Canada's Drug Agency
L'Agence des médicaments du Canada

Reimbursement Recommendation

Reimbursement Recommendation

(Draft)

Durvalumab (Imfinzi)

Indication: Imfinzi in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adult patients with primary advanced or recurrent mismatch repair deficient (dMMR) endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with Imfinzi as monotherapy.

Sponsor: AstraZeneca Canada Inc.

Recommendation: Reimburse with Conditions

Publication Date: April 2025

Canada's Drug Agency (CDA-AMC) is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.

.

Recommendation

The CDA-AMC pCODR Expert Review Committee (pERC) recommends that durvalumab be reimbursed in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with primary advanced or recurrent mismatch repair deficient (dMMR) endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with durvalumab as monotherapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, double-blind, placebo-controlled trial (DUO-E; N = 718) evaluated the efficacy and safety of durvalumab in combination with carboplatin and paclitaxel followed by durvalumab maintenance, compared with placebo plus carboplatin and paclitaxel followed by placebo maintenance in patients with primary advanced or recurrent endometrial cancer. A subgroup of patients in the DUO-E trial (N = 95) aligned with the indication under review: adults with primary advanced or recurrent dMMR endometrial cancer who are candidates for systemic therapy. Subgroup analyses suggested that, compared with placebo plus carboplatin and paclitaxel, durvalumab plus carboplatin and paclitaxel may improve median overall survival (OS) ([redacted]; hazard ratio [HR], 0.34 [95% confidence interval [CI], 0.13 to 0.79]), and median progression-free survival (PFS) (not reached vs. 7.0 months; HR = 0.42; 95% CI, 0.22 to 0.80). However, the magnitude of the results was uncertain due to the immaturity of the data, small sample size, and imprecision in the estimates (wide CIs). Additional analyses of OS at landmark 12-month ([redacted]), and 18-months ([redacted]), were supportive of the potential survival advantage demonstrated by durvalumab plus carboplatin and paclitaxel in this subgroup. The sponsor-submitted indirect evidence comparing durvalumab plus carboplatin and paclitaxel to dostarlimab plus carboplatin and paclitaxel suggested that there was insufficient evidence to detect a difference between the two treatments, although significant limitations impacted the validity and certainty of the results which precluded pERC from drawing conclusions on the comparative efficacy and safety of durvalumab versus dostarlimab. pERC also considered the safety profile of durvalumab plus carboplatin and paclitaxel to be manageable with no unexpected toxicities.

Patients identified a need for new effective and accessible treatment options that prolong survival, delay the onset of symptoms, maintain quality of life (QoL), and have fewer side effects. pERC concluded that durvalumab plus carboplatin and paclitaxel may meet some of patients' needs as it offers a new treatment that may delay disease progression and improve survival when compared to carboplatin plus paclitaxel. Based on exploratory analyses, the addition of durvalumab to carboplatin and paclitaxel did not suggest a detriment in health-related quality of life (HRQoL) from baseline to Week 18 and Week 42; however, results for HRQoL were inconclusive due to high attrition rates.

Using the sponsor submitted price for durvalumab and publicly listed prices for all other drug costs, durvalumab plus carboplatin and paclitaxel was more costly and less effective than dostarlimab plus carboplatin and paclitaxel in adult patients with primary advanced or recurrent dMMR endometrial cancer who are candidates for systemic therapy. Given that the indirect evidence did not support a difference in outcomes between these two treatments, there is insufficient evidence to justify a price premium for durvalumab.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with durvalumab plus carboplatin and paclitaxel should be reimbursed in adult patients (18 years of age or older) with primary advanced or recurrent dMMR endometrial cancer who meet at least 1 of the following criteria: 1.1. Newly diagnosed stage III or IV endometrial cancer. 1.2. Have a first recurrence and have not previously received systemic anticancer therapy for advanced disease. 1.3. Have received prior adjuvant systemic anticancer therapy at least 12 months from the date of last dose administered to the date of subsequent relapse.	Evidence from the dMMR subgroup from DUO-E suggested that treatment with durvalumab plus carboplatin and paclitaxel resulted in a clinical benefit in patients with these characteristics.	MMR status must be determined before starting treatment with durvalumab.
2. Patients should have good performance status.	Patients with an ECOG performance status of 0 or 1 were included in the DUO-E trial.	Treating patients with an ECOG performance status of 2 may be at the discretion of the treating clinician.
3. Patients must not have any of the following: 3.1. Relapse within 12 months of completing adjuvant systemic anticancer therapy 3.2. Prior therapy with an anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-PD-L2 drug for advanced disease.	There is no evidence to support the benefit of durvalumab plus carboplatin and paclitaxel in patients with these characteristics because they were excluded from the DUO-E trial.	—
Discontinuation		
4. Treatment should be discontinued upon the occurrence of any of the following: 4.1. Objective disease progression. 4.2. Unacceptable toxicity.	Patients in the DUO-E trial discontinued treatment upon progression or unacceptable toxicity consistent with clinical practice.	—
Prescribing		
5. Durvalumab (plus carboplatin and paclitaxel, as applicable) should be prescribed by clinicians with expertise in	This will ensure that treatment is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—

Reimbursement condition	Reason	Implementation guidance
advanced uterine cancer; treatment should be supervised and delivered in institutions with expertise in systemic therapy delivery.		
6. Durvalumab plus carboplatin and paclitaxel should only be reimbursed when started in combination.	In DUO-E, durvalumab was initiated in combination with carboplatin and paclitaxel.	—
Pricing		
7. The total cost of durvalumab plus carboplatin and paclitaxel should be negotiated so that it does not exceed the total drug program cost associated with dostarlimab plus carboplatin and paclitaxcel for the treatment of adult patients with primary advanced or recurrent dMMR endometrial cancer who are candidates for systemic therapy.	The findings of the indirect evidence suggested a similar clinical benefit in OS and PFS when comparing durvalumab plus carboplatin and paclitaxel to dostarlimab plus carboplatin and paclitaxel. In the economic evaluation, durvalumab plus chemotherapy was more costly and less effective (i.e., produced fewer QALYs) than dostarlimab plus chemotherapy (i.e., durvalumab was dominated). Patients treated with durvalumab will continue to receive it until disease progression or unacceptable toxicity. Patients treated with dostarlimab will discontinue treatment after 3 years. Consequently, identical drug pricing for durvalumab and dostarlimab will result in increased drug spending in patients who remain progression-free for longer than 3 years.	—

dMMR = mismatch repair deficient; ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; MMR = mismatch repair; QALY = quality-adjusted life-year.

Discussion Points

- **Unmet Need:** pERC discussed the input from patient and clinician groups as well as the clinical experts, all of whom consider prolonged survival to be the most important outcome that new treatments for advanced or recurrent endometrial cancer should address, given the poor prognosis and high proportion of patients who do not respond to current first line treatments. pERC agreed that there is an unmet need for effective and safe therapeutic options in the requested population and noted that the addition of durvalumab to carboplatin and paclitaxel may address these needs relative to carboplatin and paclitaxel alone. However, pERC was unable to ascertain whether durvalumab plus carboplatin and paclitaxel met the unmet needs identified, versus dostarlimab plus carboplatin and paclitaxel, due to a lack of direct comparative evidence and limitations associated with the submitted indirect evidence. The clinical experts also emphasized that there is no evidence to choose one immune checkpoint inhibitor over another.
- **Certainty of Evidence:** pERC discussed that the focus of the pivotal evidence submitted for this review consisted of a pre-specified subgroup of patients with dMMR status from 1 phase III RCT (DUO-E), however, the analysis was not pre-planned, and the sample sizes were small. As such, the committee only considered the results supportive of the overall effect of durvalumab. pERC also discussed the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment for durvalumab plus carboplatin and paclitaxel compared to carboplatin and paclitaxel alone, in which the certainty of evidence was rated as low or very low for all outcomes primarily due to the use of the subgroup and the immaturity of the results (median PFS and OS for the durvalumab group were not reached; and 51.0% vs. 32.6% and [redacted] vs. [redacted] of

patients in SoC and durvalumab plus carboplatin and paclitaxel arms experienced PFS or OS events, respectively). Despite the nature of the analyses, pERC acknowledged that the results from the dMMR subgroup in DUO-E were considered compelling as noted by the clinical experts and were supportive of a potential survival advantage for durvalumab plus carboplatin and paclitaxel over SoC.

