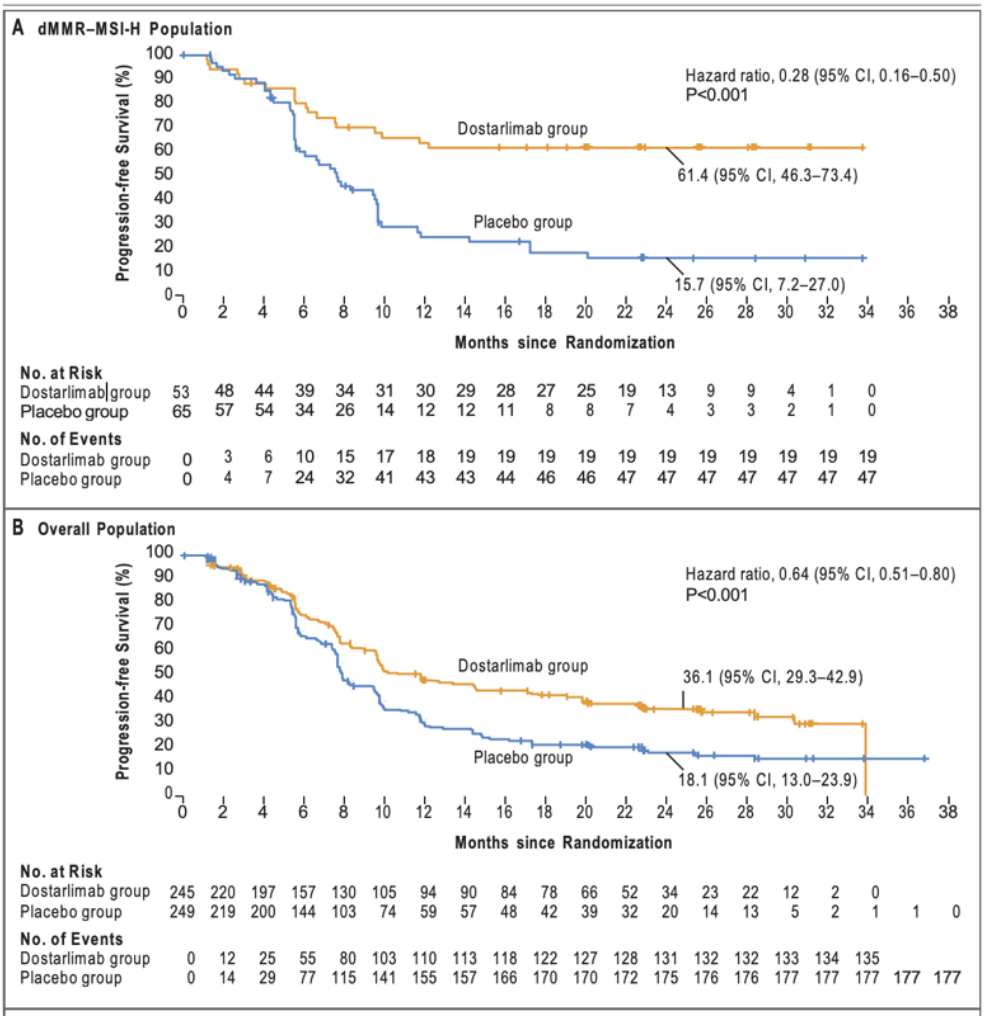


Figure 8 Progression-free Survival as assessed by the Investigator According to RECIST, Version 1.1. Shown are Kaplan–Meier estimates of progression-free survival in the population with mismatch repair–defi-cient (dMMR), microsatellite instability–high (MSI-H) disease (Panel A), the overall population (Panel B)

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Response:

Advanced and recurrent EC is associated with significant symptom burden. Women want treatment that delays disease progression and prolongs good quality life. It would be important to do this with minimum adverse effects so that the individual can continue to play the role they were playing before the cancer diagnosis and treatment, be it working in a remunerated job or looking after family. Patients do not want to become a burden to their families.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Response:

In 2012, GOG 209 established **carboplatin and paclitaxel (Taxol)** as the new standard of care in the primary treatment of advanced and recurrent EC. It continues to be the currect standard of care, but 10 years on, we need to do better. Patients go through 6 cycles of carboplatin and Taxol, lose their hair, eyebrows, tastebuds, develop neuropathy etc., and then recur 13 months. This is devastating for the patients and their loved ones, demoralizing for their health care providers, and subsequent rounds of treatments, ER visits, inpatient admissions etc add to direct and indirect costs. The RUBY trial show that in the subset of women who have dMMR tumour EC (25-30 %), giving dostarlimab with their chemo reduces the risk of death or progression by 72% and quadruples the progression free survival.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Response:

dMMR patients account for 25-30% of EC. Of the 4 molecular subtypes they (dMMR patients) have the 2nd worst survival outcome with standard of care chemotherapy. These patients can be identified by immunohistochemistry (IHC), a simple test that can be done in any tertiary care pathology lab.

