Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Dostarlimab (Jemperli)

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

Sponsor: GlaxoSmithKline Inc.

Recommendation: Reimburse with Conditions

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Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that dostarlimab in combination with carboplatin and paclitaxel be reimbursed for the first line treatment of adult patients with primary advanced or recurrent mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) endometrial cancer who are candidates for systemic therapy, only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, double-blind, placebo-controlled trial (RUBY Part 1; N = 494) evaluated the efficacy and safety of dostarlimab plus carboplatin-paclitaxel (dostarlimab + carboplatin-paclitaxel) followed by dostarlimab maintenance compared with placebo plus carboplatin-paclitaxel (placebo + carboplatin-paclitaxel) followed by placebo maintenance in patients with primary advanced (Stage III or IV) or recurrent endometrial cancer. A subgroup in the RUBY Part 1 trial (N = 118) aligned with the indication under review: adults with primary advanced or recurrent dMMR/MSI-H endometrial cancer who are candidates for systemic therapy. Subgroup analyses demonstrated that, compared with placebo + carboplatin-paclitaxel, dostarlimab + carboplatin-paclitaxel resulted in statistically significant and clinically meaningful improvements in median progression free survival (PFS) at 24.8-month median follow-up time (not reached versus 7.7 months; hazard ratio [HR] = 0.28; 95% confidence interval [CI]: 0.162 to 0.495; P < 0.0001). Overall survival (OS) was supportive of the results observed in the PFS analysis, suggesting a trend towards superiority in the dostarlimab + carboplatin-paclitaxel group (30-month OS rates at second interim analysis: [redacted] versus [redacted]). pERC considered the safety profile of dostarlimab + carboplatin-paclitaxel to be manageable with no unexpected toxicities.

Patients identified a need for effective treatment options that prolong survival, delay the onset of symptoms, maintain quality of life, have fewer side effects and the potential for cure. pERC concluded that dostarlimab + carboplatin-paclitaxel met some of the patients' needs as it delays disease progression, may prolong survival, and offers an additional treatment option. Although based on exploratory analyses, the addition of dostarlimab to chemotherapy did not suggest a detriment in health-related quality of life (HRQoL) from baseline to cycle 7; HRQoL data at later timepoints remained inconclusive due to a significant decline in the number of patients available to provide assessments over time.

Using the sponsor submitted price for dostarlimab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for dostarlimab + carboplatin-paclitaxel was $52,296 per quality-adjusted life-year (QALY) compared with carboplatin-paclitaxel. At this ICER, dostarlimab is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold. A price reduction is required for dostarlimab to be considered cost-effective at a $50,000 per QALY threshold.

Table 1. Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with dostarlimab + carboplatin-paclitaxel should be reimbursed in adult patients with dMMR/MSI-H primary advanced or recurrent EC not amenable to curative therapy who meet at least 1 of the following criteria: 1.1 Primary Stage III or IV EC 1.2 First recurrence and naïve to systemic anticancer therapy in advanced disease 1.3 Prior neoadjuvant or adjuvant systemic anticancer therapy and a first recurrence at least 6 months after completion of treatment.	Evidence from the RUBY Part 1 trial demonstrated that treatment with dostarlimab + carboplatin-paclitaxel resulted in a clinical benefit in patients with these characteristics.	MMR status needs to be determined before treatment.
2. Patients should have good performance status.	Patients with an ECOG performance status 0 or 1 were included in the RUBY Part 1 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 First recurrence within 6 months of completing neoadjuvant or adjuvant systemic anticancer therapy. 3.2 Prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent. 3.3 Uncontrolled brain metastases	There is no evidence to support a benefit of dostarlimab + carboplatin-paclitaxel treatment in patients with these characteristics as they were excluded from the RUBY Part 1 trial.	Patients with treated or stable brain metastases should be eligible for treatment.
Discontinuation		
4. Discontinuation should be based on a combination of clinical and radiological progression and/or significant adverse events potentially related to dostarlimab + carboplatin-paclitaxel.	Consistent with clinical practice, patients from the RUBY Part 1 trial discontinued treatment upon progression or unacceptable toxicity.	—
5. Dostarlimab should be reimbursed for a maximum of 3 years, i.e., 500 mg every 3 weeks (Cycles 1 to 6) and 1,000 mg every 6 weeks (Cycle 7 and thereafter).	Patients in the RUBY Part 1 trial were treated with dostarlimab for up to 3 years.	—
Prescribing		
6. Dostarlimab + carboplatin-paclitaxel should be prescribed by clinicians with expertise in advanced uterine cancer; treatment should be supervised and delivered	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
in institutions with expertise in systemic therapy delivery.		
7. Dostarlimab + carboplatin-paclitaxel should only be reimbursed when administered in combination.	In the RUBY Part 1, dostarlimab was administered in combination with carboplatin-paclitaxel.	—
Pricing		
8. A reduction in price	The ICER for dostarlimab + carboplatin-paclitaxel is $52,996 when compared with carboplatin-paclitaxel. A price reduction of 4.3% would be required for dostarlimab + carboplatin-paclitaxel to achieve an ICER of $50,000 per QALY compared to carboplatin-paclitaxel.	—
Feasibility of adoption		
9. The feasibility of adoption of dostarlimab + carboplatin-paclitaxel must be addressed	At the submitted price, the incremental budget impact of dostarlimab + carboplatin-paclitaxel is expected to be greater than $40 million in year 3.	—

dMMR = deficient mismatch repair; EC = endometrial cancer; ECOG = Eastern Co-operative Oncology Group; ICER = incremental cost-effectiveness ratio; MMR = mismatch repair; MSI-H=microsatellite instability-high; PD-1 = programmed cell death protein 1; PD-L1 = Programmed death-ligand 1; PD-L2 = Programmed death-ligand 2.

