CADTH Reimbursement Review

Provisional Funding Algorithm

Indication: Endometrial cancer
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June 2024

Background

Following a request from jurisdictions, CADTH may design or update an algorithm depicting the sequence of funded treatments for a particular tumour type. These algorithms are proposals for the jurisdictions to implement and adapt to the local context. As such, they are termed provisional. Publishing of provisional algorithms is meant to improve transparency of the oncology drug funding process and promote consistency across jurisdictions.

Provisional funding algorithms are based on 3 principal sources of information:

- CADTH pCODR Expert Review Committee (pERC) reimbursement recommendations and/or implementation guidance regarding drug place in therapy and sequencing
- implementation advice from panels of clinicians convened by CADTH concerning the sequencing of drugs in the therapeutic space of interest
- existing oncology drug reimbursement criteria and legacy funding algorithms adopted by jurisdictional drug plans and cancer agencies.

Note that provisional funding algorithms are not treatment algorithms; they are neither meant to detail the complete clinical management of each patient nor the provision of each drug regimen. The diagrams may not contain a comprehensive list of all available treatments, and some drugs may not be funded in certain jurisdictions. All drugs are subject to explicit funding criteria, which may also vary between jurisdictions. Readers are invited to refer to the cited sources of information on the CADTH website for more details.

Provisional funding algorithms also delineate treatment sequences available to patients who were never treated for the condition of interest (i.e., the incident population). The algorithm does not detail time-limited funding of new options for previously or currently treated patients (i.e., the prevalent population).

Provisional funding algorithms may contain drugs that are under consideration for funding. CADTH will not dynamically update algorithms following changes to drug funding status. Revisions and updates will occur only upon request by jurisdictions.

Jurisdictional cancer drug programs requested a CADTH provisional funding algorithm for endometrial cancer. However, no outstanding implementation issues were identified, and no additional implementation advice is provided in this report. The algorithm depicted herein is meant to reflect the current and anticipated funding landscape based on the previously mentioned sources of information.

History and Development of the Provisional Funding Algorithm

We have not previously published a provisional funding algorithm report on endometrial cancer. The purpose of this rapid provisional funding algorithm is to incorporate the latest CADTH recommendation of dostarlimab in combination with carboplatin and paclitaxel for the treatment of adult patients with primary advanced or recurrent mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H)

endometrial cancer. In addition, CADTH's recommendation of pembrolizumab and pembrolizumab plus lenvatinib would be incorporated into this provisional funding algorithm.

