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Reimbursement Recommendation

Pembrolizumab (Keytruda)

Indication: For the treatment of adult patients with primary advanced or recurrent endometrial carcinoma, in combination with carboplatin and paclitaxel and then continued as monotherapy

Sponsor: Merck Canada Inc.

Final Recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Keytruda?

Canada's Drug Agency (CDA-AMC) recommends that Keytruda be reimbursed by public drug plans for the treatment of primary advanced or recurrent endometrial carcinoma in combination with carboplatin and paclitaxel and then continued as monotherapy, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Keytruda should only be covered to treat adult patients with newly diagnosed stage III or IVA endometrial cancer with measurable disease, or stage IVB or recurrent endometrial cancer with or without measurable disease, or with metastatic or recurrent endometrial cancer of any histologic subtype except for carcinosarcoma.

What Are the Conditions for Reimbursement?

Keytruda should only be reimbursed in combination with carboplatin and paclitaxel and then continued as monotherapy if it is prescribed by clinicians with expertise in treating endometrial cancer and the cost of Keytruda is reduced.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that Keytruda plus chemotherapy followed by Keytruda monotherapy delayed progression in adults with advanced or recurrent endometrial cancer, compared to chemotherapy alone.
- Keytruda meets some of the needs that were identified by patients, as it is an additional treatment option that delays disease progression compared to chemotherapy alone.
- Based on the CDA-AMC assessment of the health economic evidence, Keytruda does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Keytruda is estimated to cost the public drug plans approximately $264 million over the next 3 years. At the submitted price, the incremental budget impact of Keytruda is expected to be greater than $40 million in all 3 years.

Additional Information

What Is Endometrial Cancer?

Endometrial cancer is a type of cancer that begins as a growth of the layer of cells that form the lining of the uterus, called the endometrium. In 2021,

Summary

it was estimated that 8,600 females in Canada would be diagnosed with endometrial cancer and 1,600 would die from it.

Unmet Needs in Endometrial Cancer

There is an unmet need for effective and accessible treatment options that control disease, prolong life, maintain quality of life, and have fewer side effects.

How Much Does Keytruda Cost?

Treatment with Keytruda is expected to cost approximately $8,800 per 21 days. The cost per patient of 21 days of treatment with Keytruda combined with carboplatin-paclitaxel ranges from $13,915 to $14,335 in the combination period.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that pembrolizumab in combination with carboplatin-paclitaxel and then continued as monotherapy be reimbursed for the treatment of adults with primary advanced or recurrent endometrial carcinoma, if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, randomized, double-blind trial (the NRG-GY018 trial) demonstrated that pembrolizumab plus carboplatin-paclitaxel followed by pembrolizumab monotherapy compared with placebo plus carboplatin-paclitaxel followed by placebo, in adults with proficient mismatch repair (pMMR) and deficient mismatch repair (dMMR) primary advanced or recurrent endometrial cancer, resulted in a clinically important increase in progression-free survival (PFS) at 12 months and 24 months, and may improve overall survival (OS) at 18 months and 36 months; however, conclusions regarding OS were limited because the data were not yet mature, and results for the all-comers population were post hoc and unadjusted for multiplicity.

At the efficacy and safety updated analyses (EUR-SUR), the median PFS was 16.8 months (95% confidence interval [CI], 13.1 to 19.8 months) in the pembrolizumab plus carboplatin-paclitaxel group versus 9.4 months (95% CI, 8.5 to 11.2 months) in the placebo plus carboplatin-paclitaxel group (hazard ratio [HR] = 0.62; 95% CI, 0.51 to 0.75; 1-sided P < 0.0001). Results for the pMMR group and dMMR group were consistent in direction with the overall population. The magnitude of effect was larger in the dMMR group than the pMMR group. At interim analysis 1 (IA1), the HR for PFS was 0.57 (95% CI, 0.44 to 0.74; 1-sided P < 0.001) in the pMMR population and 0.34 (95% CI, 0.22 to 0.53; 1-sided P < 0.001) in the dMMR population, both in favour of pembrolizumab plus carboplatin-paclitaxel. In a post hoc analysis, the HR in the all-comers population was 0.49 (95% CI, 0.39 to 0.62; 1-sided P < 0.0001) in favour of pembrolizumab plus carboplatin-paclitaxel.

At the EUR-SUR analysis, the median OS was not reached in the pembrolizumab plus carboplatin-paclitaxel group and was 32.2 months (95% CI, 27.4 to 42.7 months) in the placebo plus carboplatin-paclitaxel group (HR = 0.74; 95% CI, 0.57 to 0.97; 1-sided P = 0.0153).

The sponsor performed an anchored matching adjusted indirect comparison (MAIC) to estimate the comparative PFS benefits in patients with advanced or recurrent dMMR endometrial cancer informed by a systematic literature review that identified the randomized, double-blinded, placebo-controlled, phase III RUBY-I trial as the comparator trial to the NRG-GY018 trial. There was insufficient evidence to show a difference between pembrolizumab and dostarlimab (both plus carboplatin-paclitaxel) for PFS events based on the MAIC analysis (HR = 1.00; 95% CI, 0.48 to 2.08) for advanced or recurrent dMMR endometrial cancer.

Patients identified a need for effective and accessible treatment options that control disease, prolong life, maintain quality of life, and have fewer side effects. pERC concluded that pembrolizumab plus carboplatin-paclitaxel met some important needs identified by patients, as it offers an additional treatment option for

first-line therapy that can delay disease progression and may improve OS compared to chemotherapy alone. However, the efficacy and safety of pembrolizumab plus carboplatin and paclitaxel relative to other treatment comparators is uncertain.

Using the sponsor-submitted price for pembrolizumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for pembrolizumab plus carboplatin-paclitaxel was $57,344 per quality-adjusted life-year (QALY) gained compared with carboplatin plus paclitaxel. At this ICER, pembrolizumab is not cost-effective at a $50,000 per QALY gained willingness-to-pay threshold for adults with primary advanced or recurrent endometrial cancer. A price reduction is required for pembrolizumab to be considered cost-effective at a threshold of $50,000 per QALY gained.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with pembrolizumab plus carboplatin-paclitaxel should be reimbursed in adult patients who meet the following criteria: 1.1. newly diagnosed stage III or IVA disease according to RECIST version 1.1, for measurable disease, or stage IVB or recurrent endometrial cancer with or without measurable disease 1.2. metastatic or recurrent endometrial cancer of any histologic subtype except for carcinosarcoma.	Evidence from the NRG-GY018 trial demonstrated that treatment with pembrolizumab plus carboplatin-paclitaxel resulted in a clinical benefit in patients with these characteristics.	—
2. Patients must not have any of the following: 2.1. received prior treatment with an anti–PD-1, anti–PD-L1, or anti–CTLA-4 therapeutic antibody 2.2. received previous adjuvant chemotherapy, if chemotherapy-free interval was less than 6 months 2.3. known uncontrolled central nervous system metastases.	Criteria reflect the exclusion criteria in the NRG-GY018 trial.	—
3. Patients should have good performance status.	Patients with an ECOG performance status score of 0, 1, or 2 were included in the NRG-GY018 trial.	—