- **Indirect Evidence:** pERC discussed the indirect evidence submitted for this review which consisted of MAICs comparing durvalumab to dostarlimab, which is the most relevant comparator in the Canadian clinical setting. The results of the MAICs suggested that there was [redacted] however, the results were uncertain given the reduced sample size and the wide 95% CI. pERC also noted that the evidence on OS and harms was based on an unweighted indirect comparison and were therefore considered exploratory, though was generally consistent with the analysis for PFS. Overall, pERC emphasized the limitations of the MAIC analyses, highlighting the clinical and methodological heterogeneity between the DUO-E and RUBY Part 1 trials, including differences in patient populations pre- and post-matching, differences in follow-up and treatment duration, as well as the quality of evidence across studies with respect to data immaturity, the use of subgroups, and analysis methods within the trials, which precluded pERC from drawing conclusions on the comparative efficacy of durvalumab.
- **Testing Procedure Considerations:** pERC noted that MMR testing is currently performed as the standard of care for patients with endometrial cancer in Canada and acknowledged that evaluating MMR status prior to the initiation of durvalumab would be required. pERC also noted that considering this is already standard of care, MMR testing is not anticipated to be an implementation or access barrier.
- **Price condition:** There is insufficient evidence to support a price premium for durvalumab plus carboplatin and paclitaxel over dostarlimab plus carboplatin and paclitaxel, and the economic evaluation suggests that durvalumab is dominated by dostarlimab in this setting. However, given the uncertainty associated with the indirect treatment evidence and the overall finding of similar OS and PFS, and given that durvalumab is associated with higher overall treatment costs, reimbursing durvalumab may provide value to the health care system if the impact on drug plan budgets is similar for these two regimens.

Background

Endometrial cancer is a type of uterine cancer originating in the lining of the uterus and is the most common gynecological malignancy, accounting for approximately 95% of uterine cancers. The symptoms of advanced stage (Stage III or IV) and recurrent (return following primary treatment) disease are variable but include abnormal vaginal bleeding pelvic or back pain, the presence of a palpable mass in the lower abdomen, and unintentional weight loss. Patients often experience additional issues like sexual dysfunction, anxiety, depression, and the long-term effects of chemotherapy, all of which further reduce HRQoL. In Canada, the overall 5-year net survival for uterine cancer is 82%, with stage-specific survival rates of 30% for Stage III and 15% for Stage IV. Endometrial cancer is categorized into microsatellite instability–high (MSI-H), microsatellite instability–low (MSI-L), and microsatellite stable (MSS) based on MSI testing, and into proficient mismatch repair (pMMR) or deficient mismatch repair (dMMR) based on mismatch repair (MMR) status. According to the clinical experts consulted by the review team, MMR testing, assessed by immunohistochemistry (IHC), is currently performed as the standard of care for patients with endometrial cancer in Canada.

Durvalumab has been approved by Health Canada in combination with carboplatin and paclitaxel for the first-line treatment of adults with primary advanced or recurrent dMMR endometrial cancer who are candidates for systemic therapy, followed by durvalumab as monotherapy. Durvalumab is a fully human, high affinity, immunoglobulin G1 kappa monoclonal antibody. It is available as an intravenous (IV) infusion and the dosage recommended in the product monograph is 1120 mg in combination with carboplatin and paclitaxel every 3 weeks (21 days) for 6 cycles, followed by maintenance 1500 mg every 4 weeks as monotherapy until disease progression or unacceptable toxicity.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 RCT in in patients with newly diagnosed advanced or recurrent endometrial cancer and 1 indirect treatment comparison consisting of 2 matching-adjusted indirect comparisons (MAICs)
- patients' perspectives gathered by 1 patient group, the Colorectal Cancer Resource & Action Network (CCRAN) in collaboration with the Canadian Cancer Survivor Network (CCSN) and HPV Global Action
- input from public drug plans that participate in the reimbursement review process
- two clinical specialists with expertise diagnosing and treating patients with newly diagnosed advanced or recurrent dMMR endometrial cancer
- input from 2 clinician groups, the OH (CCO) Gynecologic Cancer Drug Advisory Committee and the Gynecologic Oncology Society of Canada
- a review of the pharmacoeconomic model and report submitted by the sponsor

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

One patient group, the CCRAN, in collaboration with the CCSN and HPV Global Action submitted input on durvalumab for endometrial cancer. Information for this submission was gathered through outreach by the CCRAN to 12 Canadian clinicians in September, 2024, and 17 U.S.-based clinician investigators involved in the DUO-E clinical trial in October, 2024, as well as the Society of Gynecologic Oncology and the Gynecologic Cancer Initiative. Additionally, HPV Global Action collaborated with several Medical Advisors to identify patients with experience using the therapy under review. These efforts led to 2 telephone interviews with patients with MSS endometrial cancer who participated in the DUO-E trial. Also, data from a previous 2023 survey, which resulted in 4 online patient experiences and six responses, was used for this input. In the survey, 2 patients reported not having endometrial cancer.

The patient group input highlighted that patients with endometrial cancer face significant inequities, including research underfunding, rising incidence rates particularly among post-menopausal women, and increasing mortality rates despite advancements in oncology.

According to the patient group input, a diagnosis of endometrial cancer is profoundly distressing, bringing significant emotional strain on both patients and their caregivers, and triggering fears related to personal health and family welfare.

Respondents to the survey reported using various treatment options, including radiation, surgical resection, targeted therapy, hormonal therapy, immunotherapy, chemotherapy, and complementary medicines. Common symptoms included neuropathy, fatigue, vaginal dryness, itching, burning sensations, changes in sexual function, fluid retention, nausea, constipation, and cognitive impairment known as "chemo brain." Many patients described chemotherapy as “tough,” with significant nausea and fatigue impacting daily life. The effects of treatment often extend to sexual health, which is frequently overlooked in clinical care and research.

The input highlighted that early-stage endometrial cancer is typically treated with surgery, often combined with chemotherapy, hormone therapy, or radiation. However, treatment options for patients with recurrent or metastatic endometrial cancer are limited, and prognosis remains poor due to stagnant access to new therapeutics over the past decades. Patient groups highlighted an urgent unmet need for additional precision therapeutics in advanced or recurrent endometrial cancer in Canada, with 60% of endometrial cancer patients ranked “prolong life” as the most important issue they hope new treatments will address.

The two patients who participated in telephone interviews shared their experiences with durvalumab in combination with olaparib during the DUO-E trial, reporting complete responses and minimal side effects, while a third patient receiving durvalumab treatment in Australia highlighted the positive impact of targeted therapies on their quality of life.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts consulted for this review noted that the goals of treatment for advanced or metastatic endometrial cancer, are to improve quality of life by reducing pain and suffering, improve disease-related symptoms, control the cancer proliferation, and improve survival if possible. They noted that achieving a longer duration of response would be strongly linked to improvement in relevant patient outcomes. In dMMR endometrial cancer, one expert noted that between 20 and 40% of patients do not respond to the current first line treatment paradigm; for context, they noted that in general approximately 40% of patients are expected not to respond to chemotherapy, and the duration of response (DoR) to chemotherapy alone is often very short. The addition of an immune checkpoint inhibitor (ICI) improves the overall treatment response rate but has the most significant improvement in the DoR. The unmet needs in patients with dMMR endometrial cancer include better identification of non-responders, determining the therapy they might respond to, and determining the ideal duration of maintenance treatment in patients who do respond to therapy.