6. Place in therapy

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

Response:

Dostarlimab has been shown in an RCT to substantially change the outcome for dMMR patients if added to the standard of care chemotherapy. dMMR tumour are hypermutated which is why they are so sensitive to dostarlimab. By giving dostarlimab with chemotherapy in the front-line setting, the cytotoxic effect of chemo results in the release of neoantigens making the tumour more sensitive to dostarlimab.

For the sake of our patients, we hope this will become the new standard of care for the primary treatment of advanced and recurrent chemotherapy

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

Response:

We should not underestimate the toll that recurrence of cancer takes on a patient who has gone through surgery and chemotherapy. There is level I evidence that with standard of care, cancer will recur in in 13 months. If dostarlimab is given with chemotherapy in the front line, the magnitude of effect is a 72% reduction of recurrence or death. Therefore, we believe it should be given in the front line with chemotherapy.

6.3. How would this drug affect the sequencing of therapies for the target condition?

Response:

When front line treatment fails, one of the key deciding factor is time to progression and the sites and number of metastasis. For oligo-metastasis, we reoperate, and or try ablation with radiotherapy. For extentive metastasis, we try 2nd line chemotherapy. Once carboplatin and taxol fails, with 2nd line chemotherapy, respose is < 10%, PFS,4 months, OS <1 year. So offen we try the combination of
Lenvatinib and Pembro which has a response rate of 30% and Median OS of 18 months albeit with grade
≥3 toxicity of 90%. In the Ruby trial, Dostarlimab added to carbo and Taxol in the primary setting is associated with prolonged PFS. The OS data was not mature but was promising with prolongation of OS.
My unit had the highest number of patients in Canada and 4th highest worldwide in the RUBY trial.
Tumours continue to shrink long after dostarlimab was discontinued for an adverse event.

6.4. Which patients would be best suited for treatment with the drug under review?

Response:

Patients with dMMR EC are identified at the time of diagnostic biopsy, or at the time of the primary surgery by carrying out staining for four MMR proteins. Interpretation is straightforward and reproducible. The cost of this test in our laboratory is $100.

6.5. How would patients best suited for treatment with the drug under review be identified?

Response:

Patients with dMMR tumours will be identified at the time of the diagnostic biopsy or at the time of primary surgery by adding IHC for the 4 MMR.

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

We would be able to judge this after the RUBY trial matures and provide outcomes in the other molecular subtypes *P53* mutated and wild type.

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

Response:

We use CT scans every 3-4 months to monitor response in patients with heavy tumour burden. As tumour burden reduces, the interval between imaging can be spaced out.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Response:

Symptoms and CT scans.

6.9. What would be considered a clinically meaningful response to treatment?

Relief of symptoms, prolongation of progression free survival, and overall survival.

6.10. How often should treatment response be assessed?

Response:

As this indication is in the frontline setting, monitoring will depend on the burden of disease at the start of treatment. Endometrial cancer does not have a reliable tumour marker, so we have to rely on symptoms and CT scans. A 3-4 month interval is standard for CT evaluations of response or if clinically indicated by symptoms, earlier scans.

6.11. What factors should be considered when deciding to discontinue treatment?

Response:

Progressive disease and toxicity

6.12. What settings are appropriate for treatment with the drug under review?

Response:

Dostarlimab is a 20 min infusion given before the chemotherapy. It is very well tolerated. During the 6 cycles of chemotherapy, we give it in the hospital's out-patient chemotherapy department. The maintenance treatment can be given in a community setting because it is very well tolerated. However, patients and care givers must be educated on immune related toxicity and advised to contact the treating team if there is a problem.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

Response:

Not applicable

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

Response:

7.1

7.2 References for CADTH review

1. https://cancer.ca/en/research/cancer-statistics/cancer-statistics-at-a-glance?gad_source=1&gclid=EAIaIQobChMIooi0IbnSggMVYR59Ch1oSwqqEAAYAiAAEgIjLvD_BwE
2. Millet et al, 2020, Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209)J Clin Oncol 38:3841-3850
3. Ch 5: Cancer Mortality [2022]." *Ch 5: Cancer Mortality [2022] | Cancer Care Ontario*, www.cancercareontario.ca/en/data-research/view-data/statistical-reports/ontario-cancer-statisticshttp://www.cancercareontario.ca/en/data-research/view-data/statistical-reports/ontario-cancer-statistics-2022/ch-5-cancer-mortality-20222022/ch-5-cancer-mortality-2022#:~:text=In%20Ontario%2C%201%20in%204,1%20in%204%20(23.2%25). Accessed 20 Nov. 2023.
4. **https://www.cancercareontario.ca/en/statistical-reports/cancer-risk-factors-ontario-evidence**https://www.cancercareontario.ca/en/statistical-reports/cancer-risk-factors-ontario-evidence-summary-0**summary-0**. 2) https://www.cancercareontario.ca/en/cancer-facts/endometrial-cancer-starting-rise-youngerhttps://www.cancercareontario.ca/en/cancer-facts/endometrial-cancer-starting-rise-younger-women-ontariowomen-ontario
5. Annual Report to the Nation 2022: National Trends in Cancer Death Rates. SEER. https://seer.cancer.gov/report_to_nation/infographics/trends_mortality.html. Published 2018. Accessed November 20, 2023.
6. Kommoss et al 2018, Final validation of the ProMisE molecular classifier forendometrial carcinoma in a large population-based case series, Annals of Oncology29: 1180–1188, 2018doi:10.1093
7. Mirza et al 2023, Dostarlimab for Primary Advancedor Recurrent Endometrial Cancer, N Engl J Med 2023;388:2145-58.DOI: 10.1056/NEJMoa2216334

8. 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.

   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

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 that 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

Clinician Information	
Name	*Lucy Gilbert*
Position	*Professor, Department of Obstetrics & Gynecology, Department of Oncology, Robert Kinch Chair of Women's Health, McGill University; Director, Division of Gynecologic Oncology, McGillUniversity Health Centre*
Date	*Please add the date form was completed (16-11-2023)*
☒	**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.

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**
GSK	☐	☐	☒	☐
Merck	☒	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Stephen Welch*
Position	*Associate Professor, Department of Oncology, Chair, Division of Medical Oncology President-Elect, Canadian Association of Medical Oncologists, Co-Chair, Gynecologic Disease Site Group, Canadian Cancer Trials Group*
Date	*17-11-2023*

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.

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**
GSK	☒	☐	☐	☐
Merck	☒	☐	☐	☐
Eisai	☒	☐	☐	☐
Astra Zeneca	x			

Declaration for Clinician 3

Clinician Information	
Name	*Aalok Kumar*
Position	*Provincial Systemic Therapy Lead for Gynecologic Oncology, British Columbia* *Medical Oncologist, BC Cancer Surrey* *Clinical Assistant Professor, Faculty of Medicine, UBC*
Date	*Please add the date form was completed (17-11-2023)*

☒ **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.

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**
GSK	☒	☐	☐	☐
Merck	☒	☐	☐	☐
AZ	☒	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Prafull Ghatage*
Position	*Professor of Obstetrics and Gynecology and Oncology, Tom Baker Cancer centre/University of Calgary, Tumour Group Lead in Gynecologic Oncology Alberta*
Date	*Please add the date form was completed (DD-MM-YYYY)*

☒	**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

Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Astra Zeneca	☒	☐	☐	☐
Merck	☒	☐	☐	☐
GSK	☒	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Dr. Puneet Bains*
Position	Medical Oncologist Clinical Assistant Professor, University of British Columbia Lions Gate Hospital, North Vancouver
Date	*17-11-2023*

☒	**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.

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**
Novartis	☒	☐	☐	☐
Pfizer	☒	☐	☐	☐
GSK	☒	☐	☐	☐

Declaration for Clinician 6

Clinician Information	
Name	*Alexandra Sebastianelli MD, FRCSC*
Position	*Associate Professor, Department of Obstetrics & Gynecology, Department of Oncology, Université Laval, CHU de Quebec*
Date	*17-11-2023*

☒	**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.

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
GSK	☒	☐	☐	☐
Merck	☒	☐	☐	☐
Eisai	☒	☐	☐	☐

Declaration for Clinician 7

Clinician Information	
Name	*Laurence Bernard*
Position	*Gynecologic Oncologist at McGill University Health Centre*
Date	*17-11-2023*

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.

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
None	☐	☐	☐	☐

Declaration for Clinician 8

Clinician Information	
Name	*Shuk On Annie Leung*
Position	*Assistant Professor, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, McGill University Health Center*
Date	*Please add the date form was completed (17-11-2023)*

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.

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
None	☐	☐	☐	☐

Declaration for Clinician 9

Clinician Information	
Name	*Victoria Mandilaras*

Position	*Medical Oncologist, Cedars Cancer Centre, McGill University Health Centre Assistant Professor, Department of Oncology, McGill University*
Date	*Please add the date form was completed (17-11-2023)*

☒ **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.

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	☒	☐	☐	☐
GSK	☒	☐	☐	☐
	☐	☐	☐	☐

Declaration for Clinician 10

Clinician Information	
Name	*Ioannis Voutsadakis*
Position	*Med. Oncologist, Sault Area Hospital*
Date	*17-11-2023*

X **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

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Eisai Limited (consultancy)	x	☐	☐	☐
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