Reimbursement condition	Reason	Implementation guidance
Discontinuation		
4. Treatment should be discontinued upon the occurrence of any of the following: 4.1. clinical or radiological disease progression 4.2. unacceptable toxicity 4.3. up to 24 months of active treatment.	Patients in the NRG-GY018 trial discontinued treatment upon progression or unacceptable toxicity, consistent with clinical practice. Patients in the NRG-GY018 trial were treated with pembrolizumab every 3 weeks in combination with carboplatin-paclitaxel for 6 cycles, followed by pembrolizumab maintenance every 6 weeks for up to 14 cycles.	—
Prescribing		
5. Pembrolizumab plus carboplatin-paclitaxel should be prescribed by clinicians with expertise in advanced endometrial cancer; treatment should be supervised and delivered in institutions with expertise in systemic therapy delivery.	This will ensure that treatment is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
Pricing		
6. A reduction in price.	The ICER for pembrolizumab with carboplatin and paclitaxel is $57,334 per QALY gained when compared with carboplatin plus paclitaxel. A price reduction of approximately 10% would be required for pembrolizumab with carboplatin and paclitaxel to achieve an ICER of $50,000 per QALY gained compared to carboplatin plus paclitaxel.	—
Feasibility of adoption		
7. The economic feasibility of adoption of pembrolizumab must be addressed	At the submitted price, the incremental budget impact of pembrolizumab is expected to be greater than $40 million in all 3 years.	—

ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; RECIST = Response Evaluation Criteria in Solid Tumours.

Discussion Points

- **Input from patient group and clinicians**: pERC highlighted the input from the patient group and clinicians noting that advanced endometrial cancer is an aggressive disease with a poor prognosis. pERC acknowledged that there is an unmet need for effective and safe therapy options in the requested patient population, particularly for patients with pMMR disease. Results for PFS for the pMMR group and dMMR group were consistent in direction with the overall population. The magnitude of effect was larger in the dMMR group than the pMMR group. Patients would be eligible

for pembrolizumab plus carboplatin-paclitaxel regardless of having pMMR versus dMMR disease, as benefit was demonstrated for both groups.

- **Side effects:** pERC acknowledged that patients expressed a need for treatments that have fewer side effects. Although a higher proportion of serious adverse events (SAEs) was reported in patients taking pembrolizumab plus carboplatin-paclitaxel than in those taking placebo plus carboplatin-paclitaxel, pERC considered the side effects to be manageable, given that treatment is expected to be prescribed and overseen by clinicians who are experienced in treating patients with endometrial cancer. pERC agreed with the clinical experts that the safety profile of pembrolizumab plus carboplatin-paclitaxel appeared consistent with expectations about immunotherapy treatment and the known safety profiles of pembrolizumab and chemotherapy.
- **Health-related quality of life (HRQoL):** pERC noted that patients and clinicians highlighted improvement in maintaining quality of life as an important outcome and treatment goal for patients with advanced or recurrent endometrial cancer. However, pERC was unable to draw definitive conclusions regarding the effects of pembrolizumab plus carboplatin-paclitaxel compared to placebo plus carboplatin-paclitaxel on HRQoL, due to an absence of HRQoL data in the all-comers population and the dMMR group. In the pMMR population, at week 18, both treatment groups had slight decreases (worsening) in Functional Assessment of Cancer Therapy Endometrial Trial Outcome Index (FACT-En TOI) score. The between-group difference in least squares (LS) mean change from baseline was −3.17 points (95% CI, −5.48 to −0.85 points; P = 0.0075), favouring placebo plus carboplatin-paclitaxel.
- **Unmet need and choice of treatment among other options**: pERC discussed unmet need and other treatment options for advanced or recurrent endometrial cancer (including dostarlimab plus carboplatin and paclitaxel, with dostarlimab maintenance; and durvalumab plus carboplatin and paclitaxel, with durvalumab and olaparib maintenance), as well as emerging agents for the treatment of primary advanced or recurrent endometrial cancer — such as CDK4/6 inhibitors, including palbociclib, abemaciclib, and ribociclib — that are currently being investigated. pERC discussed the choice of treatment options. The clinical experts noted that, in the absence of comparative efficacy and safety data to guide treatment choice between currently available treatment options and the generally similar safety profile, factors such as accessibility, oncologist comfort, and patient preference for treatment duration may influence treatment options.
- **Total duration of treatment**: pERC discussed differences with other comparators in this space, including dostarlimab and durvalumab, with respect to total duration of treatment. Dostarlimab is administered for up to 3 years, compared to pembrolizumab (which is administered for up to 2 years) and durvalumab (which is administered until disease progression). The clinical experts noted that these treatments are considered to have similar safety profiles, so factors such as accessibility, oncologist availability or system capacity, and patient preference for treatment duration may influence treatment options. pERC was unable to comment on the optimal length of maintenance therapy, as the committee reviewed no data to support it. pERC agreed that evidence from well-designed clinical trials in the future would help establish an optimal duration for maintenance therapy in this setting.

- **Testing procedure considerations:** pERC noted that mismatch repair (MMR) testing is currently performed as the standard of care for patients with endometrial cancer in Canada, and acknowledged that evaluating MMR status before the initiation of pembrolizumab would not 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.
- **Cost-effectiveness:** The estimated price reduction required to achieve cost-effectiveness at a threshold of $50,000 per QALY gained is highly uncertain. The results of the cost-effectiveness analysis comparing pembrolizumab plus carboplatin-paclitaxel to carboplatin plus paclitaxel were heavily influenced by the modelled comparative effectiveness in which the majority of the incremental clinical benefits were derived in the period beyond observed trial data. The survival models chosen by the sponsor overestimated patient survival compared to clinical expectations. Given the model structure, OS could not be modified to reflect more realistic expectations of long-term survival, and this introduces uncertainty to the incremental cost-effectiveness estimates of pembrolizumab. pERC further noted that, while dostarlimab plus carboplatin-paclitaxel is a relevant comparator in the dMMR subgroup, the cost-effectiveness of pembrolizumab compared to dostarlimab, both in combination with carboplatin and paclitaxel, remains uncertain. Different approaches were used to inform time on treatment for each regimen and, as this could not be addressed in reanalysis, the drug acquisition cost for dostarlimab is likely to be overestimated in the base-case analyses by both the sponsor and CDA-AMC.