The experts indicated that durvalumab would be an additional first line option alongside dostarlimab as an ICI option to be added to chemotherapy and used as maintenance monotherapy in patients with dMMR endometrial cancer. In general, the clinical experts noted that the choice of ICI is often based on availability but in a situation where multiple approved options are available, any of them could be offered. If a patient did not respond to ICI therapy the clinical experts noted it was unlikely they would trial the drug class again; however, if patients had a recurrence more than 12 months after therapy and had responded previously, then retreatment might be considered.

The clinical experts noted that the DUO-E trial results did not identify specific molecular subtypes of patients (beyond dMMR) that may respond to the new treatments, therefore, all patients who meet the other clinical trial criteria would likely be candidates for treatment with durvalumab.

According to the experts, the outcomes from the DUO-E trial corresponded to standard clinical assessments, with the exception of HRQoL measures which are not routinely used in clinical practice. In general, symptomatic benefit would be assessed every cycle through conversations with the patient, and radiologic treatment response would be assessed every 2 to 3 cycles. They noted that the ideal outcome to assess response would be survival, but in the face of measurable disease, achieving stability (i.e., prolongation of progression-free survival [PFS]) while being tolerated well would be a minimum response to continue therapy. They indicated that the definition of a treatment benefit may vary across physicians and patients.

Disease progression and serious adverse events (AEs) would be grounds to discontinue therapy, according to the experts. Examples of serious AEs could include grade 3 or 4 toxicities such as hepatitis, colitis, or pneumonitis as well as any other significant immune-related toxicity. Both clinical experts agreed that an oncologist or specialist in administering chemotherapy or biologic therapy would be essential to manage the complexities of treatment toxicity.

Clinician Group Input

Two inputs from the OH (CCO) Gynecologic Cancer Drug Advisory Committee (7 clinicians contributed to the input) and one from the Gynecologic Oncology Society of Canada (1 clinician contributed to the input) were provided for this review. The OH (CCO) input was gathered through conference calls and emails, while the GOC input was based on data from completed clinical trials and expert opinions from Board members on treating advanced or recurrent endometrial cancer.

According to the clinician groups, treatment for dMMR endometrial cancer involves platinum-based chemotherapy (carboplatin and paclitaxel) and radiation, with pembrolizumab funded for recurrent dMMR disease after failure of chemotherapy. There are no publicy-funded first-line immunotherapies for patients with dMMR endometrial cancer, though compassionate access to dostarlimab in combination with chemotherapy is available.

The clinician groups agreed with the experts that the primary treatment goals are to prolong survival, delay disease progression, control symptoms, improve HRQoL, and, where possible, cure the disease. The clinician input also agreed with the experts that that chemotherapy fails to provide a durable response in patients with dMMR endometrial cancer. Both clinician groups aligned with the experts and noted that durvalumab would be suitable as a first-line option for patients with advanced (stage III or IV) or recurrent endometrial cancer. They also noted that patients with dMMR endometrial cancer can receive durvalumab treatment without prior chemotherapy.

The clinician groups agreed that treatment response is assessed through imaging (computerized tomography [CT] or magnetic resonance imaging [MRI]) and clinical evaluations. The GOC added that tolerability is evaluated before each treatment cycle (i.e., every 3 weeks) with radiologic assessments every 6 to 9 weeks. A clinically meaningful response includes tolerable toxicity and improved progression-free survival.

The clinician groups indicated that treatment may be withheld due to disease progression and intolerable toxicity or adverse events. The GOC further mentioned that such decisions could also be related to patient preference. In line with the clinical experts consulted for this review, the clinician groups stated that durvalumab plus carboplatin and paclitaxel should be administered in an outpatient setting and is best prescribed by specialist physicians experienced in systemic therapy.

Drug Program Input

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
DUO-E compared treatment arms (durvalumab with carbo/taxol then maintenance durvalumab and durvalumab with carbo/taxol then maintenance with durvalumab and olaparib) to 6 cycles of carboplatin and paclitaxel chemotherapy. *In Canada, carbo/taxol is the current standard. At the time of this review, dostarlimab in combination with carbo/taxol (for patients with dMMR tumours) has completed pCPA negotiations and is currently at the jurisdictional level to approve funding.*	This is a comment from the drug programs to inform pERC deliberations.

Implementation issues	Response
Dostarlimab is under review to expand use beyond dMMR to all patients. Pembrolizumab is also under review for the first line treatment of primary advanced or recurrent endometrial cancer regardless of the MMR status.	
In DUO-E, durvalumab maintenance continued until progression or toxicity. Dostarlimab continues for a maximum of 3 years in this indication. Pembrolizumab continues for a maximum of 2 years.	This is a comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
MMR testing is not reflexive in all jurisdictions for endometrial carcinoma. Is there a standard definition of dMMR to help define treatment for eligible patients?	The clinical experts noted that MMR testing is reflexive in a majority of care settings, and the standard definition most use would be based on immunohistochemistry. pERC acknowledged and agreed with the clinical experts' response.
Can durvalumab be administered with alternate chemotherapy if a patient cannot receive or tolerate carboplatin and/or paclitaxel?	The experts indicated that patients could receive alternate chemotherapy such as single agent carboplatin, paclitaxel, or other single platinum agent. pERC acknowledged and agreed with the clinical experts' response. pERC noted that there was insufficient evidence to support combining durvalumab with other chemotherapy regimens other than those used in the DUO-E trial (i.e., carboplatin and paclitaxel). pERC noted that combining durvalumab with other chemotherapy regimens would be outside of the Health Canada indication.
Patients who received previous systemic therapy were eligible only if previous treatment was in the adjuvant setting and there was ≥12 months between last dose and subsequent relapse. Should patients be eligible for treatment if there was less than 12 months between last dose of adjuvant therapy and subsequent relapse?	The experts indicated that there is no data on this setting, but speculated that patients with dMMR endometrial cancer who have a rapid recurrence after platinum-based therapy would probably be treated with immunotherapy. pERC agreed with the clinical experts' response.
In DUO-E, patients had to complete a minimum of 4 cycles before being eligible for the maintenance phase. If patients must discontinue carboplatin-paclitaxel before the 4th cycle, should they be considered for maintenance treatment?	The clinical experts indicated that the reason for the discontinuation would be a factor in decision-making, and that it would be a clinical decision. However, for patients with dMMR status, they would likely proceed with maintenance treatment in this scenario. pERC agreed with the clinical experts' response, noting that if patients do not complete the chemotherapy phase due to toxicity, they could receive maintenance durvalumab if there was no evidence of progression during the chemotherapy phase.
In DUO-E, treatment was continued until disease progression or unacceptable toxicity. If a patient stopped treatment for a reason other than progression or unacceptable toxicity and then wanted to resume at time of progression, would they be eligible? If yes, which components of the regimen?	The clinical experts indicated that the reason for stopping treatment initially would be a factor in the decision-making. In this scenario, however, they noted that disease progression or toxicity are the main reasons they do not re-challenge with the same therapy. As such, they likely would resume treatment at time of progression, though the components of the regimen would depend on when in treatment the stoppage occurred. For example, the experts noted that if a patient stopped treatment after 1 week, they would likely be considered naïve and resume treatment at the beginning. However, if they stopped treatment after 5 cycles, then they could be considered to have received the whole chemotherapy regimen and could be evaluated for maintenance therapy.

