Canadian Journal of Health Technologies

CADTH

September 2022 Volume 2 Issue 9

CADTH Reimbursement Recommendation

Dostarlimab (Jemperli)

Indication: Monotherapy for the treatment of adult patients with mismatch repair deficient or microsatellite instability-high recurrent or advanced endometrial cancer that has progressed on or following prior treatment with a platinum-containing regimen

Sponsor: GlaxoSmithKline Inc.

Final recommendation: Do not reimburse

CADTH

ISSN: 2563-6596

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Jemperli?

CADTH recommends that Jemperli should not be reimbursed by public drug plans for monotherapy for the treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) recurrent or advanced endometrial cancer (EC) that has progressed on or following prior treatment with a platinum-containing regimen.

Why Did CADTH Make This Recommendation?

- While evidence from a clinical trial demonstrated that some patients had disease that responded during treatment with Jemperli, without a control group there is uncertainty in how much the observed responses were due to Jemperli treatment rather than chance.
- There was too much uncertainty in the reviewed evidence to determine how Jemperli compares to other treatments used in Canada.
- It is unclear whether Jemperli meets the following needs identified by patients: improved tumour response, delayed disease progression, improved quality of life, and fewer side effects.

Additional Information

What Is EC?

EC is cancer of the lining of the uterus and dMMR or MSI-H tumours have cells that are unable to properly repair certain errors in genes. In Canada, there are approximately 7,600 new cases of EC diagnosed each year. Approximately 13% to 20% of patients with EC have recurrence and half of patients with recurrent EC survive 12 months or less.

Unmet Needs in EC

There is a need for effective treatments that provide better disease control, improve quality of life, and have fewer side effects.

How Much Does Jemperli Cost?

Treatment with Jemperli is expected to cost approximately $13,655 per patient every 28 days.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that dostarlimab not be reimbursed for monotherapy for the treatment of adult patients with dMMR or MSI-H recurrent or advanced EC that has progressed on or following prior treatment with a platinum-containing regimen.

Rationale for the Recommendation

One ongoing multi-centre, phase I dose escalation and cohort expansion study (part 2B of the GARNET trial, A1 cohort) evaluated dostarlimab in patients with advanced or recurrent dMMR or MSI-H EC that had progressed on or following prior treatment with a platinum-containing regimen. An interim analysis (IA-2) of 105 patients showed an objective response rate (ORR) of 44.8% (95% confidence interval (CI), 35.0% to 54.8%); however, there was a high degree of uncertainty regarding the magnitude of clinical benefit directly attributable to dostarlimab due to the non-randomized, non-comparative, open-label study design and the small sample size and short follow-up in the study. Further, because of the single arm nature of the study, the potential clinical benefit of dostarlimab to other currently available treatment options is unknown. The sponsor submitted 6 indirect treatment comparisons (ITCs) of dostarlimab, but given the substantial limitations with the analyses (i.e., clinical heterogeneity, differences in study design, unknown mismatch repair (MMR) and microsatellite instability (MSI) status in comparator cohorts), pERC was unable to determine the comparative efficacy with respect to survival outcomes. Patients identified a need for a treatment that improves tumour response, increases quality of life, and delays disease progression. While pERC recognized the need for additional treatment options in this patient population, it is uncertain whether dostarlimab meets these needs given the limitations associated with the evidence reviewed.

Discussion Points

- pERC acknowledged the need for effective treatments in a patient population that otherwise has limited treatment options and has a poor prognosis. pERC discussed the need for treatments with fewer or more manageable adverse effects than current standard of care. No evidence comparing the relative safety of dostarlimab to standard of care therapies was identified; therefore, pERC concluded that it remains unknown whether dostarlimab addresses this patient need.
- In their request for reconsideration, the sponsor included a naïve comparison of safety data from the KEYNOTE-775 trial with the safety data from the GARNET trial. Since this was an unadjusted comparison as opposed to an ITC, it was not included in the CADTH clinical review and pERC did not use this during their deliberations.
- Key gaps in the phase I clinical evidence identified by pERC include a lack of hypothesis testing beyond ORR, small sample size, short duration of follow-up, and no comparison with treatments used in the target population. Should evidence addressing these gaps become available, the clinical value of dostarlimab may be reassessed.