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.[2] In 2024, the Canadian Cancer Society estimated that 8,600 females in Canada would be diagnosed with endometrial cancer, and 1,600 would die from it.[3] Endometrial cancer primarily affects females who are postmenopausal, with an average age of diagnosis of 60 years. Endometrial cancer is staged using the International Federation of Gynecology and Obstetrics (FIGO) system: stage I (tumour confined to the uterus), stage II (cervical stroma invasion), stage III (regional spread), and stage IV (spread to bladder, bowel, or distant organs). In Canada, the overall 5-year net survival for uterine cancer is 82%. According to the American Cancer Society, the 5-year relative survival by stage at diagnosis for the 2014 to 2020 time period was 81% for all stages, 19% for distant metastasis, 95% for localized, and 70% for regional.

Advanced-stage endometrial cancer is defined as stage III or IV, in which the cancer extends beyond the uterus, while recurrent endometrial cancer refers to its return following primary treatment. Recurrence can occur in various locations, commonly including the abdominal cavity, lymph nodes, lungs, and vagina. Both primary advanced and recurrent endometrial cancer are associated with numerous debilitating symptoms that significantly impair physical functioning and HRQoL. Key symptoms include abnormal vaginal bleeding, which may be periodic or continuous. Additional manifestations encompass pelvic or lower back pain, the presence of a palpable mass in the lower abdomen, and unintentional weight loss. Patients often

experience abdominal distension, early satiety, alterations in bowel or bladder habits, bowel obstruction, and dyspareunia. The debilitating nature of the disease has a profound impact on daily activities, confidence, and self-esteem. Symptoms such as menopausal-like effects, sexual dysfunction, anxiety, and depression, and long-term side effects of chemotherapy and radiotherapy, can further diminish HRQoL. 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.

Pembrolizumab has been approved by Health Canada for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma, in combination with carboplatin and paclitaxel and then continued as monotherapy. Pembrolizumab is a monoclonal antibody and immune checkpoint inhibitor. It is available as a 100 mg/4 mL vial, IV injection, and the dosage recommended in the product monograph is 200 mg of pembrolizumab administered intravenously in a 30-minute infusion every 3 weeks in combination with carboplatin-paclitaxel for 6 cycles, followed by 400 mg of pembrolizumab maintenance administered intravenously in a 30-minute infusion every 6 weeks for up to 14 cycles.

Sources of Information Used by the Committee

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

- a review of 1 phase III, randomized controlled trial in patients with advanced or recurrent endometrial cancer
- patients' perspectives gathered by 1 patient group
- input from public drug plans that participate in the Reimbursement Review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with endometrial cancer
- input from 1 clinician group, the Ontario Health Cancer Care Ontario (OH-CCO) Gynecologic Cancer Drug Advisory Committee
- 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 Colorectal Cancer Resource & Action Network (CCRAN), submitted input on pembrolizumab for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma, in collaboration with the Canadian Cancer Survivor Network (CCSN) and HPV Global Action.

The patients interviewed in the input reported the diagnosis of endometrial cancer being very distressing and triggering intense emotions, such as extreme fear, stress, anxiety, and shock. Caregivers also expressed similar issues they encountered as a caregivers to patients with endometrial cancer, such as emotional

drain, anxiety or worry, inability to plan ahead, feeling isolated, and feelings of helplessness. Respondents in this input further noted that pain management was the immediate concern to be controlled for patients experiencing pain. However, longevity and robust treatment options were prioritized by patients not experiencing acute pain. Respondents in the endometrial cancer survey reported using various treatment options, including radiation therapy, surgical resection, targeted therapy, hormonal therapy, immunotherapy, chemotherapy, and complementary medicines. Common side effects of these treatments experienced by patients in the input included neuropathy, fatigue, dryness, itching, tightening and/or burning in the vagina, changes in sexual functioning, fluid retention, nausea, constipation, and “chemo brain.” The input highlighted that the effects of treatment often impact sexual health and functioning, which is frequently overlooked in clinical care and research.

In terms of improved outcomes, patients in this input expressed their desire to see a decrease in time from drug development to access, along with an increase in the availability of additional lines of therapy, the development of treatments given by oral administration, improved access to targeted therapeutics rather than cytotoxic chemotherapeutics, increased funding for endometrial cancer drug research, and availability of tumour-agnostic access to biomarker-informed therapeutics. Lastly, the patient input highlighted the significant and urgent unmet need for additional precision therapeutics in the management of advanced or recurrent endometrial cancer in Canada, particularly for the patient population with microsatellite stable (MSS) or pMMR endometrial cancer.

Regarding experience with the drug under review, all 6 patients noted experiencing a robust response that was evidenced radiographically, biochemically, and/or clinically. Side effects reported by patients while on pembrolizumab monotherapy included hyperthyroidism, hypothyroidism, joint pain, fatigue, diarrhea, skin changes, and worsening allergies or asthma. Patients in the input reported these side effects to be quite tolerable and manageable, and perceived a notable difference when moving from the combination therapy to the monotherapy.

Clinician Input

Input From Clinical Experts Consulted for This Review

All CDA-AMC review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of primary advanced or recurrent endometrial cancer.

The clinical experts indicated that the treatment goals for patients with primary advanced or recurrent endometrial cancer is to control metastatic or recurrent disease, prolong PFS, prolong OS, and improve patients' symptoms and quality of life. The experts noted that initial therapy after diagnosis can often involve a combination of surgery, systemic therapies (carboplatin with paclitaxel chemotherapy with or without

immunotherapy or targeted therapy), hormonal therapy, and radiation therapy. They noted that, recently, dostarlimab has been approved in combination with chemotherapy for patients with dMMR tumours. The CDA-AMC clinical experts indicated that MMR-deficient cancers make up only 20% of endometrial cancers, with 80% being pMMR. For patients with dMMR endometrial cancer, there is an unmet need for better therapies. Currently available combination treatments are associated with toxicity. As a result, many patients are not well enough to move to a second-line chemotherapy. According to the clinical experts, there are currently no treatments available with limited toxicity. The clinical experts noted that pembrolizumab in addition to platinum-based chemotherapy would be used in the first-line setting, in combination with carboplatin and paclitaxel, for all patients with primary advanced recurrent endometrial cancer, including those with dMMR and pMMR mutations. The clinical experts indicated that, based on available evidence, pembrolizumab is currently a suitable choice for the dMMR population but its efficacy in the pMMR population might be more modest.

The clinical experts agreed that the patients best suited for treatment with pembrolizumab plus carboplatin-paclitaxel would be those with advanced or recurrent endometrial cancer. In their opinion, because carcinosarcomas were excluded from the pivotal study, their response to pembrolizumab is uncertain. The experts highlighted that patients who would be suitable for this treatment can be identified by physical examination and diagnostic tools such as CT scans, and also if they have had previous surgery for endometrial cancer. Clinicians consulted for this report noted that MMR status testing is a routine investigation for patients with endometrial cancer. Having these results can guide the selection of the most appropriate treatment based on available options. The clinical experts indicated that, in clinical practice, physical examination and diagnostic imaging (primarily CT scans), are used to determine progression on treatment. They noted that treatment response should be assessed every 3 to 4 cycles with combination therapy and less frequently with monotherapy.