Implementation issues	Response
	pERC agreed with the clinical experts' response.
If recommended for reimbursement, would it be appropriate to consider aligning the initiation criteria of the drug under review with the initiation criteria for dostarlimab and pembrolizumab in endometrial cancer?	pERC and the clinical experts noted that in the absence of direct comparative evidence they consider these treatments to be somewhat equivalent, and therefore the initiation criteria could be aligned with dostarlimab and pembrolizumab in the same care setting.
Considerations for continuation or renewal of therapy	
If there is progression during a "drug holiday", can treatment be resumed? According to what timeframe?	The experts indicated that the reason for the drug holiday would be an important factor in the decision-making for this situation, and this would likely be a patient-specific clinical decision. Examples of factors they would take into consideration included the reason for the holiday, how much treatment the patient had received prior to the holiday, and after which interval their disease recurred. For example, if a longer interval had elapsed, then the experts would be more likely to consider retreatment, while a shorter interval may imply a lack of benefit. pERC acknowledged and agreed with the clinical experts' response.
Considerations for prescribing of therapy	
Most jurisdictions use weight-based dosing up to a cap for durvalumab: 15-20mg/kg (up to a maximum of 1500mg) every 3 weeks in combination with chemotherapy, then 20mg/kg (up to a maximum of 1500mg) every 4 weeks.	This is a comment from the drug plans to inform pERC deliberations.
Generalizability	
The exclusion criteria for DUO-E study excluded patients with ECOG > 1 and patients with sarcomas. Should either of these groups of patients be considered for treatment?	The clinical experts indicated they would likely treat patients with an ECOG status of 2, but there is no data on pure sarcomas and they would not consider them for this treatment. pERC agreed with the clinical experts' response.
Should patients who are currently receiving first line chemotherapy be eligible to add durvalumab?	pERC and the experts indicated that should durvalumab become available and the patients otherwise meet the eligibility criteria, then they would add durvalumab to their chemotherapy regimen.
Should patients currently receiving dostarlimab in combination with chemotherapy be eligible to switch to durvalumab? *Should patients currently receiving dostarlimab maintenance be eligible to switch to durvalumab?*	The clinical experts indicated that they would not generally switch one ICI for another unless data were to become available to support a switch or if there were a contract change in their care centre. In general, if a patient failed to respond to ICI treatment, they also would not re-challenge with another agent from that treatment class. A treatment change may be considered from durvalumab to a more convenient treatment schedule (every 6 weeks in the maintenance setting – dostarlimab or pembrolizumab) which may improve patient QoL and reduce resource use at the treating centre. pERC agreed with the clinical experts' response, highlighting that this would only be the case if there was no evidence of disease progression.
Funding algorithm	
Durvalumab may change the place in therapy of comparator drugs and may change the place in therapy of drugs reimbursed in subsequent lines. *Under what circumstances would durvalumab be chosen over dostarlimab or pembrolizumab if reimbursed in the same line of therapy?*	The experts indicated that if all 3 treatments were available, they did not see a compelling reason to use one ICI over another, other than the potential convenience of 6 weekly infusions from agents such as dostarlimab or pembrolizumab. pERC agreed with the clinical experts' response.

Implementation issues	Response
System and economic issues	
Funding of oral agents varies by province.	These are comments from the drug plans to inform pERC deliberations.
Confidential prices exist for other treatment options.	
PAG would like to inform pERC that there is concern about the budget impact of durvalumab in the first line treatment of all patients with endometrial cancer compared to chemotherapy alone and other immune checkpoint inhibitors. Dostarlimab continues for up to 3 years, pembrolizumab continues for up to 2 years, and durvalumab would continue until progression or unacceptable toxicity with no maximum cutoff. There is no comparative data to determine whether durvalumab provides a significant advantage over dostarlimab or pembrolizumab.	

pCPA = pan-Canadian Pharmaceutical Alliance; dMMR = mismatch repair deficient; ECOG = Eastern Cooperative Oncology Group; ICI = immune checkpoint inhibitor; MMR = mismatch repair; PAG = provincial advisory committee; pERC = pCODR expert review committee.

Clinical Evidence

Systematic Review

Description of Studies

DUO-E is an ongoing Phase III, randomized, multicentre, double-blind, placebo-controlled randomized controlled trial (RCT) of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab or maintenance durvalumab in combination with olaparib in patients with newly diagnosed advanced or recurrent endometrial cancer compared to standard of care (SoC) alone (paclitaxel and carboplatin). Enrolment for DUO-E ended in March 2022, however, treatment and follow-up are still ongoing. In total, 718 patients were randomized 1:1:1 to either SoC (Arm A; N = 241), durvalumab plus SoC (Arm B; N = 239), or durvalumab plus olaparib plus SoC (Arm C; N = 238). Arm A received a chemotherapy phase regimen of platinum-based chemotherapy consisting of carboplatin and paclitaxel plus durvalumab placebo for 6 cycles; after the chemotherapy phase, patients who had no evidence of progressive disease then received maintenance phase therapy consisting of durvalumab placebo intravenous (IV) every 4 weeks (Q4W) plus olaparib placebo tablets twice daily. Arms B and C received the same platinum-based chemotherapy as the SoC arm plus durvalumab for 6 cycles, then Arm B received maintenance phase therapy consisting of durvalumab plus olaparib placebo tablets twice daily while Arm C received both durvalumab and olaparib. The primary endpoint of the DUO-E study was PFS, with secondary endpoints consisting of overall survival (OS), objective response rate (ORR), DoR, time to discontinuation or death (TDT), and HRQoL.

Of note, the DUO-E trial randomized patients with pMMR and dMMR status to all 3 study arms. In order to align with the Health Canada indication and reimbursement request (durvalumab in combination with carboplatin and paclitaxel in patients with dMMR endometrial cancer, followed by maintenance durvalumab), this clinical review report focuses only on the population of patients from DUO-E with dMMR endometrial cancer who received durvalumab in combination with carboplatin and paclitaxel (i.e., only a subset of patients included in Arm B of the DUO-E study).

Efficacy Results

Progression-Free Survival

In the dMMR subgroup, there were a total of 25 (51.0%) events in the SoC arm (N = 49 patients) and 15 (32.6%) events in the SoC plus durvalumab arm (N = 46 patients). There were [redacted] censored deaths in the SoC arm and [redacted] in the SoC plus durvalumab arm. The median PFS in the SoC arm was [redacted] months (95%, [redacted]), while the median PFS was not calculable in the SoC plus durvalumab arm (HR, [redacted] [95% CI, [redacted]], in favour of durvalumab). The risk difference between study arms for proportion of patients who were progression-free was [redacted] (95% CI, [redacted]) at 6 months; [redacted] (95% CI, [redacted]) at 12 months; and [redacted] (95% CI, [redacted]) at 18 months.

Overall Survival

In the dMMR subgroup, there were a total of [redacted] deaths in the SoC arm and [redacted] deaths in the SoC plus durvalumab arm. The median OS in the SoC arm was [redacted] months (95% CI, [redacted]), while the median OS was [redacted] in the SoC plus durvalumab arm (HR, [redacted] [95% CI, [redacted]], in favour of durvalumab). The risk difference between study arms for the proportion of patients who were alive was [redacted] (95% CI[redacted]) at 6 months; [redacted] (95% CI, [redacted]) at 12 months; and [redacted] (95% CI, [redacted]) at 18 months.