- pERC noted that results from a later interim analysis (IA-3) provide a larger sample size (N = 143) and longer follow-up compared with IA-2 (median follow-up time of 27.6 months versus 16.3 months), with similar ORR results and no new safety signals. However, the IA-3 data do not adequately address the limitations of the GARNET trial identified by pERC.
- Since there was uncertainty with the clinical evidence, the committee considered the criteria for significant unmet need that are described in section 9.3.1 of the Procedures for CADTH Reimbursement Reviews. The committee considered that advanced or recurrent dMMR or MSI-H EC that has progressed on or following prior treatment with a platinum-containing regimen is not sufficiently rare to preclude the generation of evidence that would address the uncertainty in the magnitude of clinical benefit with dostarlimab.

Background

dMMR and MSI-H tumour status represent approximately 25% of primary EC and 13% to 30% of recurrent EC and is a predictive biomarker of clinical benefit from checkpoint inhibitors. Recurrence occurs in approximately 13% to 20% of patients with EC and has a poor prognosis, with a median survival of 12 months. At first recurrence or primary advanced disease, response rates with platinum-based combination regimens in the first-line setting range from 40% to 62%. However, for patients with advanced or recurrent EC who have progressed on or after platinum-based chemotherapy, there is currently no standard second-line therapy. Single-drug chemotherapies or hormonal therapy may be administered, but they have low response rates and no clear survival benefit.

Dostarlimab is an anti-programmed cell death protein-1 (PD-1) monoclonal antibody. Dostarlimab has been approved by Health Canada for adult patients with dMMR or MSI-H recurrent or advanced EC that has progressed on or following prior treatment with a platinum-containing regimen. Dostarlimab is available as a 500 mg IV infusion administered over 30 minutes. The dosage recommended in the product monograph is 500 mg IV every 3 weeks for dose 1 through 4 and 1,000 mg IV every 6 weeks for dose 5 onwards. Treatment may continue until disease progression or unacceptable toxicity. Dose reductions are not recommended, but dosing delays and discontinuation may be required based on safety and tolerability.

Sources of Information Used by the Committee

To make their recommendation, pERC considered the following information:

- A review of a non-randomized clinical study, 3 reports of matching-adjusted indirect comparisons (MAICs), and 3 reports of inverse probability of treatment weighting (IPTW) analyses in patients with dMMR or MSI-H EC.
- Patient's perspectives gathered by patient groups from the Canadian Cancer Society.
- Input from public drug plans and cancer agencies that participate in the CADTH review process.

- Two clinical specialists with expertise diagnosing and treating patients with dMMR or MSI-H EC.
- Input from 7 clinician groups, including British Columbia Cancer Provincial Gynecological Oncology Tumour Group; McGill University Health Centre (MUHC), Division of Gynecologic Oncology; Ontario Health [Cancer Care Ontario] (OH-CCO) Gynecological Drug Advisory Committee; Princess Margaret Cancer Centre (PMCC), Gynecologic Cancers Disease Site Group, Medical Oncology Group; Saskatchewan Cancer Agency (SCA); The Society of Gynecologic Oncology of Canada (GOC); and Sunnybrook Health Sciences Centre (SBHSC).
- A review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

Patient and caregiver input used for this review was collected by the Canadian Cancer Society (CCS). The input was based on an online survey and patient and caregiver testimonials. A total of 6 testimonials and 22 survey responses were received from 20 patients with current or previous EC and 2 caregivers.

Respondents indicated that EC symptoms affected their daily activities, causing detrimental effects on their health-related quality of life (HRQoL). Respondents highlighted that the most significant side effects due to their current cancer treatment were issues with libido, sexual function and fatigue. Loss of income due to absence from work and travel costs for cancer treatment were noted as the most common financial barriers.

Respondents reported that they expect the following key outcomes for any treatment: better HRQoL, longer periods of remission, better affordability, better access, and fewer side effects. Eight out of 22 respondents indicated that they had direct experience with receiving or assisting a patient to receive dostarlimab. All respondents indicated that compared to other therapies, dostarlimab was easier to use, either due to little to no side effects, longer intervals between doses, or a shorter infusion time. Patients also reported long periods of remission and improved quality of life. Patients found dostarlimab to be more convenient for the administration schedule and infusion time, particularly for those patients living in rural areas. In feedback on the CADTH draft recommendation from the patient group, patients receiving dostarlimab expressed a strong desire to continue with their treatment and concern was raised about losing access to dostarlimab in case it is not funded.