The experts agreed that a clinically meaningful response includes reduced tumour size on physical examination and CT scan imaging. The clinical experts indicated that treatment with pembrolizumab plus carboplatin-paclitaxel should be discontinued if patients have progressive disease, as suggested by the presence of symptoms and findings from physical examination or imaging. In addition, treatment should be discontinued if there are intolerable toxicities (e.g., hematologic, neuropathic, renal, or organ-specific grade 4 immune-related toxicities). The clinical experts indicated that patients should be assessed regarding appropriateness of pembrolizumab in a specialty clinic with either a gynecologic oncologist or a medical oncologist involved in the initial decision-making. Once the patient has been assessed and a decision is made regarding treatment, it would be appropriate for patients to receive treatment in a community setting and be managed by clinicians with experience in the management of patients undergoing immunotherapy.

Clinician Group Input

One input from the OH-CCO Gynecologic Cancer Drug Advisory Committee was provided for this review. A total of 5 clinicians provided input. The clinician group highlighted that the treatment goals for patients include prolonging survival, delaying disease progression, reducing symptoms, improving HRQoL, and curing the disease whenever possible. Regarding unmet needs, the group emphasized a need for new

therapy for the pMMR population to improve oncologic outcomes and prolong life, indicating no availability of treatment for this patient population other than carboplatin-paclitaxel, which they said fails to produce a durable response.

The clinician group suggested that pembrolizumab be used as a first-line option for patients with chemotherapy, followed by maintenance, or in the platinum-sensitive recurrent setting. The group specified that pembrolizumab may be used in a similar setting to dostarlimab and durvalumab. The group added that patients least suited for pembrolizumab would be those with a contraindication to immunotherapy or poor Eastern Cooperative Oncology Group (ECOG) performance status. The clinician group noted that treatment response is assessed through a combination of imaging and clinical examination, as per physician discretion. The clinician group indicated that treatment may be withheld due to disease progression and intolerable toxicity. The group stated that the treatment regimen should be administered in outpatient settings under the care of a physician who can give systemic therapy.

Drug Program Input

Input was obtained from the drug programs that participate in the Reimbursement Review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for pembrolizumab plus carboplatin-paclitaxel:

- considerations for initiation of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues.

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

Drug program implementation questions	Clinical expert response
Relevant comparators	
Comparator in NRG-GY018 clinical trial: Placebo At the time of this input, dostarlimab plus carboplatin-paclitaxel for MSI-H and dMMR is under funding consideration by some jurisdictions, while dostarlimab plus carboplatin-paclitaxel for the all-comers population and durvalumab plus chemotherapy with or without olaparib are also under CDA-AMC review. How does pembrolizumab compare against dostarlimab- or durvalumab-containing regimens? MSI-H and dMMR population: Dostarlimab plus chemotherapy • Can patients switch between treatments for toxicity?	The clinical experts indicated that, in their experience, both treatments are generally well tolerated and have similar toxicity profiles. They mentioned that, although they are not aware of any evidence currently available to address this question directly, switching between these treatments due to intolerable toxicity should be possible. pERC clarified that switching between agents would be primarily for infusion reactions, as immune adverse reactions would happen regardless of the agent used, and switching between agents is unlikely to lead to resolution of toxicity. pERC also noted that durvalumab plus chemotherapy and olaparib is not currently a treatment option, as the Reimbursement Review was suspended by the sponsor.

Drug program implementation questions	Clinical expert response
Considerations for initiation of therapy	
Clinical trial eligibility included patients who had received previous adjuvant chemotherapy, if the chemotherapy-free interval was at least 12 months. Would it be appropriate to fund treatment for patients with a chemotherapy-free interval of less than 12 months?	pERC noted that the committee did not review any evidence for using pembrolizumab in patients with a chemotherapy-free interval of less than 12 months. However, the clinical experts stated that dostarlimab was used in patients with a chemotherapy-free interval of at least 6 months in the RUBY trial. Therefore, the clinical experts agreed that it could be reasonable for pembrolizumab to be used in patients with a chemotherapy-free interval of at least 6 months, especially in patients with dMMR tumours. pERC agreed with the clinical experts that it may be reasonable to treat patients who received prior adjuvant chemotherapy if there was a disease-free interval of 6 months or greater after completion of adjuvant therapy, similar to the criteria used for dostarlimab.
If pembrolizumab is discontinued for reasons other than disease progression or intolerability after the initial 24 months of treatment, are patients eligible for an additional 12 months of treatment if disease recurs?	pERC agreed with the clinical experts that it would be reasonable to readminister pembrolizumab at the time of recurrence (up to 17 additional doses every 3 weeks, or 12 months of treatment) at the discretion of the treating physician for patients who have discontinued pembrolizumab with the completion of 2 years of treatment and before any disease progression, or after achieving a complete response. The clinical experts indicated that although they are not aware of any evidence to address this question, it would be reasonable to have a 12-month or 24-month treatment-free interval before a patient could be eligible for re-treatment, if the disease were to recur.
Consider alignment with dostarlimab for dMMR patient population.	This is a comment from the drug plans to inform pERC deliberations.
Considerations for prescribing of therapy	
Jurisdictions will likely use weight-based dosing (2 mg/kg every 3 weeks to a maximum of 200 mg), similar to other indications. Dosing every 6 weeks was not used in the clinical trial. Would it be a reasonable option when funded?	pERC agreed with the clinical experts that there is no difference between dosing every 3 weeks and every 6 weeks in terms of efficacy. It was noted that pembrolizumab 6-week dosing was permitted and used during maintenance in the NRG-GY018 trial. The clinical experts were not aware of any data regarding endometrial cancer but mentioned that the efficacy of pembrolizumab plus chemotherapy administered every 6 weeks was similar to that of therapy given every 3 weeks in the treatment of other cancers.
Can alternative chemotherapy regimens be used in combination with pembrolizumab if there is a contraindication to platinum chemotherapy? If the patient is not able to tolerate platinum-containing chemotherapy, can treatment be continued with pembrolizumab monotherapy?	The clinical experts indicated that the standard chemotherapy in combination with pembrolizumab is platinum-based therapy. Carboplatin and cisplatin can be used interchangeably. However, as the committee did not review data, they could not comment on other alternative chemotherapy regimens. The clinical experts indicated that they were not aware of any available data on what alternative therapies could be used in combination with pembrolizumab for this indication for patients with severe allergies to platinum regimens. pERC agreed with the clinical experts that if patients cannot tolerate pembrolizumab plus platinum-based therapy, it is