Table 1: Relevant CADTH Recommendations

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Dostarlimab (Jemperli)	May 22, 2024	The pCODR Expert Review Committee (pERC) recommends that dostarlimab in combination with carboplatin-paclitaxel be reimbursed for the first-line treatment of adult patients with primary advanced or recurrent mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) endometrial cancer who are candidates for systematic therapy only if the following conditions are met: **Initiation** 1. Treatment with dostarlimab + carboplatin-paclitaxel should be reimbursed in adult patients with dMMR or MSI-H primary advanced or recurrent endometrial cancer not amenable to curative therapy who meet at least 1 of the following criteria: 1.1. have primary stage III or IV endometrial cancer 1.2. have a first recurrence and have not previously received systematic anticancer therapy in advanced disease 1.3. have received prior neoadjuvant or adjuvant systemic anticancer therapy and a first recurrence at a minimum of 6 months after completion of treatment. 2. Patients should have a good performance status. 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 drug for advanced disease 3.3. uncontrolled brain metastases. **Discontinuation** 4. Discontinuation should be based on a combination of clinical and radiological progression and/or significant adverse events potentially related to dostarlimab plus carboplatin-paclitaxel. 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]). **Prescribing** 6. Dostarlimab + carboplatin-paclitaxel should be prescribed by clinicians with expertise in advanced uterine cancer; treatment should be supervised and delivered in institutions with expertise in systemic therapy delivery. 7. Dostarlimab + carboplatin-paclitaxel should only be reimbursed when started in combination. **Pricing:** 8. A reduction in price. **Feasibility of adoption:** 9. The feasibility of adoption of dostarlimab + carboplatin-paclitaxel must be addressed. **Guidance on Treatment Sequencing** **Consideration for initiation of therapy** • The clinical experts we consulted consider patients with variant cancers who experience disease relapse within 6 months after treatment to be platinum-resistant.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		Although this definition has not been applied to patients with endometrial cancer, the experts we consulted would consider those with disease relapse within 6 months after 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 within 6 months from neoadjuvant or adjuvant systemic therapy. • Based on studies of single-drug PD-1 inhibitors (e.g., GARNET study), the clinical experts we consulted consider patients who have disease relapse within 6 months after treatment may be eligible for treatment with a single-drug PD-1 inhibitor. • pERC noted that there is insufficient evidence to support using single-drug dostarlimab in patients who experience disease relapse less than 6 months from neoadjuvant or adjuvant systemic therapy. • According to the clinical experts we consulted, patients with disease progression within 6 months of treatment tend to have poor prognosis, treatment options may include radiation, chemotherapeutic drugs, experimental drugs, or single-drug PD-1 inhibitors. pERC agreed with the clinical experts' response. • Given the absence of data, the clinical experts we consulted 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 re-treatment 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. **Consideration for discontinuation of therapy** • The clinical experts we consulted would offer dostarlimab monotherapy to patients who are unable to tolerate chemotherapy, based on evidence that single-drug PD-1 inhibitors have demonstrated excellent responses among patients with primary advanced and recurrent dMMR endometrial cancer. • The clinical experts we consulted 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. **Generalizability** • The clinical experts we consulted 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** • Based on current approval and funding status, pembrolizumab monotherapy is indicated for the treatment of adult patients with unresectable or MSI-H or dMMR endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options. pERC agreed with the review team that it is not possible to comment on potential future comparators.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Pembrolizumab (Keytruda)	February 22, 2023	The CADTH pCODR Expert Review Committee (pERC) recommends that pembrolizumab be reimbursed as monotherapy for the treatment of adult 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, only if the following conditions are met: **Initiation:** 1. Treatment with pembrolizumab should only be reimbursed in adult patients with unresectable or metastatic MSI-H or dMMR endometrial cancer whose tumours have progressed following prior therapy or who are intolerant of prior therapy. 2. Patients must have good PS. 3. Patients must not have any of the following: 3.1. prior treatment with a PD-1 or PD-L1 inhibitor 3.2. active CNS metastases 3.3. active autoimmune disease. **Discontinuation:** 4. Discontinuation should be based on a combination of clinical and radiological progression and/or significant adverse events potentially related to pembrolizumab. 5. Pembrolizumab should be reimbursed for a maximum of 35 cycles (for 200 mg dosing), or 18 cycles (for 400 mg dosing) or 2 years, whichever is longer. **Prescribing:** 6. Pembrolizumab should be prescribed in an outpatient oncology clinic; treatment should be supervised and delivered in institutions with expertise in systemic therapy delivery. 7. Pembrolizumab should not be used in combination with other systemic therapies for dMMR or MSI-H endometrial cancer. **Pricing:** 8. A reduction in price. **Guidance on Treatment Sequencing:** • pERC agreed with clinical experts that there is uncertainty regarding the number of previous platinum-based treatments before pembrolizumab monotherapy. As such, pERC did not have evidence to specify eligibility criteria for pembrolizumab based on the number of prior lines of platinum therapy. • Clinical experts suggested that pembrolizumab might be preferable to a different treatment after platinum because of the toxicity of alternative chemotherapy options (such as doxorubicin). • pERC agreed with the clinical experts that re-treatment with the same regimen is a valid question. pERC noted that it would be reasonable to readminister pembrolizumab (up to 17 additional administrations of 200 mg) at the discretion of the treating physician for patients who have discontinued pembrolizumab at the time of relapse only if the treatment was discontinued before disease progression or disease progression occurred during a treatment break. • pERC agreed with the clinical experts that patients who had started next-line therapy after platinum-based chemotherapy should be given the choice to switch to pembrolizumab on a time-limited basis. However, the preference would be to continue with the current regimen and switch to pembrolizumab when progression occurs, particularly if patients are responding to current treatment.