Clinician Input

Input From Clinical Experts Consulted by CADTH

All CADTH 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 EC.

The clinical experts consulted by CADTH indicated that currently there are no standard funded second-line treatment options for advanced or recurrent EC. The clinical experts agreed that patients who would most benefit from dostarlimab include those with an identified dMMR or MSI-H recurrent or advanced EC. One of the clinical experts noted that dostarlimab could be used as monotherapy in first-line or later in the absence of effective treatments. The clinical experts noted that treatment with dostarlimab would not be suitable in patients with the following characteristics: very poor performance status; prior history of severe autoimmune disease; prior immunotherapy use; known uncontrolled central nervous system metastases and/or carcinomatous meningitis; poor medical risk due to a serious uncontrolled medical disorder; non-malignant systemic disease or active infection requiring systemic therapy; or microsatellite-stable (MSS) EC.

In the opinion of the clinical experts consulted by CADTH, treatment with dostarlimab should be discontinued if there is disease progression, severe toxicity, or intolerability of the treatment for the patient. The clinical experts indicated that the following outcomes would best assess response to treatment: overall survival (OS); response rate based on clinical and radiological investigations; progression-free survival (PFS); reduction of cancer burden and symptomatic improvement in activities of daily living; HRQoL; durability of response; and response to subsequent therapies.

In terms of clinically meaningful response, the clinical experts recommended that in addition to clinical assessment of disease symptoms and duration of disease control, the use of standard immune-related Response Evaluation Criteria in Solid Tumours (irRECIST) for the assessment of response to immunotherapeutic treatments may be useful.

Clinician Group Input

A total of 7 clinician group inputs were submitted from the following groups: British Columbia Cancer Provincial Gynecological Oncology Tumour Group; McGill University Health Centre (MUHC); Ontario Health-Cancer Care Ontario (OH-CCO) Gynecological Drug Advisory Committee; Princess Margaret Cancer Centre (PMCC), Gynecologic Cancers Disease Site Group; Saskatchewan Cancer Agency (SCA); The Society of Gynecologic Oncology of Canada (GOC); and Sunnybrook Health Sciences Centre (SBHSC).

The views of the clinician groups were overall consistent with those of the clinical experts consulted by CADTH. The clinician groups indicated that the most important treatment goals are achieving disease control, delaying worsening of symptoms, prolonging survival, maintaining HRQoL, delaying disease progression, and the drug having an acceptable safety profile. All the clinician groups indicated that all patients with recurrent EC would benefit from an effective immunotherapy, but patients with dMMR or MSI-H subtypes would most benefit from an immune checkpoint inhibitor therapy. All groups recommended that patients diagnosed with metastatic EC should be offered platinum-based chemotherapy as first-line therapy. However, the BC Cancer Provincial Gynecological Oncology Tumour Group did acknowledge that treatment with an immune checkpoint inhibitor may be an appropriate first-line therapy for patients for whom chemotherapy is contraindicated or not desirable.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for dostarlimab:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions.

Clinical Evidence

Pivotal Study

Description of Study

The GARNET trial (Study 4010-01-001) is an ongoing non-randomized, non-comparative, multi-centre, open-label, phase I dose escalation and cohort expansion study in patients with recurrent or advanced solid tumours. The objective of part 2B of the GARNET trial was to evaluate the safety and anti-tumour activity of dostarlimab in patients with advanced solid tumours. Cohort A1 included patients with advanced or recurrent dMMR or MSI-H EC that had progressed on or following prior treatment with a platinum-containing regimen. Patients were enrolled from 123 sites in 8 countries (including 8 Canadian sites). Enrolment started on April 10, 2017 and is ongoing.

To be eligible, patients had to be at least 18 years of age, diagnosed with recurrent or advanced dMMR or MSI-H EC, and had progressed on or after no more than 2 lines of prior systemic therapy, with at least 1 of these being platinum-based doublet therapy. In addition, patients had to have adequate organ function and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The study consisted of 3 phases, the screening phase (up to 35 days before treatment), the treatment phase, and the follow-up phase. A total of 129 patients were enrolled into Cohort A1. All patients received dostarlimab via IV infusion (500 mg every 3 weeks for cycles 1 to 4, and 1,000 mg every 6 weeks from cycles 5 and onward) for up to 2 years or until disease progression, treatment discontinuation, or patient withdrawal from the study.