Discussion Points

- Input from patient groups and clinicians highlighted that advanced endometrial cancer is an aggressive disease with poor prognosis. Patients with advanced or recurrent disease have limited first-line treatment options and few patients survive 5 or more years. pERC agreed with the clinical experts consulted by CADTH that there is an unmet need for effective and safe therapy options in the requested patient population.
- pERC noted that PFS was identified as a clinically relevant outcome by patients and clinicians in the target patient population. The committee discussed that the PFS subgroup analysis in patients with dMMR/MSI-H disease was part of the primary efficacy analysis of the RUBY Part 1 trial and was statistically significant in favour of dostarlimab + carboplatin-paclitaxel. Given poor disease outcomes in the requested patient population, with a median PFS of less than 1 year on first-line chemotherapy, the benefits observed with the addition of dostarlimab to chemotherapy were considered clinically meaningful. pERC noted that the RUBY Part 1 trial was not designed to assess comparative OS in the dMMR/MSI-H patient subgroup and OS results were considered as supportive.
- pERC noted that patients with endometrial cancer identified a need for alternative treatment options with fewer side effects. While comparative safety from the RUBY Part 1 trial indicated that immune-related adverse events were more common in patients treated with dostarlimab + carboplatin-paclitaxel, treatment discontinuation as a consequence was relatively rare. pERC heard from the clinical experts that the safety profile of dostarlimab + carboplatin-paclitaxel appeared consistent with expectations about immunotherapy treatment and the known safety profiles of dostarlimab and chemotherapy.
- pERC discussed that the extended 3-year duration of dostarlimab maintenance therapy will increase the need for treatment administration, monitoring, and toxicity management. Further comparison of a more conventional 2-year duration of immune-checkpoint inhibitor therapy would be of benefit to investigate an optimal duration of therapy.

Background

Uterine cancers are commonly endometrial cancers caused by the development of malignant tumours in the cells of the uterus that can spread to other parts of the body. In Canada, an estimated 8,500 women will be diagnosed with and 1,550 will die from uterine cancer in 2023. Patients with endometrial cancer may present with abnormal vaginal bleeding, pelvic pain, back pain, feeling of a mass, or unintentional weight loss. Signs and symptoms of metastatic disease may include, but are not limited to vaginal, bladder or rectal bleeding, abdominal or pelvic pain, lower abdominal or extremity swelling, shortness of breath, and chest or bone pain. Patients with endometrial cancer that is high-risk (serous adenocarcinoma, clear cell adenocarcinoma, grade 3 deeply invasive endometrioid carcinoma, pathologic stage III or IV disease of any histology) or recurrent (including disease localized to the vagina or pelvis, or metastatic disease) tend to have poor prognosis, such that treatment goals are palliative rather than curative. Most patients' primary advanced or recurrent endometrial cancer recur within 3 years with median OS of less than 3 years. Treatment of endometrial cancer is based on a patient's stage, risk level at presentation, and previous treatments. Prognostic factors impacting local disease control and survival include site of recurrence, previous use of radiotherapy or chemotherapy, relapse-free interval, and histology. Approximately 25% of patients with endometrial cancer possess deficiencies in DNA repair mechanisms resulting in two correlated phenotypes dMMR/MSI-H. Frontline standard of care (SOC) treatment for advanced (stage III or IV) or recurrent endometrial cancer is doublet chemotherapy with carboplatin and paclitaxel. There is currently no SOC for second-line or later treatments. Response rates in the setting of progression on or following treatment with platinum-containing regimens are poor. According to the clinical experts consulted by CADTH, treatment goals in the indicated population are aimed at prolonging life, delaying disease progression, and maintaining HRQoL.

Dostarlimab in combination with carboplatin and paclitaxel has been approved by Health Canada for the treatment of adult patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer who are candidates for systemic therapy. Dostarlimab is an anti-programmed death receptor-1 (PD-1) monoclonal antibody. It is available as an IV infusion and the dosage recommended in the product monograph is 500 mg every 3 weeks for 6 doses followed by 1,000 mg every 6 weeks for all cycles thereafter.

Sources of Information Used by the Committee

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

- a review of 1 randomized controlled trial (RCT) in adult patients with primary advanced or recurrent endometrial cancer
- patients' perspectives gathered by 1 patient group, the Canadian Cancer Survivor Network (CCSN)
- input from public drug plans and that participate in the CADTH review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with endometrial cancer
- input from 3 clinician groups, including the Society of Gynecologic Oncology of Canada (GOC), Canadian Clinician Group coordinated by the Canadian Cancer Society (CCS), and Ontario Health (CCO) Gynecology Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

CADTH received one input from the CCSN. CCSN conducted an online survey which also was reviewed and commented on by both the Colorectal Cancer Resource & Action Network (CCRAN) and the CCS. The survey respondents identified as female patients from Canada who had endometrial cancer but did not have experience with dostarlimab.

Survey respondents highlighted, lack of screening and early diagnosis, lack of help for after-care, lack of mental health support during treatment, limited local access to treatment and biopsy, and difficulty in driving to clinic as some of the issues related to accessing health care. CCSN also highlighted that patients with advanced endometrial carcinoma have limited treatment options. Current treatments are associated with treatment induced toxicities that compromise patients' quality of life and fail to extend

patients' longevity in a meaningful way. CCSN stated that caregivers also have a difficult experience while taking care of their patients.

Patients expect the following from a new treatment option, according to 5 survey respondents: maintenance of quality of life, delayed onset of symptoms and reduced recurrence, access to a new option of treatment, reduced side effects, ease of use, prolonged life, and ability to cure.

CCSN added that people with endometrial cancer are looking for another option that will provide them with better quality of life and that patients are willing to experience some greater side effects if the treatment will extend survival for a longer period of time.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The current SOC for patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer is systemic therapy. According to the clinical experts consulted by CADTH, patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer experience poor response rates to current treatments that are of short duration, and as such, require treatments that can prolong life, delay disease progression, and maintain HRQoL. The clinical experts consulted by CADTH expressed that dostarlimab has a mechanism of action that is distinct from chemotherapy and has the potential to address the underlying disease process among patients with dMMR/MSI-H endometrial cancer. Dostarlimab, in combination with carboplatin and paclitaxel would be considered as first-line therapy for patients with advanced endometrial cancer who are chemotherapy-naïve and eligible for carboplatin and paclitaxel, and for patients with recurrent endometrial cancer who are chemotherapy-naïve or with more than 6 months since their last line of chemotherapy, according to the clinical experts consulted by CADTH. The clinical experts consulted by CADTH highlighted that patients who are chemotherapy-naïve at diagnosis or with recurrent disease are at greatest need for long-term durable therapy and therefore, most likely to respond to first-line treatment with dostarlimab plus chemotherapy. Eligible patients for dostarlimab in combination with carboplatin and paclitaxel would be diagnosed with primary endometrial cancer (via tissue biopsy) and further characterization of the cancer would include a companion diagnostic for MMR/MSS status that is SOC for endometrial cancer in Canada (via immunohistochemistry [IHC], next generation sequencing [NGS] or polymerase chain reaction [PCR]), and identification of stage of the disease (either via imaging or clinical pathologic assessment). The clinical experts consulted by CADTH noted that eligible patients should be able to tolerate chemotherapy and PD-1 inhibitor and have an absence of significant exclusion criteria (e.g., severe endocrine disease, undergoing immunotherapy). According to the clinical experts consulted by CADTH, treatment response would be best assessed with survival, survival without progressive disease, performance status, disease symptoms, and HRQoL, such that treatment should be discontinued in the event of disease progression or intolerance to treatment. The clinical experts consulted by CADTH indicated that dostarlimab may be prescribed by gynecologic or medical oncologists who are familiar with managing immune-related side effects, in an inpatient or outpatient setting.