Drug program implementation questions	Clinical expert response
	reasonable to use pembrolizumab monotherapy, especially in patients with dMMR tumours.
Generalizability	
Can patients currently on alternative treatment regimens (e.g., dostarlimab) but who otherwise meet eligibility criteria be eligible to switch to pembrolizumab plus chemotherapy?	pERC agreed with the clinical experts that it would be reasonable for patients to be able to switch treatment regimens on a time-limited basis if pembrolizumab were to be reimbursed. However, the clinical experts indicated that they generally would not switch patients to pembrolizumab if they are doing well on their current treatment regimen. The clinical experts noted that the duration of therapy and patients' preferences (i.e., shorter therapy and cost-related considerations) may be factors that could influence the decision to switch treatments.
Funding algorithm	
Under what clinical circumstances would pembrolizumab plus chemotherapy be preferred over dostarlimab plus chemotherapy or durvalumab plus chemotherapy with or without olaparib, and vice versa?	The clinical experts indicated that, based on available evidence and the absence of direct comparisons, they do not currently perceive any meaningful differences between these treatments. The clinical experts noted that there may be individual preferences based on the duration of therapy, which differs between the treatment options. pERC further noted that the sponsor-submitted ITC was insufficient to show a difference between pembrolizumab and dostarlimab (both with carboplatin-paclitaxel) for PFS. pERC also noted that durvalumab plus carboplatin-paclitaxel and olaparib is not currently funded by public drug plans, as the Reimbursement Review was suspended.

CDA-AMC = Canada's Drug Agency; dMMR = deficient mismatch repair; ITC = indirect treatment comparison; PFS = progression-free survival; pMMR = proficient mismatch repair; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; MSI-H = microsatellite instability-high

Clinical Evidence

Systematic Review

Description of Studies

One trial, the NRG-GY018 trial (N = 819), was included in the systematic review conducted by the sponsor. The NRG-GY018 trial is an ongoing phase III, randomized, multicentre, double-blind, placebo-controlled, parallel group interventional study that included female adult patients with newly diagnosed, measurable stage III or stage IVA endometrial cancer, or stage IVB or recurrent endometrial cancer. The study was designed essentially as 2 parallel trials to assess efficacy and safety among patients who had pMMR and dMMR tumours, separately. Enrolled patients did not receive prior chemotherapy unless it was adjuvant chemotherapy that had been completed at least 12 months before the study. The main objectives of the NRG-GY018 trial were to evaluate the efficacy and safety of pembrolizumab plus carboplatin-paclitaxel followed by continued pembrolizumab monotherapy compared with placebo plus carboplatin-paclitaxel followed by continued placebo in patients with advanced-stage (measurable stage III or IVA), stage IVB, or recurrent endometrial cancer. The primary outcome was PFS. The additional outcomes of interest to this

review were OS and FACT-En TOI (secondary outcomes), and immune-mediated adverse reactions. PFS, OS, and immune-mediated adverse reaction outcomes were analyzed in pMMR and dMMR populations at the preplanned IA1, with data cut-offs of December 6, 2022, and December 16, 2022, respectively. Following positive PFS results in both populations at IA1, the trial was unblinded. The sponsor provided a post hoc analysis (the EUR-SUR analysis), which pooled the data from both MMR populations to provide findings for the all-comers population (as well as the populations with dMMR and pMMR tumours, separately) with approximately 9 months of additional follow-up (data cut-off of August 18, 2023).

The median age of the participants was approximately 66 years (range, 29 to 94 years), and more than half of the patients were aged 65 years or older. Most patients had an ECOG performance status score of 0 (approximately 66%), indicating good overall performance status; endometroid histology at diagnosis (approximately 59%); recurrent (57%) or primary stage IV (41%) disease status; FIGO stage III or IV at diagnosis (approximately 52%); central MMR status of pMMR (72%); and had not received prior radiotherapy (approximately 58%) or chemotherapy (approximately 80%).

This report focuses on outcomes based on the results from the EUR-SUR analyses, which will serve as the efficacy outcomes for the all-comers population and align with the reimbursement request. Results for the dMMR and pMMR populations are provided for additional context. Data for HRQoL end points, which are not reported in EUR-SUR Clinical Study Reports, will be presented based on the IA1 analysis for the pMMR population (not yet tested in the dMMR population).

Efficacy Results

The outcomes relevant to the CDA-AMC review included the primary outcome of PFS per investigator assessment and secondary outcomes of OS and HRQoL measured via FACT-En TOI. At the IA1 data cut-off, the median follow-up duration was 13.3 months in the pembrolizumab plus carboplatin-paclitaxel group and 13.7 months in the placebo plus carboplatin-paclitaxel group. At the data cut-off on August 18, 2023 (EUR-SUR analysis), the median follow-up duration was 16.7 months in the pembrolizumab plus carboplatin-paclitaxel group and 16.0 months in the placebo plus carboplatin-paclitaxel group, in the all-comers cohort.

PFS (All-Comers Population)

Interim Analysis 1

The success criterion for the primary PFS hypothesis was met for both the group with pMMR tumours (1-sided $P < 0.001162$) and the group with dMMR tumours (1-sided $P < 0.002074$) at IA1. The HR was 0.57 (95% CI, 0.44 to 0.74; 1-sided $P < 0.001$) in the pMMR population and 0.34 (95% CI, 0.22 to 0.53; 1-sided $P < 0.001$) in the dMMR population, both in favour of pembrolizumab plus carboplatin-paclitaxel. In a post hoc analysis for this submission, the HR in the all-comers population was 0.49 (95% CI, 0.39 to 0.62; 1-sided $P < 0.0001$) in favour of pembrolizumab plus carboplatin-paclitaxel.

EUR-SUR Analysis

PFS events were reported for 199 patients (48.8%) in the pembrolizumab plus carboplatin-paclitaxel group and 257 patients (62.5%) in the placebo plus carboplatin-paclitaxel group. The median PFS was 16.8 months (95% CI, 13.1 to 19.8 months) in the pembrolizumab plus carboplatin-paclitaxel group versus 9.4

months (95% CI, 8.5 to 11.2 months) in the placebo plus carboplatin-paclitaxel group. The between-group HR was 0.62 (95% CI, 0.51 to 0.75) favouring pembrolizumab plus carboplatin-paclitaxel (1-sided P < 0.0001). The Kaplan-Meier (KM)-estimated probability of being progression free was 55.9% (95% CI, 50.7% to 60.8%) versus 38.5% (95% CI, 33.4% to 43.6%) at 12 months (risk difference [RD] = 17.4%; 95% CI, 10.2% to 24.6%), and 43.2% (95% CI, 37.4% to 48.8%) versus 24.9% (95% CI, 19.6% to 30.5%) at 24 months (RD = 18.3%; 95% CI, 10.4% to 26.2%), in the pembrolizumab plus carboplatin-paclitaxel group and the placebo plus carboplatin-paclitaxel group, respectively. Results for the pMMR group and dMMR group were consistent in direction with the overall population. The magnitude of effect was larger in the dMMR group than the pMMR group. Sensitivity analyses in each MMR group showed similar results to the primary analysis.