The co-primary outcomes of the GARNET trial were ORR and duration of response (DOR). The secondary outcomes were OS, disease control rate (DCR), immune-related DCR (irDCR), PFS, immune-related PFS (irPFS), immune-related ORR (irORR), and immune-related DOR (irDOR). HRQoL was an exploratory outcome assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the EQ-5D-5L. The safety outcomes assessed included treatment-emergent adverse events (TEAEs), serious adverse events, immune-related adverse events (irAEs), ECOG performance status, clinical laboratory measures, vital signs, electrocardiogram, physical examination, serum pregnancy testing and concomitant medications.

The GARNET trial has 3 planned interim analyses (IA) that are contingent on a combined enrolment and 24 weeks of follow-up of 100, 200, and 300 patients, respectively, between

Cohort A1 and Cohort F. The data cut-off dates were July 8, 2019, March 1, 2020, and November 1, 2021 for IA-1, IA-2 and IA-3 interim analysis (N = 143), respectively. The GARNET trial was sponsored by GlaxoSmithKline Inc.

Since only 2 (< 2%) enrolled patients had MMR-unknown but MSI-H tumours (MMR-unk/MSI-H), these patients were included among those patients with dMMR tumours. The median age was 64 years (range 39 to 80 years). Median weight was 71 kg (range 34.0 to 141.4), and median body mass index (BMI) was 27.97 kg/m^2 (range: 13.6 to 53.9 kg/m^2). Most patients were White (> 75%). The most common histology type of EC was type 1 endometrioid carcinoma (67.6%) with grade 2 being the most common histology grade at diagnosis (39%). More than 2/3 (67.6%) of patients had stage IV EC. ECOG performance status of 1 was the most common (60%) followed by ECOG 0 (40%). All patients received prior anticancer treatment. Most patients (88.6%) had 2 or fewer lines of prior anticancer regimens, and a smaller proportion had 2 or more lines of therapy (11.5%). More than half (56.2%) of patients had received prior regimens for metastatic disease. The patient subgroups of interest, as identified in the CADTH systematic review protocol, included the following: FIGO stage, histology of tumour type (e.g., type I, type II) and subtypes (e.g., clear cell carcinoma), number and type of prior systemic therapies (e.g., chemotherapy, hormonal therapy), prior radiation, and progression-free interval from the last platinum-containing prior anticancer therapy.

Outcomes

At the time of the second interim analysis (IA-2), the median duration of follow up was 16.3 months and the median duration of treatment was 26 weeks. At IA-3, the median duration of follow up was 27.6 months.

At IA-2, the proportion of patients who achieved an ORR (complete response [CR] or partial response [PR]) was 44.8% (95% CI, 35.0 to 54.8). The best overall response (BOR) was CR in 11 patients (10.5%), PR in 36 patients (34.3%), and stable disease in 13 patients (37.1%). The DCR was 57.1% (95% CI, 35.0 to 54.8). Of those who responded, 89.5% had an ongoing response. The median DOR was not reached, but 79% of patients who achieved an objective response had a DOR of at least 6 months.

At the time of IA-2, a considerable proportion of patients (66.7% and 45.7%, respectively) had no OS or PFS events. The median OS was not reached, but Kaplan–Meier (KM) estimates for the probability of survival at 6, 9, and 12 months were 80.9% (95% CI, 71.7 to 87.4), 75.1% (95% CI, 65.2 to 82.6), and 68.9% (95% CI, 58.3 to 77.4) respectively. The median PFS was 5.5 months (95% CI, 3.2 to not reached), with KM estimates of PFS by RECIST v.1.1 of 48.6% (95% CI, 38.6 to 57.9) at month 6 and 47.5% (95% CI, 37.4 to 56.8) at month 9 as well as month 12. In terms of HRQoL, EQ-VAS and EORTC QLQ-C30 scores appeared stable over time. Summary data for the EQ-5D-5L descriptive system were not provided.