Clinician Group Input

Three clinician groups: the GOC (based on 5 clinicians), Canadian Clinician Group with expertise in treating women with advanced and recurrent endometrial cancer, coordinated by the CCS (based on 10 clinicians), and CCO Gynecology Cancer Drug Advisory Committee (based on 5 clinicians) provided input to this review.

The clinician groups agreed that patients' unmet needs include improved overall and progression-free survival (PFS), durable disease control, sustained response to chemotherapy, and minimal adverse effects on quality of life. Moreover, CCO identified the absence of molecular directed therapy as a treatment gap. The goals of treatment were reported as to prolong life, delay disease progression, reduce severity of symptoms, improve QoL, reduce burden on caregivers, maintain independence, and minimize toxicities.

The clinician groups stated that patients with primary advanced state or metastatic dMMR endometrial cancer are best suited for treatment with the dostarlimab combination. The clinician groups agreed that response to therapy would be evaluated based on patient symptoms and tumour assessment through imaging. GOC added that assessment of tumour markers where applicable would be another factor to evaluate response to therapy. The clinician groups noted that discontinuation of treatment would be based on disease progression, toxicity, intolerability, and patient preference.

Drug Program Input

The clinical experts consulted by CADTH 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	
The choice of comparator in RUBY Part 1 was carboplatin (AUC 5) + paclitaxel (175 mg/m2), which is aligned with the current standard of care in Canada in this setting. The main treatment choice is platinum-based chemotherapy in combination with a taxane. Other funded options can include single agent chemotherapy in cases of patient hypersensitivity or toxicity to platinum or taxane agents, as well as hormonal therapy in patients who are estrogen and/or progesterone receptor positive.	The clinical experts consulted by CADTH consider platinum doublet chemotherapy with carboplatin and paclitaxel to be the most appropriate comparator among patients with primary advanced (stages III and IV) endometrial cancer as it is the current standard of care, and also applicable to patients with recurrent disease who are chemotherapy naïve. Among patients with recurrent disease who have had prior chemotherapy, multiple treatment options are available including a PD-1 inhibitor, doublet chemotherapy, singlet chemotherapy, or hormone therapy (for low grade cancers with limited disease). The clinical experts anticipated that clinicians would continue to prescribe a single agent PD-1 inhibitor for patients for first recurrence after prior chemotherapy. In the RUBY Part 1 trial in patients with dMMR/MSI-H disease, not more than 10 patients in each treatment group received prior anti-cancer treatment. pERC acknowledged and agreed with the clinical experts' response.
Considerations for initiation of therapy	
Testing for MSI/MMR and the test results are required to identify eligible patients. This testing is currently being done to identify patients in later lines of therapy but would not need to be done to identify eligibility for frontline use of dostarlimab. a) When should testing for MSI-H or dMMR take place in patients with endometrial cancer?	a) The clinical experts consulted by CADTH indicated that while there is variability across cancer centres regarding timeframe for MMR/MSI testing (e.g., shortly upon diagnosis, post-biopsy, post-surgery), most patients are tested early during diagnosis/treatment as standard of care to identify markers in addition to MSI/MMR (e.g., Lynch syndrome). MSI/MMR testing is universally performed and funded, according to the clinical experts consulted by CADTH. pERC acknowledged and agreed with the clinical experts' response.
Dostarlimab was combined with platinum-containing chemotherapy in RUBY Part 1. a) Are patients with dMMR/MSI-H recurrent endometrial cancer with a contraindication to platinum-containing regimens eligible for treatment with dostarlimab? b) Can alternate chemotherapy be used in combination with dostarlimab for patients with a contraindication to platinum-containing chemotherapy?	a) The clinical experts consulted by CADTH indicated that for patients with a contraindication to a platinum-containing regimen for any reason (e.g., hypersensitivity, complications due to renal disease), the option of single chemotherapy only (e.g., paclitaxel) or single chemotherapy plus dostarlimab should be offered at the discretion of the treating clinician. pERC noted that there was insufficient evidence to support combining dostarlimab with chemotherapy regimens other than those used in the RUBY Part 1 trial, i.e., carboplatin-paclitaxel. pERC noted that combining dostarlimab with other chemotherapy regimens would be outside of the Health Canada indication. b) The clinical experts consulted by CADTH noted the absence of evidence from clinical trials to support use of chemotherapeutic regimens other than carboplatin-paclitaxel for patients who are contraindicated to platinum-based chemotherapy, and therefore, there is uncertainty regarding alternate chemotherapy that may be offered to patients in combination with dostarlimab. Acknowledging this, the experts

Implementation issues	Response
	indicated that it would be reasonable to provide another chemotherapy combination or single agent as options for patients with contraindications or hypersensitivity. c) While pERC acknowledged the clinical experts' response, the committee supported using the chemotherapy regimens studied in the RUBY Part 1 trial at treatment initiation but noted that patients who develop contraindications to a chemotherapy regimen may continue with nab-paclitaxel instead of paclitaxel and/or cisplatin instead of carboplatin.
Neoadjuvant or adjuvant systemic therapy was permitted in the trial, as long as 6 months had elapsed since the completion of treatment. a) Are patients who experience disease relapse less than 6 months from neoadjuvant or adjuvant systemic therapy eligible? b) If not, should these patients receive single agent dostarlimab? c) What treatment options are available for patients who experience disease progression within 6 months of treatment?	a) The clinical experts consulted by CADTH consider patients with variant cancers who experience disease relapse less than 6 months to be platinum resistant. Although this definition has not been applied to patients with endometrial cancer, the experts consulted by CADTH would consider those with disease relapse fewer than 6 months from neoadjuvant or adjuvant systemic therapy to be ineligible due to an absence of evidence and uncertainty in response to treatment among this patient population. pERC agreed with the clinical experts that there is insufficient evidence to treat patients with dostarlimab + carboplatin-paclitaxel who relapse less than 6 months from neoadjuvant or adjuvant systemic therapy. b) Based on studies of single agent PD-1 inhibitors (e.g., GARNET study[1]), the clinical experts consulted by CADTH consider patients who have disease relapse less than 6 months may be eligible for treatment with a single agent PD-1 inhibitor. pERC noted that there is insufficient evidence to support using single agent dostarlimab in patients who experience disease relapse less than 6 months from neoadjuvant or adjuvant systemic therapy. c) According to the clinical experts consulted by CADTH, patients with disease progression within 6 months of treatment tend to have poor prognosis, and treatment options may include radiation, chemotherapeutic drugs, experimental drugs, or single agent PD-1 inhibitors. pERC agreed with the clinical experts' response.
a) Are patients who experience disease relapse after completing 3 years of maintenance dostarlimab eligible for retreatment with chemotherapy in combination with dostarlimab? b) If patients are eligible for retreatment with chemotherapy in combination with dostarlimab, is the PD-1 inhibitor specific to dostarlimab, or would patients be eligible for combination therapy specifically with dostarlimab or any PD-1 inhibitor?	a) Given the absence of data, the clinical experts consulted by CADTH indicated that it is challenging to determine whether patients who experience disease relapse after 3 years of maintenance therapy with dostarlimab would be considered eligible for retreatment with dostarlimab with chemotherapy. Overall, pERC agreed with the clinical experts that it would be reasonable to readminister dostarlimab at the time of relapse (up to 1 year), with carboplatin-paclitaxel, at the discretion of the treating physician for patients who have discontinued dostarlimab before any disease progression or disease progression occurred during a treatment break.