Objective Response Rate

In the dMMR subgroup, a total of [redacted] patients had a response out of [redacted] patients with measurable disease at baseline in the SoC arm, and [redacted] patients had a response out of [redacted] with measurable disease at baseline in the SoC plus durvalumab arm. The odds ratio (OR) (95% CI) for response was [redacted] in favour of durvalumab.

Duration of Response

In the dMMR subgroup, [redacted] patients out of the [redacted] with a response subsequently progressed or died in the SoC arm. The median duration of response (measured from the onset of response) was [redacted] months. In the SoC plus durvalumab arm[redacted] patients out of the [redacted] with a response subsequently progressed or died; the median duration of response was not calculable. The difference between study arms for the proportion of patients remaining in response was [redacted] (95% CI, [redacted]) at 6 months, [redacted] (95% CI, [redacted]) at 12 months, and [redacted] (95% CI, [redacted]) at 18 months.

Time to Treatment Discontinuation or Death

In the dMMR subgroup, 37 (75.5%) patients in the SoC arm and 22 (47.8%) patients in the SoC plus durvalumab arm had an event of treatment discontinuation or death (HR, 0.47 [95% CI, 0.27 to 0.79], in favour of durvalumab).

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) functional scales range from 0 to 100, with higher scores indicating better functioning. In the dMMR subgroup, the mean baseline score was [redacted] points (standard deviation [SD] = [redacted]) in the SoC arm and [redacted] points (SD = [redacted]) in the SoC plus durvalumab arm. At week 18 (corresponding to the 6th cycle of the chemotherapy phase) the mean change in score from baseline was [redacted] points (SD = [redacted]) in the SoC arm (N = [redacted]), and [redacted] points (SD = [redacted]) in the SoC plus durvalumab arm (N = [redacted]). The absolute mean difference between study arms was [redacted] points (95% CI, [redacted]). At week 42 (corresponding to the 6th month of the maintenance phase), the mean change in scores from baseline was [redacted] points (SD = [redacted]) in the SoC arm (N = [redacted]), and [redacted] points (SD = [redacted]) in the SoC plus durvalumab arm (N = [redacted]). The absolute mean difference between study arms was [redacted] points (95% CI, [redacted]).

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Endometrial Cancer Module Pain in Back and Pelvis Score

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Endometrial Cancer Module (EORTC QLQ-EN24) functional scales range from 0 to 100, with higher scores indicating better functioning, and the 10 symptom scales range from 0 to 100, with higher scores indicating more severe symptoms. In the dMMR subgroup, the mean baseline score was [redacted] points (SD = [redacted]) in the SoC arm and [redacted] points (SD = [redacted]) in the SoC plus durvalumab arm. At week 18 the mean change in score from baseline was [redacted] points (SD = [redacted]) in the SoC arm (N = [redacted]), and [redacted] points (SD = [redacted]) in the SoC plus durvalumab arm (N = [redacted]). The absolute mean difference between study arms was [redacted] points (95% CI, [redacted]). At week 42, the mean change in scores from baseline was [redacted] points (SD = [redacted]) in the SoC arm (N = [redacted]), and [redacted] points (SD = [redacted]) in the SoC plus durvalumab arm (N = [redacted]). The absolute mean difference between study arms was [redacted] points (95% CI, [redacted]).

EORTC QLQ-EN24 Urological Symptoms Score

In the dMMR subgroup, the mean baseline score was [redacted] points (SD = [redacted]) in the SoC arm and [redacted] points (SD = [redacted]) in the SoC plus durvalumab arm. At week 18 the mean change in score from baseline was [redacted] points (SD = [redacted]) in the SoC arm (N = [redacted]), and [redacted] points (SD = [redacted]) in the SoC plus durvalumab arm (N = [redacted]). The absolute mean difference between study arms was [redacted] points (95% CI, [redacted]). At week 42, the mean change in scores from baseline was [redacted] points (SD = [redacted]) in the SoC arm (N = [redacted]), and [redacted] points (SD = [redacted]) in the SoC plus durvalumab arm (N = [redacted]). The absolute mean difference between study arms was [redacted] points (95% CI, [redacted]).

Harms Results

Adverse Events

In the dMMR subgroup, all patients in each study arm experienced an AE during the DUO-E trial. A total of [redacted] of patients in the SoC arm and [redacted]% of patients in the SoC plus durvalumab arm experienced an AE with maximum Grade 3 or 4. The most common AEs were nausea ([redacted] of patients in the SoC plus durvalumab arm, [redacted] of patients in the SoC arm), alopecia ([redacted] in the SoC plus durvalumab arm, [redacted] in the SoC arm), arthralgia ([redacted] in the SoC plus durvalumab arm, [redacted] in the SoC arm), and anemia ([redacted] in the SoC plus durvalumab arm, [redacted] in the SoC arm).

There were differences between study arms in the proportion of patients with several AEs. Of note, a numerically higher proportion of patients in the SoC plus durvalumab arm reported nausea ([redacted] vs. [redacted] in the SoC arm), alopecia ([redacted] vs. [redacted] in the SoC arm), arthralgia ([redacted] vs. [redacted] in the SoC arm), hypomagnesemia ([redacted] vs. [redacted] in the SoC arm), cough ([redacted] vs. [redacted] in the SoC arm), peripheral neuropathy ([redacted] vs. [redacted] in the SoC arm), dyspnea ([redacted] vs. [redacted] in the SoC arm), and injury, poisoning or procedural complications ([redacted] vs. [redacted]).

Serious Adverse Events

In the dMMR subgroup, a total of [redacted] of patients in the SoC arm and [redacted] in the SoC plus durvalumab arm experienced a serious adverse event (SAE) during the DUO-E trial. The most common SAEs were as follows: gastrointestinal disorders ([redacted] in the SoC plus durvalumab arm consisting of [redacted] reports of fecaloma, [redacted] report each of abdominal hernia, colitis, intestinal obstruction and nausea and [redacted] in the SoC arm consisting of [redacted] report each of diarrhea, nausea, and vomiting), blood and lymphatic system disorders ([redacted] in the SoC arm consisting of [redacted] reports of anemia, [redacted] reports of febrile neutropenia, and [redacted] reports of neutropenia, and [redacted] in the SoC plus durvalumab arm consisting of 1 report of autoimmune hemolytic anemia), infections and infestations ([redacted] in the SoC arm consisting of [redacted] report each of COVID-19, neutropenic sepsis, urinary tract infection and urosepsis, and [redacted] in the SoC plus durvalumab arm consisting of [redacted] report each of appendicitis, gastroenteritis, and sepsis), and renal and urinary disorders ([redacted] in the SoC arm consisting of [redacted] report each of acute kidney injury, renal failure, ureteric obstruction and urinary bladder hemorrhage, and [redacted] in the SoC plus durvalumab arm).

Withdrawals Due to Adverse Events

In the dMMR subgroup. a total of [redacted] of patients experienced AEs leading to the withdrawal of durvalumab in the SoC plus durvalumab arm, and [redacted] reported this in the SoC arm. In the SoC plus durvalumab arm, the reasons for discontinuation were anemia, interstitial lung disease, maculopapular rash, symmetrical drug-related intertriginous and flexural exanthema, fatigue, and procedural pain (each reported in [redacted] patient) In the SoC arm, the reasons for discontinuation of durvalumab placebo were anemia ([redacted] patients), cerebrovascular accident, tinnitus, and asthenia (each reported in [redacted] patient). A total of [redacted] of patients in the SoC plus durvalumab arm and [redacted] of patients in the SoC arm experienced an AE leading to discontinuation of SoC.

Mortality

In the dMMR subgroup, a total of [redacted] patients died in the SoC arm and [redacted] patients died in the SoC plus durvalumab arm. The submission did not provide details on the specific causes of death in patients in the dMMR subgroup.