As part of the sponsor's feedback on the CADTH reimbursement review report, the sponsor provided CADTH with the IA-3 data for baseline characteristics and efficacy and safety outcomes in the GARNET trial. The results of the updated analysis were overall consistent with those reported for IA-2. The proportion of patients who achieved an ORR (CR or PR) was 45.5% (95% CI, 37.1% to 54.0%). The BOR was CR in 23 patients (16.1%), PR in 42 patients (29.4%), and stable disease in 21 patients (14.7%).

Harms Results

Almost all patients (95.3%) experienced at least 1 TEAE. The most common serious TEAEs were abdominal pain, acute kidney injury, sepsis, pulmonary embolism, pyrexia, and urinary tract infection. Grade 3 or higher TEAEs occurred in 48.1% of patients, with the most common being anemia (14.7%), abdominal pain (5.4%) and hyponatremia (3.9%). No patient withdrew due to an adverse event (AE) as a primary reason. Study treatment discontinuation due to AEs occurred in 11.6% of patients, while AEs that led to study treatment interruption occurred in 24% of patients. The most common AEs leading to study interruption were anemia (3.1%) and diarrhea (2.3%).

One patient died due to a TEAE (aspiration) during the treatment period and 4 patients died due to TEAEs during the 90-day safety follow-up (i.e., pleural effusion, pneumonia, sepsis, and shock). None of the TEAEs leading to death were considered treatment-related; and no TEAEs were the primary cause of death during the long-term follow-up period.

The notable harms associated with dostarlimab included immune-related toxicity. The incidence of irAEs was 34.9% in patients in Cohort A1. The most frequently reported irAEs (≥ 5%) were diarrhea and hypothyroidism. A total of 7.9% of patients had a serious irAE, 12.7% of patients had at least a grade 3 irAE, and 4.8% had an irAE that led to study treatment discontinuation. Most of the irAEs were considered related to study treatment.

Data were provided on AEs for IA-3. Overall, the incidence of AEs, including notable harms, were similar between IA-2 and IA-3, with no new safety signals identified.

Critical Appraisal

Internal Validity

The main limitation of the GARNET trial is the single-arm design, which makes it challenging to interpret the data and determine whether the efficacy and safety events observed were attributable to dostarlimab. Formal hypothesis and statistical significance testing were not performed aside from ORR, thus limiting the ability to draw conclusions. Given that results were based on an interim analysis, some time-to-event outcomes, including median OS and DOR, were not reached due to data immaturity; therefore, the treatment effect observed with dostarlimab may be overestimated. The risk of overestimating HRQoL benefit and known subjective harms is also high given the open-label trial design whereby treatment was not blinded. To mitigate bias, the sponsor used a blinded independent central review to evaluate treatment response using standardized criteria for certain efficacy outcomes (i.e., ORR, DOR, PFS, and DCR). Therefore, bias is less of a concern for these objective end points and OS, and more of a concern for subjective end points including HRQoL and safety. It is also acknowledged that mature OS data will be confounded by the use of subsequent anticancer therapy received by some patients after disease progression. No analyses were undertaken to account for the potential of confounding treatments. Overall, the magnitude and direction of bias is unclear. The clinical experts agreed that in the absence of robust comparative data on PFS and OS, no firm conclusions could be drawn on how dostarlimab compares with other relevant treatment options, as causal inferences cannot be made based on the results of a single-arm trial design.

HRQoL was identified as an important outcome by the patient and clinician groups providing input for this review. However, no conclusions could be drawn based on the HRQoL data from the GARNET trial due to several limitations. Given the wide and overlapping CIs, the reduced number of patient responses over time, and the lack of statistical testing and a definition of

what constituted a clinically meaningful response, it is not possible to draw conclusions with precision based on the available data.

External Validity

Overall, the clinical experts consulted by CADTH agreed that the inclusion and exclusion criteria, baseline patient characteristics, concomitant medications, and prohibited medications present in Cohort A1 of the GARNET trial were reflective of patients they see in clinical practice for the indication under review. There were no barriers to identifying patients who would most benefit from the treatment given that testing for MMR/MSI status is standard practice in Canada. The clinical experts indicated that no difference in treatment effect would be expected based on variation in disease management practices across participating countries. In the opinion of the clinical experts, as long as patients have dMMR or MSI-H tumour status, dostarlimab would be appropriate to administer after any of the prior therapies received by patients in the trial. However, they noted that clinical benefit may be diminished in patients with more prior lines of systemic therapy. There were a limited number of patients included in the primary efficacy dataset (N = 105) and very few patients from various ethnic backgrounds, which may reduce the generalizability of the results to a real-world practice setting. Furthermore, the subgroup analyses had no statistical comparisons and even smaller sample sizes, which limits the generalizability to a broader population.