Implementation issues	Response
	b) pERC agreed with the clinical experts that there is insufficient evidence to support retreatment with a PD-1 inhibitor other than dostarlimab.
Considerations for discontinuation of therapy	
a) If a patient cannot tolerate the chemotherapy combination, are they able to continue with dostarlimab monotherapy? b) Is there a minimum number of chemotherapy cycles that must be given concurrently with dostarlimab? c) If treatment is interrupted, can it be resumed? Is there a specific time frame?	a) The clinical experts consulted by CADTH would offer dostarlimab monotherapy to patients who are unable to tolerate chemotherapy, based on evidence that single agent PD-1 inhibitors have demonstrated excellent responses among patients with primary advanced and recurrent dMMR endometrial cancer. b) According to the clinical experts consulted by CADTH, patients with recurrent disease are prescribed treatments in accordance with their response rate in clinical practice, rather than as a standardized number of chemotherapy cycles. c) It would be reasonable to resume combination treatment (dostarlimab with carboplatin and paclitaxel) if treatment was interrupted while on maintenance therapy with dostarlimab monotherapy, according to the clinical experts consulted by CADTH; the timing and duration of treatment resumption for an interruption unrelated to disease progression (e.g., surgery unrelated to cancer, toxicity) would be at the discretion of the treating clinician. pERC acknowledged and agreed with the clinical experts' response.
Can pERC confirm the treatment duration for dostarlimab? The trial protocol appears to indicate treatment may be continued if there is clinical benefit.	The clinical experts consulted by CADTH agreed that there is currently insufficient evidence to guide a decision on prolonging treatment with dostarlimab beyond 3 years. It was noted that treatment with dostarlimab for 3 years, was longer in duration than was employed in other studies (e.g., NRG-GY018 trial with pembrolizumab and chemotherapy [NCT03914612]). pERC agreed with the clinical experts' response.
Considerations for prescribing of therapy	
Cycles 1 to 6: dostarlimab 500 mg (flat dose) IV + platinum-containing chemotherapy every 21 days Cycle 7 onwards: dostarlimab 1,000 mg (flat dose) IV monotherapy every 42 days for up to 3 years total a) Is there evidence to support weight-based dosing to a maximum capped dose?	a) The RUBY trial employed a flat dose of 500 mg for 3-week cycles up to 6 cycles followed by 1,000 mg every 6-week cycles from cycle 7 onwards. For management of adverse events, dose delays or discontinuations were permitted according to specified dosage recommendations. Dose reductions were not permitted. The clinical experts consulted by CADTH were not aware of evidence to support weight-based dosing. pERC agreed with the clinical experts' response.
Generalizability	
Should patients with ECOG greater than 1 be eligible?	According to the clinical experts consulted by CADTH, patients with ECOG PS 0 to 2 would be considered eligible for treatment with dostarlimab in combination with carboplatin and paclitaxel if they were able to tolerate therapy. Patients with ECOG PS of greater than 2 would likely be unable to tolerate the combination of 2 chemotherapy drugs and immunotherapy. pERC agreed with the clinical experts' response.

Implementation issues	Response
a) Patients with HER2-overexpressing serous endometrial cancer may have trastuzumab added to front-line chemotherapy. Is HER2-overexpression and MSI-H mutually exclusive, or can they occur in the same patient? b) If they can occur at the same time, what is the percentage of patients where this may occur, and which treatment should be used preferentially, or can trastuzumab and dostarlimab be used together?	a) The clinical experts consulted by CADTH have seen patients with HER2-overexpression and MSI-H in clinical practice, although such combinations were noted to be infrequent. b) Patients with both HER2-overexpressing serous and MSI-H endometrial cancer represent a very small population, according to the clinical experts consulted by CADTH, noting that treatment decisions would be based on shared decision-making. The clinical experts were not aware of evidence available to inform using trastuzumab and dostarlimab in combination with carboplatin and paclitaxel. pERC acknowledged and agreed with the clinical experts' response.
There is a time-limited need to allow patients currently on platinum-containing chemotherapy to add dostarlimab. a) What time frame is appropriate to add dostarlimab for patients on chemotherapy alone or who have recently completed chemotherapy?	a) The clinical experts consulted by CADTH considered patients who are already on chemotherapy to be able to add dostarlimab irrespective of what cycle of treatment they are at. pERC agreed with the clinical experts that there should be the opportunity to add dostarlimab to chemotherapy as long as the patient is on chemotherapy with no progression of disease.
Funding algorithm (oncology only)	
Pembrolizumab monotherapy is currently available in this setting for patients with unresectable or metastatic MSI-H or dMMR endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options.	This is a comment from the drug plans to inform pERC deliberations.
There is an anticipated submission to CADTH for pembrolizumab in the same setting based on the NRG-GY018 trial. a) Under what circumstances would dostarlimab be preferred over pembrolizumab?	a) Based on current approval and funding status, pembrolizumab monotherapy is indicated for the treatment of adult patients with unresectable or metastatic microsatellite instability-high or mismatch repair deficient endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options. pERC agreed with the CADTH review team that it is not possible to comment on potential future comparators.
Care provision issues	
Dostarlimab vials are available as 500 mg strength, thus drug wastage is not expected if using a flat dose schedule.	This is a comment from the drug plans to inform pERC deliberations.
Eligible patients will require earlier MMR/MSI testing than is currently required in this setting, as patients do not require testing for frontline therapy at this time (testing is done for later lines of therapy).	This is a comment from the drug plans to inform pERC deliberations.
System and economic issues	
Cost per cycle as well as duration of treatment of dostarlimab is anticipated to be significantly higher than currently funded chemotherapy comparators.	This is a comment from the drug plans to inform pERC deliberations.
Pembrolizumab (available in later line) has confidential pricing in place.	This is a comment from the drug plans to inform pERC deliberations.