Point estimates of most subgroup analyses were aligned in direction with the overall population. Tests of treatment-by-subgroup interaction were significant at a 0.05 alpha level for prior chemotherapy, prior radiation therapy, disease status, and MMR status at baseline. The magnitude of benefit was smaller for patients with prior chemotherapy (versus no prior chemotherapy), prior radiation therapy (versus no prior radiation therapy), recurrent or persistent disease (versus primary disease), and pMMR status (versus dMMR).

OS (All-Comers Population)

Interim Analysis 1

The information fraction was approximately 27% in the pMMR population and 18% in the dMMR population at IA1. The HR was 0.79 (95% CI, 0.53 to 1.17; 1-sided P = 0.1157) in the pMMR population and 0.55 (95% CI, 0.25 to 1.19; 1-sided P = 0.0617) in the dMMR population. Sensitivity analyses were generally consistent with the primary analyses. Results for the all-comers population were not reported.

EUR-SUR Analysis

At the time of the EUR-SUR analysis, the information fraction was approximately 46% in the pMMR population and 29% in the dMMR population. Overall, 94 patients (23.0%) in the pembrolizumab plus carboplatin-paclitaxel group died, while 119 patients (29.0%) in the placebo plus carboplatin-paclitaxel group died. The median OS was not reached in the pembrolizumab plus carboplatin-paclitaxel group, and was 32.2 months (95% CI, 27.4 to 42.7 months) in the placebo plus carboplatin-paclitaxel group. The HR was 0.74 (95% CI, 0.57 to 0.97; 1-sided P = 0.0153) favouring pembrolizumab plus carboplatin-paclitaxel. The KM-estimated probability of OS was 75.8 (95% CI, 70.3 to 80.4) versus 69.2 (95% CI, 63.4 to 74.2) (RD = 6.6%; 95% CI, −0.8 to 14.0) at 18 months, and 59.8% (95% CI, 50.9 to 67.6) versus 45.9% (95% CI, 34.6 to 56.5) (RD = 13.9%; 95% CI, 0.1 to 27.7) at 36 months, in the pembrolizumab plus carboplatin-paclitaxel versus placebo plus carboplatin-paclitaxel groups, respectively. The sponsor did not provide sensitivity analyses for the all-comers population at the EUR-SUR analysis. Results for the dMMR and pMMR populations were aligned in direction with the all-comers population, but statistical significance was not reached in their group. Point estimates suggested a somewhat larger magnitude of effect in the dMMR population, but CIs overlapped. Sensitivity analyses for each MMR group showed similar results to the primary analysis.

Point estimates for most subgroup analyses were aligned in direction with the overall population. Tests of treatment-by-subgroup interaction were significant at a 0.05 alpha level for prior chemotherapy, prior radiation therapy, and measurable disease at baseline. The magnitude of OS benefit was smaller for patients with prior chemotherapy (versus no prior chemotherapy), prior radiation therapy (versus no prior radiation therapy), and no measurable disease at baseline (versus measurable disease at baseline).

HRQoL by FACT-En TOI Score (pMMR Population)

The sponsor did not report the patient-reported outcomes including FACT-En TOI scores in the updated (EUR-SUR) analysis. Therefore, this section is from the IA1 analysis. Baseline FACT-En TOI scores in the pMMR population were similar for both treatment groups. At week 18, both treatment groups had slight decreases (worsening) in FACT-En TOI score. The between-group difference in LS mean change from baseline was −3.17 points (95% CI, −5.48 to −0.85 points; P = 0.0075) favouring placebo plus carboplatin-paclitaxel. No results were available for the all-comers population (or for the dMMR population).

Harms Results

The sponsor reported that 775 patients experienced at least 1 adverse event (AE): 99.2% in the pembrolizumab plus carboplatin-paclitaxel arm and 99.7% in the placebo plus carboplatin-paclitaxel arm. Overall, similar frequencies of AEs, grade 3 or 4 AEs, and SAEs were observed in the dMMR and pMMR cohorts. The most frequent AEs in both arms were fatigue (70.3% versus 63.9%), anemia (59.8% versus 56.7%), alopecia (55% versus 57.5%), nausea (51.2% versus 45.9%), constipation (47.1% versus 41.8%), and diarrhea (42.2% versus 35.6%) for pembrolizumab plus carboplatin-paclitaxel versus placebo plus carboplatin-paclitaxel, respectively. Grade 3 or higher AEs were reported in 21.3% of patients in the pembrolizumab plus carboplatin-paclitaxel group, and in 18.5% of patients in the placebo plus carboplatin-paclitaxel group. Exposure-adjusted event rates of frequently reported grade 3 to 5 AEs (incidence ≥ 5%) remained generally low and similar between the 2 treatment groups (877 per 100 patient-months in the pembrolizumab plus carboplatin-paclitaxel group, versus 511 per 100 patient-months in the placebo plus carboplatin-paclitaxel group). The most frequently reported grade 3 or higher AEs in the pembrolizumab plus carboplatin-paclitaxel group and placebo plus carboplatin-paclitaxel group were anemia (16.9% versus 11.6) and decreased neutrophil count (14.1% versus 14.4%).

In addition, 237 patients experienced at least 1 SAE: 39.6% in the pembrolizumab plus carboplatin-paclitaxel group and 21.1% in the placebo plus carboplatin-paclitaxel group. The most frequently reported SAEs in the pembrolizumab plus carboplatin-paclitaxel group and placebo plus carboplatin-paclitaxel group were anemia (4.1% versus 4.1%), febrile neutropenia (2.8% versus 1.3%), urinary tract infection (2.6% versus 1.5%), dyspnea (2.3% versus 0%), hyperglycemia (2.3% versus 0%), pulmonary embolism (2.3% versus 2.1%), and sepsis (2% versus 1.3%). Anemia (56.7%) and pulmonary embolism (2.1%) were the most frequent SAEs reported in the placebo plus carboplatin-paclitaxel group. Adverse events of special interest (AESIs) were reported as immune-mediated events and infusion. The overall pattern of AESIs associated with the combination treatment of pembrolizumab plus carboplatin-paclitaxel is similar to the AESIs identified in IA1, with no meaningful changes in AESIs. AESIs were reported as 39.6% in the pembrolizumab plus carboplatin-paclitaxel group and 26.3% in the placebo plus carboplatin-paclitaxel group.