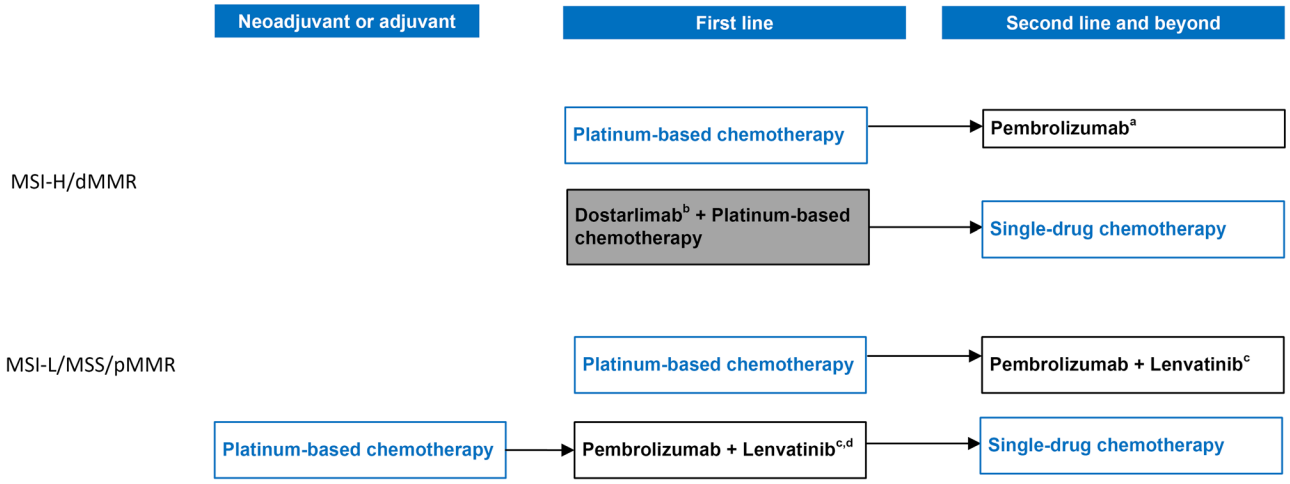
Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
Pembrolizumab plus Lenvatinib	September 20, 2022	The CADTH pCODR Expert Review Committee (pERC recommends that Keytruda in combination with Lenvima (Keytruda-Lenvima) should be reimbursed by public drug plans for the treatment of adult patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior platinum-based systemic therapy, and are not candidates for curative surgery or radiation if the following conditions are met: **Initiation:** 1. Treatment with PEM-LEN should be initiated in patients who have all of the following: 1.1. advanced, recurrent, or metastatic endometrial carcinoma 1.2. radiographic evidence of disease progression after 1 prior systemic, platinum-based chemotherapy regimen 1.3. have received up to 2 regimens of platinum-based chemotherapy in total, as long as 1 was given in the neoadjuvant or adjuvant treatment setting. 2. Patient must not have either of the following: 2.1. MSI-H 2.2. dMMR disease. 3. Patients must not have any of the following: 3.1. unstable CNS metastases 3.2. carcinosarcoma and sarcomas 3.3. active autoimmune disease 4. Patients should have a good performance status **Discontinuation:** 5. Discontinuation should be based on a combination of clinical and radiological progression or significant adverse events potentially related to PEM-LEN. 6. PEM should be reimbursed for a maximum of 35 cycles (200 mg every 3 weeks), 18 cycles (400 mg every 6 weeks), or 2 years, whichever is longer. LEN can be continued beyond this time. **Prescribing:** 7. PEM-LEN should be prescribed in an outpatient oncology clinic; treatment should be supervised and/or delivered in institutions with expertise in systemic therapy delivery. 8. PEM-LEN should only be reimbursed when administered in combination. **Pricing:** 9. A reduction in price. **Feasibility of adoption:** 10. The feasibility of the adoption of PEM-LEN must be addressed. **Guidance on Treatment Sequencing** **Considerations for initiation of therapy:** • According to the KEYNOTE-775 eligibility criteria, patients had to have progressive disease after 1 prior systemic, platinum-based chemotherapy regimen. Patients were excluded if they had received more than 1 prior systemic chemotherapy regimen (other than adjuvant or neoadjuvant therapy). In the PEM-LEN group, 77.7%, 21.7% and 0.3% of patients had received 1, 2 and 3 or more lines of prior platinum-based chemotherapy respectively. • pERC agreed with the clinical experts consulted by CADTH that the results of the KEYNOTE-775 trial could be generalized to patients with multiple prior lines of platinum- and nonplatinum-based chemotherapy who otherwise met the trial's eligibility criteria.