Indirect Comparisons

Description of Studies

The sponsor submitted a total of 6 reports of ITCs; 3 reports of MAICs, and 3 reports of IPTW analyses, which aimed to compare survival between dostarlimab from the phase I GARNET trial to the current treatment paradigm in advanced or recurrent EC.

Efficacy Results

The primary end points for all comparisons were OS. Other outcomes included PFS, ORR, DOR, time to treatment discontinuation, duration of treatment, time to next treatment, time to deterioration in HRQoL and AEs; however, these were less frequently investigated, and outcomes specifically important to patients including HRQoL were not assessed. The results of the MAIC and IPTW analyses generally suggest that dostarlimab is favoured for OS over all the included comparators.

Harms Results

The sponsor submitted MAIC and IPTW reports did not assess safety outcomes.

Critical Appraisal

Though the results of the MAIC and IPTW analyses generally suggest that dostarlimab is favoured for OS over all the included comparators, there was significant uncertainty in the results based on the clinical heterogeneity of the included populations resulting in reduced sample sizes and wide CIs. There were significant differences in the design of the comparator studies that limit the ability to draw strong conclusions about the effectiveness of dostarlimab compared with other treatments. An important limitation of all analyses was that MMR and MSI-H status were unknown for all or most patients in the comparator trial. Therefore, it is uncertain whether the comparator population in the ITC analyses would be eligible for treatment with dostarlimab, providing further uncertainty about the comparative effectiveness.

Economic Evidence

Cost and Cost-Effectiveness

Table 1: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult patients with dMMR/MSI-H advanced or recurrent EC that have been previously treated with platinum-based chemotherapy (PBCT) (Cohort A1 of GARNET study)
Treatment	Dostarlimab
Submitted price	Dostarlimab, 50 mg/mL, single-use vial: $10,270.00 per 500 mg vial
Treatment cost	At a submitted price of $10,270.00 per 10 mL vial (50 mg/mL), the 28-day cost of dostarlimab is $13,655.
Comparator	Current mix of treatments (CMT), a weighted distribution of chemotherapies and hormone therapies, which included cisplatin plus doxorubicin, carboplatin plus gemcitabine, cisplatin, cisplatin in combination with cyclophosphamide plus doxorubicin, and gemcitabine. Single-drug and combination therapies were also included as individual comparators. • Doxorubicin monotherapy. • Carboplatin monotherapy • Pegylated liposomal doxorubicin (PLD). • Paclitaxel monotherapy. • Carboplatin + paclitaxel. • Carboplatin + PLD.
Outcomes	QALYs, LYs
Time horizon	Lifetime (40 years)
Key data source	Treatment efficacy of dostarlimab (i.e., OS and PFS) was informed by the GARNET study, a non-randomized, single-arm, multi-centre, open-label study. Comparative efficacy of comparator treatments was estimated using a combination of approaches based on unanchored ITCs, including the use of HRs estimated from MAICs, inverse probability treatment weighting (IPTW) methods, and/or parametric survival distributions, and was sourced from a UK real-world evidence (RWE) cohort (National Cancer Registration and Analysis Service [NCRAS] database).
Submitted results	The sponsor conducted both a series of pairwise comparisons and sequential analyses. Sequential analyses were not presented due to the lack of comparability among patient populations. Dostarlimab vs PLD: (ICER = $138,486 per QALY). Dostarlimab vs. doxorubicin: (ICER = $139,936 per QALY). Dostarlimab vs. paclitaxel: (ICER = $147,467 per QALY). Dostarlimab vs. CMT: (ICER = $159,352 per QALY). Dostarlimab vs carboplatin + PLD: (ICER = $160,664 per QALY). Dostarlimab vs. Carboplatin + paclitaxel: (ICER = $164,193 per QALY). Dostarlimab vs carboplatin: (ICER = $171,989 per QALY).