Notable Harms

Immune-mediated AEs (exact conditions not specified) and infusion reactions were identified as adverse events of special interest (AESIs) by the clinical experts. In the dMMR subgroup, [redacted] of patients experienced an immune-mediated AE in the SoC plus durvalumab arm and [redacted] experienced this in the SoC arm. A total of [redacted] of patients experienced infusion reactions in the SoC plus durvalumab arm, and [redacted] of patients in the SoC arm.

A total of [redacted] of patients in the SoC plus durvalumab arm, and [redacted] of patients in the SoC arm experienced an AESI for durvalumab. The most common AEs in both arms were diarrhea ([redacted] in the SoC plus durvalumab arm, [redacted] in the SoC arm) and rash ([redacted] in the SoC plus durvalumab arm, [redacted] in the SoC arm). Hypothyroidism ([redacted] of patients) was the next most common reason in the SoC plus durvalumab arm, and hyperthyroidism ([redacted] of patients) the next most common in the SoC arm.

Critical Appraisal

DUO-E is an ongoing Phase III trial assessing the efficacy and safety of durvalumab plus SoC compared to SoC alone in the treatment of primary advanced or recurrent endometrial cancer. Despite the adequate randomization, concealment, and blinding, there were numerically higher numbers of patients who discontinued treatment the SoC arm relative to the SoC plus durvalumab arm, which suggests the possibility that patients may have become unblinded to their treatment arm and discontinued treatment more readily than those in the SoC plus durvalumab arm. As part of the study design, patients with no evidence of progressive disease during the 6-cycle chemotherapy phase were eligible to proceed to the maintenance phase. Results for efficacy outcomes were not provided separating the chemotherapy and maintenance phases, thus the impact of the chemotherapy phase versus the maintenance phase individually on response to treatment remains unknown. The design of DUO-E contained patients with endometrial cancer with both dMMR and pMMR status. However, given the Health Canada indication and reimbursement request, the focus of this review was based on a subgroup of patients with dMMR endometrial cancer. Therefore, all results focusing on the dMMR subgroup can only be considered exploratory and supportive of the overall effect of durvalumab. Furthermore, the subgroup was not controlled for multiple comparisons, and there is an increased risk of Type I error which is particularly important given the sample sizes in each study arm were small. Results from the DUO-E trial were from an interim analysis (IA) and the *P* value cutoff for the IA of the subgroups themselves is not known; this carries an increased risk of overestimating the true effect. While the primary endpoint was reached for the ITT population, the median PFS and OS were not estimable for the dMMR subgroup in the respective analyses. In the ITT population, this analysis was based on an information fraction of [redacted], while in the dMMR subgroup, only [redacted] of PFS events had occurred, suggesting the data was immature, particularly for OS. As a result, there is increased uncertainty in the PFS and OS results, and it is therefore unclear how confidently the long-term results associated with durvalumab can be predicted. For HRQoL endpoints, baseline estimates and the estimates at weeks 18 and 42 have a substantial amount of missing data. The endpoints were analyzed by a mixed model for repeated measures (MMRM) model which assumes that the missing data are missing at random, however given the nature of the disease and design of the trial the missing-at-random assumption is not appropriate. As patients are censored at disease progression or death; among other reasons, it is likely they are systematically different from patients who are included in the analysis and there is a likelihood of bias in the results.

Per the clinical experts, the inclusion and exclusion criteria were broadly representative of patients who would be candidates for durvalumab. However, the study is subject to some limitations impacting external validity. The results of patient screening were not available for the dMMR subgroup, and therefore the reasons for study failure and the distribution of screening failures between study arms is not known, so it is unclear whether there are systematic differences between the patients who failed screening and those who did not. Similarly, the exact causes of death in participants who died throughout the study was not reported, and it is therefore not known whether there are systematic differences between the patients who died and those who did not. Patients with Eastern Cooperative Oncology Group (ECOG) status greater than 1 were not included in the trial, and according to the clinical experts consulted for this review, these patients would likely be considered for treatment with durvalumab in clinical practice. Apart from this, the study did not assess whether other molecular subtypes (e.g., POLE, HER expression, p53 mutated) would have an impact on the results observed. The clinical experts noted that additional molecular classifications are usually undertaken in clinical practice and that there are a proportion of patients with dMMR cancer who do not respond to current ICI therapy, the reason for which is not always clear. Therefore, it is possible the same non-responder population may also exist for patients treated with durvalumab.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for

a clinically important effect (when a threshold was available) or to the null. For the PFS and OS outcomes, the target of the assessment was the presence or absence of an important effect based on thresholds provided by the clinical experts. For the HRQoL outcomes, the target of the assessment was the presence or absence of any effect based on a null threshold.

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- PFS (difference in the proportion of patients progression-free at 12 months and 18 months)
- OS (difference in the proportion of patients alive at 12 months and 18 months)
- EORTC QLQ-C30 (change from baseline to 18 weeks and change from baseline to 42 weeks)
- EORTC QLQ-EN24 (change from baseline to 18 weeks and change from baseline to 42 weeks)
- Notable harms: infusion-mediated adverse events and infusion-related reactions

Table 3: Summary of Findings for Durvalumab in Combination with Carboplatin and Paclitaxel Versus Placebo in Combination with Carboplatin and Paclitaxel for Patients with Primary Advanced or Recurrent dMMR Endometrial Cancer

Outcome and follow-up	Patients (studies), N	Absolute effects (95% CI)			Certainty	What happens
		SoC	SoC + Durvalumab	Difference		
Survival Outcomes						
Progression-free Survival [a]						
Proportion of patients who are progression free at 12 months Median follow-up: [redacted]	95 (1 RCT)	[redacted]	[redacted]	[redacted]	Low [d,e]	Durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab monotherapy, may result in an increase in the proportion of patients who are progression-free at 12 months when compared to carboplatin and paclitaxel.
Proportion of patients who are progression free at 18 months Median follow-up: [redacted]	95 (1 RCT)	[redacted]	[redacted]	[redacted]	Low [d,e]	Durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab monotherapy, may result in an increase in the proportion of patients who are progression-free at 18 months when compared to carboplatin and paclitaxel.
Overall Survival [a]						
Proportion of patients who are alive at 12 months Median follow-up: [redacted]	95 (1 RCT)	[redacted]	[redacted]	[redacted]	Low [f,g]	Durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab monotherapy, may result in an increase in the proportion of patients who are alive at 12 months when compared to carboplatin and paclitaxel.
Proportion of patients who are alive at 18 months Median follow-up: [redacted]	95 (1 RCT)	[redacted]	[redacted]	[redacted]	Low [f,g]	Durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab monotherapy, may result in an increase in the proportion of patients who are alive at 18 months when compared to carboplatin and paclitaxel.
Health-related Quality of Life [a]						
EORTC QLQ-C30 Global Health Status Score (100 [best] to 0 [worst]) [c]						
Change from baseline, points Follow-up: [redacted]	95 (1 RCT)	[redacted]	[redacted]	[redacted]	Very Low [h,i]	The evidence is very uncertain about the effect of durvalumab in combination with carboplatin and paclitaxel followed by durvalumab monotherapy on the change in EORTC QLQ-C30 Global Health