dMMR = deficient mismatch repair; ECOG PS = Eastern Co-operative Oncology Group Performance Status; HER2 = human epidermal growth factor receptor 2; MMR = mismatch repair; MSI = microsatellite instability; MSI-H=microsatellite instability-high; MSS = microsatellite stable; PD-1 = programmed cell death protein 1; pMMR/MSS = proficient mismatch repair/microsatellite stable.

[1] Oaknin A, Gilbert L, Tinker AV, et al. Safety and antitumor activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient/microsatellite

instability-high (dMMR/MSI-H) or proficient/stable (MMRp/MSS) endometrial cancer: interim results from GARNET-a phase I, single-arm study. J Immunother Cancer. 2022;10(1).

Clinical Evidence

Description of Studies

One phase III, multi-centre, randomized, double-blind trial assessed the efficacy and safety of dostarlimab in combination with carboplatin and paclitaxel (hereafter referred to as carboplatin-paclitaxel) followed by dostarlimab monotherapy, compared with placebo in combination with carboplatin-paclitaxel followed by placebo. RUBY Part 1 is an ongoing trial that enrolled 118 patients aged 18 years or older with primary advanced (stage III or IV) or first recurrent dMMR/MSI-H endometrial cancer. The primary objectives of RUBY Part 1 were to evaluate PFS among patients with primary advanced or recurrent endometrial cancer (overall trial population) and patients with dMMR/MSI-H primary advanced or recurrent endometrial cancer (i.e., dMMR/MSI-H subpopulation), and OS among the overall population. OS assessment in the dMMR/MSI-H subpopulation was an additional analysis in RUBY Part 1. Secondary end points that were evaluated for the overall population and in the dMMR/MSI-H subpopulation included response outcomes, HRQoL (European Organization for Research and Treatment of Cancer Core Quality [EORTC QLQ-C30] Global Health Status), and notable treatment-emergent adverse events (TEAEs) (immune-related adverse events, and infusion-related reactions). This review presents data from the RUBY trial Part 1 for patients in the dMMR/MSI-H subpopulation, which aligns with the Health Canada indication. The Clinical Study Report with a data cut-off of date of September 28, 2022 (first interim analysis), was the primary data source for the RUBY Part 1 trial. At this data cut-off, the median follow-up was 24.6 months in the dostarlimab + carboplatin-paclitaxel group and 25.1 months in the placebo + carboplatin-paclitaxel group. In addition, CADTH received updated data from the sponsor for OS and notable harms for the dMMR/MSI-H subpopulation from RUBY Part 1 second interim analysis (data cut-off date of September 22, 2023; median follow-up was 34.0 months in the dostarlimab + carboplatin-paclitaxel group and 24.0 months in the placebo + carboplatin-paclitaxel group) which have been included in this review. At this time the OS stopping boundary in the overall population was met and no further inferential testing for OS is planned.

Patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer in RUBY Part 1 were white (84.7%) with a median age of 64 years (range, 39 to 85), Eastern Co-operative Oncology Group Performance Status (ECOG PS) of 0 (57.3%), and endometrioid carcinoma (83.9%). Nearly half of the enrolled patients had recurrent disease. The treatment groups were generally similar in medical history (histology and grade at diagnosis, International Federation of Gynecological and Obstetrics [FIGO] stage at initial diagnosis) and disease status (stage III, stage IV, recurrent disease). Approximately 14% of patients had received prior anticancer therapy and 92.4% of patients had received prior anticancer surgical interventions for endometrial cancer. While 34.7% of patients had received prior radiotherapy for endometrial cancer, fewer patients received external pelvic radiotherapy in the dostarlimab + carboplatin-paclitaxel group compared with the placebo + carboplatin-paclitaxel group (15.1% versus 20.0%, respectively).

Efficacy Results

Efficacy results were summarized for OS, PFS (investigator-assessed), and the EORTC QLQ-C30 Global Health Status among patients in the dMMR/MSI-H subpopulation.

OS

At the interim analysis 2 data cut-off date (September 22, 2023), median OS was not reached in the dostarlimab + carboplatin-paclitaxel group with 40% OS maturity. The 24-month OS probability (95% confidence interval [CI]) was 82.8% (69.5 to 90.7) and 57.5% (44.4 to 68.6) in the dostarlimab + carboplatin-paclitaxel and placebo + carboplatin-paclitaxel group, respectively. The between-group difference (95% CI) was [redacted]. The 30-month OS probability (95% CI) was [redacted] and [redacted] in the dostarlimab + carboplatin-paclitaxel and placebo + carboplatin-paclitaxel group, respectively. The between-group difference (95% CI) was [redacted]. The hazard ratio ([HR] [95% CI]) in the intention to treat (ITT) dMMR/MSI-H subpopulation was 0.32 (0.166 to 0.629; 1-sided P value = 0.0002) for dostarlimab + carboplatin-paclitaxel versus placebo + carboplatin-paclitaxel. This analysis was uncontrolled for multiplicity and considered supportive. No further testing for OS is planned, because the prespecified stopping boundary was met in the overall population at the second interim analysis.

PFS (Investigator-Assessed)

At the interim analysis 1 data cut-off date (September 28, 2022), median PFS based on investigator assessment was not reached in the dostarlimab + carboplatin-paclitaxel group compared with 7.7 months in the placebo + carboplatin-paclitaxel group with 56% PFS maturity in the dMMR/MSI-H subpopulation. The 12-month investigator-assessed PFS probability (95% CI) was 63.5% (48.5 to 75.3) and 24.4% (13.9 to 36.4) in the dostarlimab + carboplatin-paclitaxel and placebo + carboplatin-paclitaxel group, respectively. The between-group difference was [redacted]. The 24-month investigator-assessed PFS probability (95% CI) was 61.4% (46.3 to 73.4) and 15.7% (7.2 to 27.0) in the dostarlimab + carboplatin-paclitaxel and placebo + carboplatin-paclitaxel group, respectively. The between-group difference was [redacted]. The HR (95% CI) in the dMMR/MSI-H subpopulation was 0.28 (0.162 to 0.495; 1-sided P value < 0.0001) for dostarlimab + carboplatin-paclitaxel versus placebo + carboplatin-paclitaxel. Findings for PFS based on BICR assessment were consistent with results for PFS based on investigator assessment. No further testing of PFS occurred, because the prespecified stopping boundary was met at the first interim analysis.