Critical Appraisal

- Randomization and allocation concealment procedures were appropriate. Key baseline characteristics of patients including disease severity appeared balanced between groups (for the all-comers population, and both the pMMR and dMMR populations).
- The NRG-GY018 analyses were planned separately for the pMMR and dMMR populations. The success criterion for PFS was met in both groups at IA1. The post hoc EUR-SUR analysis had a longer follow-up and combined the results of the pMMR and dMMR populations. The post hoc EUR-SUR analyses were not adjusted for multiplicity but produced similar PFS results to the protocol-defined IA1 analyses in the pMMR and dMMR populations. Sensitivity analyses supported the robustness of the PFS analyses.
- Participants, study personnel, and the investigator were blinded until the database lock at IA1. Thereafter, the study became unblinded and a substantial number of patients in the placebo plus carboplatin-paclitaxel group discontinued the protocol treatment to receive anti–PD-1 and anti–PD-L1 therapies (primarily pembrolizumab with or without lenvatinib) before progression. As a result, there is a risk of bias in the PFS and OS results from the EUR-SUR analysis that is directed toward the null.
- There was a small information fraction for OS. In the post hoc EUR-SUR analysis, a benefit in OS in the all-comers population was observed, although this analysis was unadjusted for multiplicity and at increased risk of type I error (false-positive results). The separate analyses of the pMMR and dMMR populations did not reach statistical significance.
- Disease-related HRQoL was measured in the NRG-GY018 study using the FACT-En-TOI, with results available only in the pMMR population at IA1. This tool is not routinely used in clinical practice. Results of the HRQoL outcome are at risk of bias due to missing data. The direction and extent of bias is unclear. It is not possible to generalize the results to the dMMR population.
- Clinicians consulted by CDA-AMC indicated that the population included in the NRG-GY018 trial reflects patients with advanced or recurrent endometrial cancer commonly seen in clinical practice in Canada. Based on their experience, the proportion of patients with an ECOG performance status score of 2 was lower in the NRG-GY018 trial compared to their own clinical practice. Patients with carcinosarcomas were not eligible for inclusion, so it is not possible to generalize the findings to that group.
- The timing and dose of pembrolizumab administration in combination with carboplatin-paclitaxel aligns with clinical practice in Canada.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for Grading of Recommendations Assessment, Development and Evaluation (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
- OS

- FACT-En TOI score
- immune-mediated and injection-related AEs.

Table 3: Summary of Findings for Pembrolizumab Plus Carboplatin-Paclitaxel Versus Placebo Plus Carboplatin-Paclitaxel for Patients With Primary Advanced or Recurrent Endometrial Cancer (All-Comers Population)

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo plus carboplatin-paclitaxel	Pembrolizumab plus carboplatin-paclitaxel	Difference		
PFS – ITT population, EUR-SUR analysis data cut-off date of August 18, 2023							
Probability of PFS at 12 months Median follow-up for all patients: 16.3 months	819 (1 RCT)	NA	385 per 1,000	559 per 1,000 (507 to 608)	174 more per 1,000 (102 to 246 more per 1,000)	High[a]	Pembrolizumab plus carboplatin-paclitaxel results in a clinically important increase in PFS at 12 months when compared with placebo plus carboplatin-paclitaxel.
Probability of PFS at 24 months Median follow-up for all patients: 16.3 months	819 (1 RCT)	NA	249 per 1,000	432 per 1,000 (374 to 488)	184 more per 1,000 (104 to 262 more per 1,000)	High[b]	Pembrolizumab plus carboplatin-paclitaxel results in a clinically important increase in PFS at 24 months when compared with placebo plus carboplatin-paclitaxel.
OS – ITT population, EUR-SUR analysis data cut-off date of August 18, 2023							
Probability of survival at 18 months Median follow-up for all patients: 16.3 months	819 (1 RCT)	NA	692 per 1,000	758 per 1,000 (703 to 804)	66 more per 1,000 (8 fewer to 140 more per 1,000)	Low[c]	Pembrolizumab plus carboplatin-paclitaxel may result in a clinically important increase in survival at 18 months when compared with placebo plus carboplatin-paclitaxel.
Probability of survival at 36 months Median follow-up for all patients: 16.3 months	819 (1 RCT)	NA	459 per 1,000	598 per 1,000 (509 to 676)	139 more per 1,000 (1 to 277 more per 1,000)	Low[d]	Pembrolizumab plus carboplatin-paclitaxel may result in a clinically important increase in survival at 36 months when compared with placebo plus carboplatin-paclitaxel.

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo plus carboplatin-paclitaxel	Pembrolizumab plus carboplatin-paclitaxel	Difference		
FACT-En TOI score for pMMR population – ITT population, first interim analysis data cut-off date of December 6, 2022							
LS mean change from baseline in global health status; scores range from 0 to 120, with higher scores indicating better health status Follow-up: 18 weeks	534 (1 RCT)	NA	–0.84	–4.01 (–5.65 to –2.36)	−3.17 (−5.48 to −0.85)	Moderate[e]	Pembrolizumab plus carboplatin-paclitaxel likely results in little to no clinically important difference in FACT-En TOI score compared to placebo plus carboplatin-paclitaxel in the pMMR population. No evidence is available for the all-comers population (or for the dMMR population).
Harms – safety population, second interim analysis data cut-off date of August 18, 2023							
Any immune-related AEs and infusion-related reactions Median follow-up for all patients: 16.3 months	779 (1 RCT)	RR = 1.51 (1.23 to 1.85)	263 per 1,000	396 per 1,000 (NR)	134 more per 1,000 (68 more to 198 more)	High[f]	Pembrolizumab plus carboplatin-paclitaxel results in a clinically important increase in immune-related AEs and infusion-related reactions when compared with placebo plus carboplatin-paclitaxel.

AE = adverse event; CI = confidence interval; EUR = efficacy updated results; FACT-En TOI = Functional Assessment of Cancer Therapy-Endometrial-Trial Outcome Index; IA1 = interim analysis 1; ITT = intention to treat; LS = least squares; MID = minimum important difference; NA = not applicable; NR = not reported; OS = overall survival; PD-1 = programmed cell death 1; PFS = progression-free survival; RCT = randomized controlled trial; RR = risk ratio; SUR = safety updated results.

Note: Study limitations (which refer to internal validity or risk of bias), 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]A threshold of 10% (100 per 1,000 patients) for a clinically important between-group difference, as informed by the clinical experts consulted was used to inform the target of the certainty rating and the precision of the effect estimate.

[b]A between-group threshold of 10% (100 per 1,000 patients) for a clinically important between-group difference, as informed by the clinical experts consulted was used to inform the target of the certainty rating and the precision of the effect estimate.

[c]Rated down 1 level for serious study limitations; the OS data have not yet matured, and the analysis was undertaken with a relatively small information fraction which increases the uncertainty in the results. Did not rate down for unblinding and substantial use of anti–PD-1 or anti–PD-L1 therapies in the placebo group after IA1, as the bias is directed toward the null. Rated down 1 level for serious imprecision; the 95% CI included the possibility of little to no difference based on the threshold of 5% (50 per 1,000 patients) suggested by the clinical experts.