Outcome and follow-up	Patients (studies), N	Absolute effects (95% CI)			Certainty	What happens
		SoC	SoC + Durvalumab	Difference		
						Status score from baseline to 18 weeks, when compared with carboplatin and paclitaxel.
Change from baseline, points Follow-up: [redacted]	95 (1 RCT)	[redacted]	[redacted]	[redacted]	Low [i]	Durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab monotherapy, may result in an increase in EORTC QLQ-C30 Global Health Status score from baseline to 42 weeks when compared with carboplatin and paclitaxel.
EORTC QLQ-EN24 Pain in Back and Pelvis Score (100 [best] to 0 [worst]) [c]						
Change from baseline, points Follow-up: [redacted]	95 (1 RCT)	[redacted]	[redacted]	[redacted]	Very Low [h,i]	The evidence is very uncertain about the effect of durvalumab in combination with carboplatin and paclitaxel followed by durvalumab monotherapy on the change in EORTC QLQ-C30 Global Health Status score from baseline to 18 weeks, when compared with carboplatin and paclitaxel.
Change from baseline, points Follow-up: [redacted]	95 (1 RCT)	[redacted]	[redacted]	[redacted]	Very Low [h,i]	The evidence is very uncertain about the effect of durvalumab in combination with carboplatin and paclitaxel followed by durvalumab monotherapy on the change in EORTC QLQ-C30 Global Health Status score from baseline to 42 weeks, when compared with carboplatin and paclitaxel.
EORTC QLQ-EN24 Urological Symptoms Score (100 [best] to 0 [worst]) [c]						
Change from baseline, points Follow-up: [redacted]	95 (1 RCT)	[redacted]	[redacted]	[redacted]	Very Low [h,i]	The evidence is very uncertain about the effect of durvalumab in combination with carboplatin and paclitaxel followed by durvalumab monotherapy on the change in EORTC QLQ-C30 Global Health Status score from baseline to 18 weeks, when compared with carboplatin and paclitaxel.
Change from baseline, points Follow-up: [redacted]	95 (1 RCT)	[redacted]	[redacted]	[redacted]	Very Low [h,i]	The evidence is very uncertain about the effect of durvalumab in combination with carboplatin and paclitaxel followed by durvalumab monotherapy on the change in EORTC QLQ-C30 Global Health Status score from baseline to 42 weeks, when compared with carboplatin and paclitaxel.
Harms						
Proportion of patients with immune-mediated adverse events	95 (1 RCT)	[redacted]	[redacted]	[redacted]	Low [j]	Durvalumab in combination with carboplatin and paclitaxel, followed by durvalumab monotherapy, may result in an increase in the proportion of patients

Outcome and follow-up	Patients (studies), N	Absolute effects (95% CI)			Certainty	What happens
		SoC	SoC + Durvalumab	Difference		
Follow-up: [redacted]						with immune-mediated adverse events when compared with carboplatin and paclitaxel.
Proportion of patients with infusion reactions Follow-up: [redacted]	95 (1 RCT)	[redacted]	[redacted]	[redacted]	Very Low [j]	The evidence is very uncertain about the effect of durvalumab in combination with carboplatin and paclitaxel followed by durvalumab monotherapy on the proportion of patients with infusion reactions when compared with carboplatin and paclitaxel.

CAR = carboplatin; CI = confidence interval; dMMR = mismatch repair deficient; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EORTC QLQ-EN24 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Endometrial Cancer Module; NR = not reported; PAC = paclitaxel; RCT = randomized controlled trial; SoC = standard of care (carboplatin + paclitaxel for 6 cycles).

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a] In the trial, testing for this outcome in the dMMR subgroup was not adjusted for multiplicity. The results are considered supportive evidence.

[b] Follow-up presented as durvalumab + CAR-PAC versus placebo + CAR-PAC.

[c] Additional information was requested from the sponsor to obtain absolute differences and 95% confidence intervals. This information was not necessarily part of the sponsor's statistical plan and is considered exploratory evidence.

[d] Rated down 1 level for serious indirectness. Median PFS was not reached at the time of data cutoff and the study did not meet the primary endpoint in the dMMR subgroup at the time of data cutoff. This implies that the PFS data are immature and there is high uncertainty in the trends observed to date, therefore the confidence with which the results predict the outcome in the long term is not clear.

[e] Rated down 1 level for serious imprecision. Based on a non-trivial target certainty assessment with a minimal important difference threshold of 150 per 1000 at 12 months and 100 per 1000 at 18 months, provided by the clinical experts, the point estimate of the effect is larger than the threshold but the 95% confidence interval includes the possibility of a trivial effect as well as a non-trivial effect at 12 months, the number of PFS events in each arm was not provided by the sponsor, and the sample size is very small, raising concern for prognostic imbalance and potential overestimation of the true effect.

[f] Rated down 1 level for serious indirectness. Median OS was not reached at the time of data cutoff and the study did not meet the secondary endpoint in the dMMR subgroup at the time of data cutoff. This implies that the OS data are immature and there is high uncertainty in the trends observed to date, therefore the confidence with which the results predict the outcome in the long term is not clear.

[g] Rated down 1 level for serious imprecision. Based on a non-trivial target certainty assessment with a minimal important difference threshold of 100 per 1000 provided by the clinical experts, the point estimate of the effect is larger than the threshold but the 95% confidence interval includes the possibility of a trivial effect as well as a non-trivial effect, the number of OS events at 12 months and 18 months in each arm was not provided by the sponsor, and the sample size is very small, raising concern for prognostic imbalance and potential overestimation of the true effect.

[h] Rated down 2 levels for serious study limitations. A considerable number of patient data was missing at the timepoints, and based on the study design it is likely that the missingness is informative.

[i] Rated down 1 level for serious imprecision. Based on a non-null target certainty assessment, the confidence interval for the estimate contains the possibility of reduced HRQoL as well as improved HRQoL.

[j] Rated down 2 levels for very serious imprecision due to the small number of events in a small patient population, and the lack of specified follow-up duration.

Source: Details included in the table are from the sponsor's Summary of Clinical Evidence and additional information provided by the sponsor.

Long-Term Extension Studies

The submission did not contain any long-term extension studies.

Indirect Comparisons

The DUO-E trial included SoC chemotherapy (carboplatin plus paclitaxel) but did not include a comparison with dostarlimab, a relevant first-line comparator for patients with dMMR endometrial cancer, and information from indirect comparisons were included in the pharmacoeconomic model. Therefore, a review of the indirect evidence was undertaken. The body of indirect evidence consisted of 2 sponsor-submitted MAICs.

Description of Studies

A systematic literature review (SLR) was conducted with a focus on systemic anti-cancer treatments, and which excluded all other therapies. The patient population of interest were those newly diagnosed with stage III/IV disease or recurrent disease, who were either naïve to first-line therapy or had been treated with one prior line of chemotherapy. The submission did not provide details on the date when the SLR was conducted, the range of publication dates that were used in the search terms, or the search terms used.

An anchored MAIC was performed using a frequentist approach and Bucher methodology. The treatment effects for the two efficacy outcomes, PFS and OS, were reported as HR and associated 95% CI for SoC plus durvalumab vs. SoC plus dostarlimab, with an HR less than 1 favouring SoC plus durvalumab. For safety endpoints, odds ratios (ORs) were calculated for SoC plus durvalumab vs. SoC plus dostarlimab, with ORs less than 1 favouring SoC plus durvalumab. ORs were estimated from AE frequency data and the number of patients included in the safety analysis sets.

Efficacy Results

The submission did not provide a PRISMA diagram of results from the SLR but reported that the SLR identified two phase 3 double-blind placebo-controlled RCTs relevant to the indirect treatment comparison: DUO-E and RUBY Part 1. Differences were noted in the median duration of follow up as well as the molecular characteristics of patients; the primary analysis for the MAICs used data from the *post hoc* subgroup of DUO-E which contained only patients with dMMR and/or MSI-H cancer (and therefore could contain patients with MSI-H pMMR endometrial cancer), and the main analysis in RUBY Part 1 enrolled patients who had either dMMR or MSI-H tumours. The submission did not provide a breakdown of other baseline characteristics before and after matching. Of note, after the matching procedure, minor differences remained in the proportion of patients who were Black or African American (4.1% in DUO-E post-weighting, and 8.5% in RUBY Part 1), and the proportion of patients who were 65 years of age and older (52.1% in DUO-E post-weighting, and 49.2% in RUBY Part 1).