EORTC QLQ-C30

At the data cut-off of date of September 28, 2022, the least squares mean (LSM) change from baseline (95% CI) in the EORTC QLQ-C30 Global Health Status at day 1 of cycle 7 was [redacted] and [redacted] in the dostarlimab + carboplatin-paclitaxel and placebo + carboplatin-paclitaxel group, respectively, (difference in LSM change from baseline = 9.4 points; 95% CI, 2.0 to 16.8; P = 0.0125). The LSM change from baseline (95% CI) in the EORTC QLQ-C30 Global Health Status at day 1 of cycle 13 was [redacted] and [redacted] in the dostarlimab + carboplatin-paclitaxel and placebo + carboplatin-paclitaxel group, respectively, (difference in LSM change from baseline = [redacted]. The analyses of EORTC QLQ-C30 were uncontrolled for multiplicity and considered supportive.

Harms Results

The analysis population for harms included all patients who received any amount of study drug, with patients grouped according to the treatment received. Safety data were from the interim safety analyses (data cut-off of September 28, 2022) and updated for notable harms (interim analysis 2 with data cut-off September 22, 2023).

All patients in the dMMR/MSI-H subpopulation experienced at least 1 TEAE. The most common TEAEs occurring in greater than 20% of patients in the dostarlimab + carboplatin-paclitaxel or placebo + carboplatin-paclitaxel group, respectively, were alopecia (56% versus 60%), fatigue (50% versus 55%), nausea (56% versus 46%), anemia (35% versus 52%), peripheral neuropathy (42% versus 43%), arthralgia (42% versus 40%), diarrhea (40% versus 31%), constipation (29% versus 34%), myalgia (23% versus 26%), hypomagnesemia (19% versus 29%), vomiting (27% versus 22%), rash (29% versus 15%), dyspnea (14% versus 28%), neutropenia (21% versus 17%), abdominal pain (15% versus 22%), peripheral sensory neuropathy (23% versus 19%), decreased neutrophil count (10% versus 23%), urinary tract infection (8% versus 25%), hypertension (21% versus 11%), and hypothyroidism (21% versus 6%).

The number of patients in the dMMR/MSI-H subpopulation with at least 1 SAE was 14 (27%) patients in the dostarlimab + carboplatin-paclitaxel group and 20 (31%) patients in the placebo + carboplatin-paclitaxel group. Serious adverse events (SAEs) occurring in at least 2% of patients in either the dostarlimab + carboplatin-paclitaxel or placebo + carboplatin-paclitaxel group, respectively, were urinary tract infection (0 versus 6.2%), anemia (0 versus 4.6%), asthenia (0 versus 4.6%), sepsis (3.8% versus 0), and pulmonary embolism (0 versus 3.1%). The number of patients with at least 1 TEAE of grade 3 or greater was 37 (71%) patients in the dostarlimab + carboplatin-paclitaxel group and 42 (65%) patients in the placebo + carboplatin-paclitaxel group. Grade 3 or greater TEAEs occurring in at least 10% of patients in either the dostarlimab + carboplatin-paclitaxel or placebo + carboplatin-paclitaxel group, respectively, were anemia (15% versus 22%), neutropenia (17% versus 12%), decreased neutrophil count (8% versus 19%), and decreased white blood cell count (4% versus 12%).

The number of patients in the dMMR/MSI-H subpopulation who discontinued study treatment due to an AE was 9 (17.3%) patients in the dostarlimab + carboplatin-paclitaxel group and 11 (16.9%) patients in the placebo + carboplatin-paclitaxel group. Withdrawals due to AEs in the dostarlimab + carboplatin-paclitaxel group were due to (1 [1.9%] patient each) neurotoxicity, myelosuppression, drug hypersensitivity, infusion-related reaction, chronic kidney disease, rash maculo-papular, keratitis, muscular weakness, fatigue, and general physical health deterioration. Withdrawals due to AEs in the placebo + carboplatin-paclitaxel group were due to

peripheral neuropathy (3 patients [4.6%]) and thrombocytopenia (2 patients [3.1%]), cardiovascular accident (1 patient [1.5%]), infusion-related reaction (1.5%), increased amylase (1.5%), decreased platelet count (1.5%), peritonitis (1.5%), myelodysplastic syndrome (1.5%), and vaginal hemorrhage (1.5%). The number of deaths in the dMMR/MSI-H subpopulation were 7 (13.5%) patients in the dostarlimab + carboplatin-paclitaxel group and 24 (36.9%) patients in the placebo + carboplatin-paclitaxel group. Most deaths (5 patients and 19 patients) were due to disease progression in the dostarlimab + carboplatin-paclitaxel and placebo + carboplatin-paclitaxel group, respectively. Two patients treated with dostarlimab + carboplatin-paclitaxel experienced TEAEs leading to death (1 patient each of myelosuppression, and of hypovolemic shock).

Notable harms

Immune-related AEs occurred in 39 (75.0%) patients and 26 (40.0%) patients in the dostarlimab + carboplatin-paclitaxel and placebo + carboplatin-paclitaxel group, respectively, (between-group difference of [redacted]). Infusion-related reactions occurred in 12 (23.1%) patients and 13 (20.0%) patients in the dostarlimab + carboplatin-paclitaxel and placebo + carboplatin-paclitaxel group, respectively, (between-group difference of [redacted]).