Component	Description
Key limitations	• The clinical evidence available for dostarlimab was from a single-arm phase I trial (i.e., no comparator arm was included). In the absence of direct comparative trial evidence for dostarlimab, the sponsor submitted a model with survival parameters based on a series of indirect treatment comparisons (ITCs). The CADTH clinical review of these ITCs identified key limitations in their interpretability. The estimated effectiveness of dostarlimab compared to relevant comparators is therefore highly uncertain. • The sponsor derived survival data from an RWE cohort from the UK in the base case and included alternative sources for survival estimates as part of the scenario analyses. The dMMR/MSI-H status of members of the RWE cohort and other sources was unknown, and therefore they did not match the indicated population. Input from clinical experts consulted by CADTH indicated that dMMR/MSI-H status had important implications for survival and clinical management. Given the lack of alignment between the comparator cohort and the pivotal trial cohort, the cost-effectiveness of dostarlimab relative to all comparator treatments within the indicated population is unknown. • The sponsor's use of a partitioned survival model suggests a post-progression survival bias in favour of dostarlimab, which is not supported by the single-arm phase I trial. • Long-term extrapolations of OS and PFS were highly uncertain and likely overestimated the incremental benefit in favour of dostarlimab. • The sponsor's choice of comparators did not reflect current standard of care in Canada, as the sponsor excluded several relevant comparators and included others; among included treatments, hormonal therapies were rarely used in Canada in this setting. • Additional issues in the model included no treatment discontinuation nor treatment-waning effects over the lifetime time horizon, which overestimated the costs and QALYs associated with dostarlimab; and the health state utility value for patients in the progressed disease health state lacked validity, which likely overestimated patients' quality of life post-progression, in favour of dostarlimab.
CADTH reanalysis results	• Due to the significant uncertainty associated with the comparative clinical efficacy and safety evidence, as well as the sponsor's use of an inappropriate modelling approach, CADTH was unable to estimate the cost-effectiveness of dostarlimab in the indicated population. The cost-effectiveness of dostarlimab compared to currently available treatment options is unknown. CADTH conducted exploratory analyses, and found the cost-effectiveness results are highly sensitive to the choice of survival extrapolation function. • CADTH's exploratory analysis included: applying an alternate parametric distribution for the overall survival of dostarlimab (Exponential); applying an alternate parametric distribution for the progression-free survival of dostarlimab (Log-Normal); applying a stopping rule at 2 years with 60% of patients discontinuing treatment; and applying a treatment-waning effect, starting at 2 years for patients who received dostarlimab. Results from CADTH's exploratory scenario reanalyses demonstrate the ICER's ranged from $185,452 to $446,759 per QALY, up to 4 times higher than the ICER reported in the sponsor's submission. • The exploratory analysis suggested that a price reduction of 83% would be needed for dostarlimab to be considered cost-effective at a willingness-to-pay threshold of $50,000. The exploratory analysis is still subject to the limitations within the sponsor's submission — most crucially the inappropriateness of the estimated efficacy of comparator treatments in the dMMR-MSI-H population. An additional price reduction may be warranted.

CMT = current mix of treatments; dMMR = deficient mismatch repair; EC = endometrial cancer; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; LY = life-year; MSI-H = microsatellite instability high; PBCT = platinum-based chemotherapy; PLD = pegylated liposomal doxorubicin; PSM = partitioned survival model; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis. There is uncertainty around the estimates used to determine the size of the population eligible for treatment with dostarlimab; the market share distribution in the reference scenario does not align with the frequency of use expected in the second-line setting for the indicated population; the anticipated market uptake of dostarlimab was underestimated; and

inappropriate assumptions were made regarding the proportion of patients who were alive and on treatment over the 3-year time horizon. CADTH undertook a reanalysis to derive the CADTH base case by revising estimates used to determine the size of the population; revising market share assumptions in the reference and new drug scenarios; revising assumptions related to treatment discontinuation; and applied changes to the projected proportion of patients predicted to remain alive and on treatment. The estimated budget impact with the reimbursement of dostarlimab was $17,210,255 in year 1, $24,691,144 in year 2, $28,464,789 in year 3, for a total incremental budget impact of $70,366,188 over the 3-year time horizon. However, there remains uncertainty with the sponsor's estimated budget impact due to uncertainty in the potential population size, anticipated market uptake, and the exclusion of relevant comparators.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Initial meeting date: March 8, 2022

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

Reconsideration meeting date: August 10, 2022

Regrets: Three expert committee members did not attend.

Conflicts of interest: None