[redacted], weighted MAIC suggested there was insufficient evidence to detect a difference between durvalumab plus SoC and dostarlimab plus SoC (adjusted HR, [redacted] effective sample size [ESS] = [redacted]). Similarly, the results of OS using the anchored, unweighted MAIC suggested there was insufficient evidence to detect a difference between durvalumab plus SoC and dostarlimab plus SoC (adjusted HR, [redacted]).

Harms Results

The harms results from the anchored, unweighted MAIC suggested there was insufficient evidence to detect a difference between durvalumab plus SoC and dostarlimab plus SoC for AEs leading to discontinuation (adjusted OR, [redacted] and any SAEs (adjusted OR, [redacted]), however, for Grade 3 or greater AEs, durvalumab plus SoC was favoured over dostarlimab plus SoC (adjusted OR, 0[redacted]).

Critical Appraisal

The procedures as described for screening, data extraction, and quality assessment steps used were considered generally accepted methods. However, the date on which the SLR was undertaken is not provided, and it is not known whether the most recent publications on any relevant comparators would have been captured in the search. The submission did not provide results of the quality assessment, therefore the risk of bias in the studies is not known, however, since DUO-E and RUBY were phase III trials, the

risk of bias may be lower. For both MAIC analyses, data from a subgroup of RUBY Part 1 and subgroup from DUO-E were used (dMMR and/or MSI-H patients). In the case of the DUO-E trial, this resulted in the inclusion of some pMMR patients with MSI-H status in the subgroup used for the analysis, which is likely to somewhat bias the results as MMR status is a known treatment effect modifier. The 2 studies also differ considerably in the median follow-up time as the follow-up in RUBY Part 1 was longer than DUO-E (twice as long for PFS). This increases the likelihood of bias to possibly favour durvalumab as there was a shorter follow-up period over which events could accrue. Lastly, in both studies the subgroup arms had small sample sizes and a low number of events, which impacts the power of the analysis. In addition, other baseline characteristics not included in the matching were not reported, and therefore it is not known whether there are other potential sources of confounding in these characteristics. There were also no details reported on model fit, convergence, or model selection, which is another potential source of bias or uncertainty.

In addition to the limitations in the comparability of the studies and matching, there are additional limitations specific to each efficacy outcome. The MAIC for PFS was a weighted, anchored MAIC and the weighting procedure was largely able to balance the baseline characteristics reported. However, the ESS was approximately [redacted] smaller (N = [redacted]) than the number of patients pre-matching (N = [redacted]), suggesting that data from a smaller number of patients may be driving the results, which increases the imprecision. These results are subject to high uncertainty due to the limitations in the comparability of the studies as well as the limitations around the size of the ESS. The analyses undertaken for OS and harms, were unweighted, anchored MAICs which did not employ the propensity score measurement process to re-weight the results and was considered a naïve comparison of DUO-E and RUBY Part 1. For OS this was due to the small number of events observed (8 events for dMMR/MSI-H in SoC plus durvalumab and 7 events for SoC plus dostarlimab) which would generate potentially unstable results if re-weighted and compared using MAIC methodology. There were still notable differences between the two studies at baseline, and it is not known how the sample size in the 2 studies compares to the sample in the MAIC for OS. It is highly likely that not all possible effect modifiers were controlled for in the analysis for these outcomes. The limitations in the comparability of the studies and analysis method significantly undermines the validity of the results for OS and harms.

Studies Addressing Gaps in the Evidence from the Systematic Review

The submission did not contain any studies addressing gaps in the evidence from the systematic review.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis PSM
Target populations	Adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair deficient.
Treatments	Carboplatin and paclitaxel (CAR-PAC) plus durvalumab
Dose regimen	1,120 mg durvalumab in combination with platinum-based chemotherapy every 21 days for four to six cycles, followed by maintenance with 1,500 mg every 4 weeks as monotherapy
Submitted price	Durvalumab (50 mg/mL): $938.67 per 2.4 mL vial; $3,911.11 per 10 mL vial.
Submitted treatment cost	Chemotherapy Phase: $13,996 every 21 days (durvalumab = $8,671; carboplatin = $1,195; paclitaxel = $4,040) Maintenance Phase: $11,733 every 28 days.
Comparators	CAR-PAC alone CAR-PAC plus dostarlimab
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (37.4 years)
Key data sources	DUO-E trial, Sponsor submitted ITC

Component	Description
Submitted results	CAR-PAC plus durvalumab was dominated by CAR-PAC plus dostarlimab: CAR-PAC plus durvalumab is more costly by $231,661 and results in a 0.61 loss of incremental QALYs
Key limitations	• PFS and OS parameter estimates, as derived from the DUO-E trial and sponsor submitted ITC, were subject to a high degree of uncertainty due to issues related to imprecision, immature data, sample size, and power of the analyses. Because the model relies heavily on these parameters, the outputs of the model (estimates of costs and QALYs) are also subject to this uncertainty. • The model relied on an improper method to calculate the way patients move through a PSM. The decision to cap OS by the general population mortality risk is inappropriate. • The assumption that the RDI was less than 100% for durvalumab, but no other treatment, may underestimate the incremental treatment acquisition costs. • Time on treatment was longer than expected. Clinical experts suggested that most patients would discontinue treatment after 24 months, rather than the 48 months assumed by the sponsor. In addition, the sponsor did not consider a decline in the relative effectiveness of treatment over time (treatment waning). • The sponsor inappropriately assumed that the general population utilities from the United Kingdom were generalizable to Canada.
CDA-AMC reanalysis results	• The CDA-AMC base case reflected several changes to the sponsor's submission: the removal of the cap on OS; the removal of the age-adjusted utility values; and setting the RDI for durvalumab to 100%. • In the CDA-AMC base case, CAR-PAC plus durvalumab was dominated by CAR-PAC plus dostarlimab (incremental costs: $234,585; incremental QALYs lost: 0.68).

CAR = carboplatin; ITC = indirect treatment comparison; LY = life years; OS = overall survival; PAC = paclitaxel; PFS = progression-free survival; PSM = partitioned survival model; QALY = quality-adjusted life-year; RDI = relative dose intensity

Budget Impact

CDA-AMC identified the following key limitations from the sponsor's analysis: uncertainty in the proportion initiating subsequent therapy. No reanalysis was performed. CDA-AMC conducted three scenario analyses to assess the impact of changes to subsequent therapy assumptions. The first scenario explored how initiating subsequent therapy for 70% of patients in the durvalumab and dostarlimab arms and 80% in the CAR-PAC arm would affect the total budget impact. The second scenario examined the effect of increasing the subsequent market share for doxorubicin to 30%. The third scenario assessed the impact of a 47% price reduction in the value of durvalumab on the budget impact. In the submitted base case, the budget impact of reimbursing durvalumab with carboplatin and paclitaxel among dMMR patients was estimated to be $5,782,905 in Year 1, $10,330,546 in Year 2, and $11,916,217 in Year 3. The three-year net-budget impact was estimated to be $28,029,667. CADTH's scenario analyses demonstrated that an increase in the proportion of patients initiating subsequent treatment and a reduction in the unit price of durvalumab resulted in a decreased budget impact.

pERC Information

Members of the Committee:

Dr. Catherine Moltzan (Chair), Dr. Philip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney.

Meeting date: March 4, 2025

Regrets:

5 expert committee members did not attend.

Conflicts of interest:

None