Critical Appraisal

Randomization using an interactive web response system was considered adequate for concealment of allocation sequence. MMR/MSI status used to stratify randomization for the overall population of patients with primary advanced or recurrent endometrial cancer resulted in a between-groups imbalance in the number of patients with dMMR/MSI-H; however, sensitivity analyses for OS and investigator-assessed PFS showed results for randomization data were consistent with verified sources. Although a greater proportion of patients in the placebo + carboplatin-paclitaxel group were older than 65 years, with ECOG PS of 0, and had prior external pelvic radiotherapy, imbalances did not systematically favour either treatment group and are likely compatible with chance. Nevertheless, prognostic balance requiring a large sample size was unlikely to have been fully achieved in RUBY Part 1 despite adequate randomization methods. Interim analyses were preplanned with adequately justified stopping boundaries to provide confidence that statistical significance of effects for PFS did not arise from type 1 error. There was a risk for magnitude of observed treatment effects to be overestimated as neither median PFS nor median OS in the dostarlimab + carboplatin-paclitaxel group had been reached at time of analysis and the information fraction for OS was notably small (40%). The small number of patients with dMMR/MSI-H and low number of events may render the observed effects to be unstable. Among patients in the dMMR/MSI-H subpopulation, OS and HRQoL were not included in the hierarchical testing strategy, increasing the risk of type I error. The potential for unblinding among patients who experienced an AE in the dostarlimab group at cycle 7 onwards (without carboplatin-paclitaxel) was neither evidenced in protocol deviations nor outcome measurement. While there were multiple protocol amendments for PFS based on investigator versus BICR assessments, sensitivity analyses demonstrated consistency in findings between both methods of assessment which reduced concerns of potential bias. Significant missing HRQoL data which were implicitly imputed through statistical analyses cannot provide confirmation that such missing data occurred at random which was assumed in the methods employed. The lack of sensitivity analyses to explore the impact of other imputation techniques (with assumptions for different missing data mechanisms) on treatment effect estimates resulted in a risk of bias from significant missing data that likely compromised randomization with an unknown direction of potential bias.

The population enrolled in RUBY Part 1 was representative of patients with primary advanced or recurrent dMMR/MSI-H endometrial cancer in clinical practice, according to the clinical experts consulted by CADTH. Further, the clinical experts noted that the timing of administering dostarlimab or placebo in combination with carboplatin and paclitaxel appeared to be aligned with the chemotherapy regimens in current clinical practice, although 3 years' duration of therapy was not considered typical as patients with primary advanced or recurrent dMMR/MSI-H have increased likelihood of disease recurrence over time. Further, radiographic evaluations to assess disease status were reported to be more frequent in RUBY than would be feasible in clinical practice (every 3 to 4 months). Doublet chemotherapy with carboplatin and paclitaxel were reported by the clinical experts consulted by CADTH to be current clinical practice among patients with primary advanced disease and among patients with recurrent disease who are chemotherapy-naïve. Current treatments for patients with recurrent disease and prior chemotherapy include other options. Concomitant medications were reported by the clinical experts consulted by CADTH to be appropriate and aligned with clinical practice in Canada for systemic glucocorticoid use and G-CSF for clinicians who elect to use it in current practice. Subsequent treatment types, including pembrolizumab, hormonal therapy, and radiation therapy among a greater proportion of patients in the placebo group, were aligned with higher rates of progressive disease in this group and expectations of the clinical experts consulted by CADTH. As a result, OS

reflects treatment with dostarlimab versus placebo (each with carboplatin and paclitaxel) in addition to subsequent treatments, such that survival results may be partially attributable to treatments administered after disease progression (rather than to the study treatment); nevertheless, the comparison is relevant because it is reflective of the intervention and comparator in clinical practice. OS and PFS were important outcomes to the clinical experts consulted by CADTH for clinical decision-making and were included in the RUBY trial. There is some evidence to suggest that a within-arm change in PFS is strongly correlated with a change in the OS in the same direction of effect based on trials of first-line therapies among patients with primary advanced or recurrent endometrial cancer. However, evidence to support that a treatment effect on PFS will correspond to a treatment effect on OS was not identified. Longer follow-up would be useful to demonstrate whether a sustained survival benefit is observed. The clinical experts consulted by CADTH expressed that clinicians may opt to use practical tools (e.g., ECOG PS) over formal HRQoL evaluations to assess patients' overall well-being.

GRADE Summary of Findings and Certainty of the Evidence

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: survival (OS, PFS based on investigator assessment), HRQoL (EORTC QLQ-C30 Global Health Status), and harms (immune-related AEs, and infusion-related reactions).

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. The target of the certainty of evidence assessment was the presence or absence of a clinically important effect for probability of survival (OS, and PFS), and harms (immune-related AEs, and infusion-related reactions) based on a threshold informed by the clinical experts consulted by CADTH for this review. The target of certainty of evidence assessment was the presence or absence of a clinically important effect for HRQoL (EORTC QLQ-C30 Global Health Status) based on a threshold identified in the literature.

Table 3 presents the GRADE summary of findings for dostarlimab + carboplatin-paclitaxel versus placebo + carboplatin-paclitaxel in patients with endometrial cancer.

Table 3. Summary of Findings for Dostarlimab in Combination With Carboplatin-Paclitaxel Versus Placebo in Combination With Carboplatin-Paclitaxel for Adult Patients With Primary Advanced or Recurrent dMMR/MSI-H Endometrial Cancer

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo + CAR-PAC	Dostarlimab + CAR-PAC	Difference		
Survival							
Overall Survival							
Probability of overall survival at 24 months Median follow-up: 34.0 months versus 24.0 months[a]	118 (1 RCT)	NR	575 per 1,000	828 per 1,000 (695 to 907 per 1,000)	[redacted][b]	Low[c]	Dostarlimab plus CAR-PAC may result in a clinically important increase in the probability of overall survival at 24 months when compared with placebo plus CAR-PAC.
Probability of overall survival at 30 months Median follow-up: 34.0 months versus 24.0 months[a]	118 (1 RCT)	NR	[redacted]	[redacted]	[redacted][b]	Low[c]	Dostarlimab plus CAR-PAC may result in a clinically important increase in the probability of overall survival at 30 months when compared with placebo plus CAR-PAC.
Progression-Free Survival, Investigator-Assessed							
Probability of progression-free survival at 12 months Median follow-up: 24.6 months versus 25.1 months[a]	118 (1 RCT)	NR	244 per 1,000	635 per 1,000 (485 to 753 per 1,000)	[redacted][b]	Moderate[d]	Dostarlimab plus CAR-PAC likely results in a clinically important increase in the probability of progression-free survival at 12 months when compared with placebo plus CAR-PAC.
Probability of progression-free survival at 24 months Median follow-up: 24.6 months versus 25.1 months[a]	118 (1 RCT)	NR	157 per 1,000	614 per 1,000 (463 to 734 per 1,000)	[redacted][b]	Moderate[d]	Dostarlimab plus CAR-PAC likely results in a clinically important increase in the probability of progression-free survival at 24 months when compared with placebo plus CAR-PAC.
Health-Related Quality of Life							
EORTC QLQ-C30 (0 [worst health-related quality of life] to 100 [best health-related quality of life])							