[d]Rated down 1 level for serious study limitations; the OS data have not yet matured, and the analysis was undertaken with a relatively small information fraction which increases the uncertainty in the results. Did not rate down for unblinding and substantial use of anti–PD-1 or anti–PD-L1 therapies in the placebo group after IA1, as the bias is directed toward the null. Rated down 1 level for serious imprecision; the 95% CI difference included the possibility of little to no difference based on the threshold of 5% (50 per 1,000 patients) suggested by the clinical experts.

[e]Rated down 1 level for serious study limitations; there is a risk of bias due to missing outcome data.

[f]A between-group difference of 5% (50 per 1,000 patients) was clinically important according to the clinical experts. The point estimate and entire CI exceeded the threshold. The relative risk and risk difference were supplied by the sponsor following an additional information request by the review team, and were not part of their testing strategy.

Source: NRG-GY018 Clinical Study Report.[30] Details included in the table are from the sponsor's Summary of Clinical Evidence.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target populations	Adults with primary advanced (stage III and IV) or recurrent endometrial cancer Subgroup analyses submitted by MMR status (i.e., dMMR and pMMR)
Treatments	Pembrolizumab in combination with carboplatin-paclitaxel and then continued as monotherapy for the maintenance phase
Dose regimen	Combination phase: Pembrolizumab 200 mg every 3 weeks for 6 cycles in combination with carboplatin-paclitaxel, administered at a dose of 750 mg and 175 mg/m^2, respectively, every 3 weeks for up to 6 cycles Maintenance phase: 400 mg of pembrolizumab every 6 weeks until progression or for up to a maximum of 14 cycles
Submitted price	$4,400.00 per 100 mg/4 mL vial
Submitted treatment cost	Combination phase: Pembrolizumab: $8,800 every 3 weeks Maintenance phase: Pembrolizumab: $17,600 every 6 weeks
Comparators	• Carboplatin plus paclitaxel • Dostarlimab plus carboplatin-paclitaxel (for dMMR subgroup only)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (35 years)
Key data sources	• NRG-GY018 (KEYNOTE-868) study: A multicentre, open-label, randomized, phase III trial that compared pembrolizumab in combination with carboplatin-paclitaxel to chemotherapy alone (i.e., carboplatin-paclitaxel) • The sponsor assumed the efficacy (OS and PFS) to be identical between dostarlimab plus carboplatin-paclitaxel and pembrolizumab plus carboplatin-paclitaxel, for the dMMR subgroup.
Key limitations	• The sponsor incorrectly calculated the overall population results by independently estimating the OS and PFS curve for the overall population and for the subgroups by MMR status rather than deriving the overall population results by weighing the estimates for each subgroup by their respective prevalence. This resulted in illogical results, as the ICER for the overall population was lower than for both subgroups. • Long-term extrapolations of OS were likely overestimated for both pembrolizumab plus carboplatin-paclitaxel (7.75 LYs) and carboplatin-paclitaxel (4 LYs). The impact of this overestimation is uncertain, given that no statistical distributions produced plausible estimates according to clinical experts consulted by CDA-AMC. Given that the majority of incremental QALYs in the sponsor's base case are derived from the extrapolation period (98%), extrapolation of OS is a key model driver. • Assumptions regarding subsequent therapy were inconsistent with Canadian clinical practice, according to clinical expert feedback received by CDA-AMC. More patients in the chemotherapy group are expected to receive immune-modulating therapies. However, the clinical effects from a greater proportion of patients receiving subsequent treatment could not be explicitly captured

Component	Description
	in the sponsor's model due to the structural assumptions imposed by a PSM. This introduces uncertainty to the postprogression survival benefit observed within the sponsor's results that favours pembrolizumab plus carboplatin-paclitaxel. • The health-state utility values used in the sponsor's base case lacked face validity. The sponsor applied health-state utility scores (i.e., 0.82 for progressed disease and 0.85 for progression-free), but their source was not reported and, as such, could not be validated. These values suggest a quality of life similar to the general population and that there would be a minimal decline with disease progression, which is unlikely according to clinical expert input received by CDA-AMC. • Time on treatment for dostarlimab was based on PFS data. Because patients may discontinue treatment while maintaining disease control, using PFS to define time on treatment could overestimate dostarlimab's costs in the model. • Assumptions regarding the fixed-dose regimen of pembrolizumab do not reflect clinical practice in Canada.
CDA-AMC reanalysis results	• In the CDA-AMC reanalysis, stratified analyses were conducted by MMR status with the overall population results weighted by the subgroup's prevalence. CDA-AMC addressed 2 of the key limitations by revising health-state utility values and applying a weight-based dose. • In the CDA-AMC base-case reanalysis, the ICER for pembrolizumab plus carboplatin-paclitaxel compared to carboplatin-paclitaxel was as follows: ◦ dMMR population: ICER = $53,432 per QALY gained (incremental costs = $139,066; incremental QALYs = 2.60); pembrolizumab plus carboplatin-paclitaxel dominated dostarlimab plus carboplatin-paclitaxel (i.e., less costly, identical efficacy) ◦ pMMR population: ICER = $58,778 per QALY gained (incremental costs = $72,310; incremental QALYs = 1.23) ◦ overall population: ICER = $57,334 per QALY gained (incremental costs = $90,334; incremental QALYs = 1.60) • Caution is required in interpreting these results, given the inability to select more clinically plausible OS curves. The majority of incremental QALY gains (95%) were observed in the extrapolated period.

dMMR = deficient mismatch repair; ICER = incremental cost-effectiveness ratio; LY = life-year; MMR = mismatch repair; OS = overall survival; PFS = progression-free survival; pMMR = proficient mismatch repair; PSM = partitioned survival model; QALY = quality-adjusted life-year.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: the proportion starting second-line treatment and distributions of subsequent treatments are uncertain; market uptake of pembrolizumab is likely underestimated; dostarlimab's market capture in the dMMR subgroup may be underestimated; time-on-treatment assumptions for dostarlimab may be inappropriate; and the gradual uptake of pembrolizumab is inappropriate, as it would not facilitate a consistent interpretation and comparison of the results and the fixed dosing of pembrolizumab does not reflect clinical practice. The CDA-AMC reanalysis revised the market uptake rate for pembrolizumab to better align with the expectation of clinical experts, revised the gradual initiation of pembrolizumab, and assumed weight-based dosing for pembrolizumab. In the CDA-AMC base case, the 3-year budget impact of reimbursing pembrolizumab is expected to be $264,475,351 (year 1 = $49,400,994; year 2 = $97,116,184; year 3 = $117,958,173).

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: April 9, 2025

Regrets: Two members were absent.

Conflicts of interest: None

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