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Placebo + CAR-PAC	Dostarlimab + CAR-PAC	Difference		
Global Health Status, LSM change from baseline, points Follow-up: cycle 7 day 1	118 (1 RCT)	NR	[redacted]	[redacted]	9.4 (2.0 to 16.8)	Low[e]	Dostarlimab plus CAR-PAC may result in little-to-no difference in EORTC QLQ-C30 Global Health Status at day 1 of cycle 7 when compared with placebo plus CAR-PAC.
Global Health Status, LSM change from baseline, points Follow-up: cycle 13 day 1	118 (1 RCT)	NR	[redacted]	[redacted]	[redacted]	Very low[f]	The evidence is very uncertain about the effect of dostarlimab plus CAR-PAC on EORTC QLQ-C30 Global Health Status at day 1 of cycle 13 when compared with placebo plus CAR-PAC.
Harms							
Immune-related adverse events Follow-up: 34.0 months versus 24.0 months[a]	117 (1 RCT)	NR	400 per 1,000	750 per 1,000 (NR)	[redacted][b]	Low[g]	Dostarlimab plus CAR-PAC may result in an a clinically important increase in immune-related adverse events when compared with placebo plus CAR-PAC.
Infusion-related reactions Follow-up: 34.0 months versus 24.0 months[a]	117 (1 RCT)	NR	200 per 1,000	231 per 1,000 (NR)	[redacted][b]	Low[h]	Dostarlimab plus CAR-PAC may result in little-to-no difference in infusion-related reactions when compared with placebo plus CAR-PAC.

CAR-PAC = carboplatin-paclitaxel; CI = confidence interval; dMMR/MSI-H = deficient mismatch repair/microsatellite instability-high; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire; LSM = least squares mean; NR = not reported; RCT = randomized controlled trial.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] Follow up presented as dostarlimab + CAR-PAC versus placebo + CAR-PAC.
[b] Risk difference (95%CI) was not included in the sponsor's planned analyses; the absolute risk difference was requested by the CADTH review team for interpretation purposes.
[c] Rated down 2 levels for very serious imprecision. The effect resulting from the second interim data cut is large (above the 5% to 10% threshold suggested by the clinical experts) and the sample size and number of events is very small, raising concern for prognostic imbalance and potential overestimation of the true effect. The number of OS events were 36 at 24 months and 38 at 30 months. OS in the dMMR/MSI-H subpopulation was not included in the statistical hierarchy.
[d] Rated down 1 level for serious imprecision. The effect resulting from the first interim data cut is large (above the 10% to 15% threshold suggested by the clinical experts) and the sample size and number of events is small, raising concern for prognostic imbalance and potential overestimation of the true effect. The number of PFS events were 61 at 12 months and 66 at 24 months.
[e] Rated down 1 level for serious study limitations. There is risk of bias due to missing outcome data. Rated down 1 level for serious imprecision. Based on a 10-point MID identified in the literature, the 95% CI included the possibility of little to no difference and clinically important benefit. This analysis was not adjusted for multiplicity and the results are considered to be supportive evidence.
[f] Rated down 2 levels for very serious study limitations. There is risk of bias due to significant and imbalanced missing outcome data. Rated down 2 levels for very serious imprecision. Based on a 10-point MID identified in the literature, the 95% CI included the possibility of little to no difference and clinically important benefit. This analysis was not adjusted for multiplicity and the results are considered to be supportive evidence.
[g] Rated down 2 levels for very serious imprecision. Effect estimate seems to be large based on a between-group difference of 5% identified as clinically important by the clinical experts consulted by CADTH, but the total sample size and number of events is low (n = 62).
[h] Rated down 2 levels for very serious imprecision. Based on a 5% threshold suggested as clinically important by the clinical experts, the 95% CI for the difference between groups included the possibility of clinically important benefit and harm (increased adverse event).

Source: RUBY Clinical Study Report.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-Utility Analysis PSM
Target population	Adult women with primary advanced (stage III or stage IV) or recurrent dMMR/MSI-H endometrial cancer.
Treatment	dostarlimab plus carboplatin-paclitaxel
Dose regimen	Dostarlimab: 500 mg every 3 weeks in combination with carboplatin-paclitaxel for 6 cycles, followed by 1,000 mg of dostarlimab monotherapy every 6 weeks.
Submitted price	Dostarlimab, 50 mg / mL, solution for infusion: $10,031.08 per 10 mL vial
Treatment cost	$10,031 every 21 days
Comparator	carboplatin-paclitaxel
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (36.7 years)
Key data source	RUBY Part 1 Trial
Key limitations	PFS and OS parameter estimates, as derived from the RUBY trial, were subject to a high degree of uncertainty due to issues related to sample size. Because the model relies heavily on these parameters, estimates of costs and QALYs are also subject to this uncertainty. The selected parametric approaches to predict long-term estimates for OS and PFS resulted in unrealistic survival predictions and over-estimated the expected benefit from treatment. Clinical experts consulted by CADTH suggested that less optimistic predictions of long-term survival were required. The model did not consider an appropriate approach to the characterization of parameter uncertainty for a partitioned survival model. As such, the model does not accurately estimate the probability of cost-effectiveness.
CADTH reanalysis results	The CADTH base case addressed the identified limitation of the selected parametric approach, instead OS and PFS were predicted assuming exponential and Weibull distributions, respectively. In the CADTH base case, dostarlimab plus carboplatin-paclitaxel was associated with an ICER of $52,296 per QALY gained (incremental costs: $285,186; incremental QALYs: 5.45). A 4.3% price reduction would be required for dostarlimab plus carboplatin-paclitaxel to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained.

Abbreviations: ICER = incremental cost-effectiveness ratio; LY = life-year; OS = overall survival; PFS = progression-free survival; PSM = partitioned survival model; QALY= quality-adjusted life-year; dMMR = deficient mismatch repair; MSI-H = microsatellite instability-high.

Budget Impact

CADTH identified one key limitation with the sponsor's submitted BIA. The analysis relied on uncertain estimates of market size due to an assumption that [redacted]% of patients with primary advanced or recurrent endometrial cancer will receive first-line therapy. CADTH performed a reanalysis which explored how a reduction in the proportion of patients that will receive first-line therapy will affect the estimated budget impact. In the CADTH base case, the budget impact from the introduction of dostarlimab plus carboplatin-paclitaxel is expected to be $11,724,779 in Year 1, $28,027,157 in Year 2, and $41,120,222 in Year 3. The three-year net budget impact was estimated to be $80,890,158.

pERC Information

Members of the Committee:

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Phillip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: March 13, 2024

Regrets:

1 expert committee member did not attend.

Conflicts of interest:

None