Generic name (brand name)	Date of recommendation	Recommendation and guidance on treatment sequencing
		• pERC acknowledged input from the clinical experts that most patients would not have received more than 3 lines of platinum-based chemotherapy in clinical practice, given the toxicity concerns with repeated chemotherapy treatments. • In the KEYNOTE-775 trial, PEM treatment was given for a maximum of 35 cycles (i.e., for up to 24 months). Patients who discontinued treatment with PEM-LEN and had stable disease or better were allowed to receive an additional year of treatment (17 cycles) with PEM with or without LEN if they progressed after stopping study treatment during the initial treatment period. If LEN was discontinued due to toxicity during the initial treatment period, only PEM was allowed to be administered during the second course; otherwise, LEN was permitted to be administered with PEM during the second course. Subsequent PEM-LEN was received by 3 patients in the PEM-LEN study group of the KEYNOTE-775 trial. • pERC agreed with the clinical experts consulted by CADTH that re-treatment per the previously outlined KEYNOTE-775 criteria would be reasonable and consistent with pERC guidance on PEM for other indications. • pERC agreed with the clinical experts that at the discretion of the treating physician, patients could continue with 1 drug if the other drug in the treatment combination is not well tolerated or was discontinued.
Pembrolizumab and Lenvatinib	Withdrawn	NA
Dostarlimab (Jemperli)	September 12, 2022	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.

CNS = central nervous system; dMMR = mismatch repair deficient; EC = endometrial cancer; ECOG = Eastern Cooperative Oncology Group; KN-158 = KEYNOTE-158; MMR = mismatch repair; MSI-H = microsatellite instability-high; NA = not applicable; PCC = physician's choice of chemotherapy; PD-1 = programmed cell death 1 protein; PD-L1 = programmed cell death 1 ligand 1; PEM-LEN = pembrolizumab- lenvatinib; PS = performance status.

Provisional Funding Algorithm

Figure 1: Provisional Funding Algorithm Diagram for Endometrial Cancer



[a] Patients must not have any of the following: prior treatment with a PD-1 or PD-L1 inhibitor, active CNS metastases or active autoimmune disease. Note that patients may also receive multiple prior lines (e.g., not limited to second line only) as long as the eligibility criteria are met. Pembrolizumab should be reimbursed for a maximum of 35 cycles (for 200 mg dosing), or 18 cycles (for 400 mg dosing) or 2 years, whichever is longer.

[b] Patients must not have any of the following: first recurrence within 6 months of completing neoadjuvant or adjuvant systemic anticancer therapy, prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent and uncontrolled brain metastases. 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).

[c] Patients must have disease progression following platinum-based chemotherapy. Pembrolizumab should be reimbursed for a maximum of 35 cycles (200 mg every 3 weeks), 18 cycles (400 mg every 6 weeks), or 2 years, whichever is longer. Lenvatinib can be continued beyond this time.

[d] For patients with disease progression within 6 months of neoadjuvant or adjuvant platinum-based chemotherapy.

Note that for patients with HER2 positive serous disease, trastuzumab with platinum-based chemotherapy may be funded in some jurisdictions.

Legend

Therapy funded across most jurisdictions	Therapy under review for funding (pCPA or province/cancer agency)

Abbreviations: CNS = central nervous system; dMMR = mismatch repair deficient; EC = endometrial cancer; ECOG = Eastern Cooperative Oncology Group; KN-158 = KEYNOTE-158; MMR = mismatch repair; MSI-H = microsatellite instability-high; MSI-L = microsatellite instability – low; MSS = microsatellite stable; PCC = physician's choice of chemotherapy; PD-1 = programmed cell death 1 protein; PD-L1 = programmed cell death 1 ligand 1; PEM-LEN = pembrolizumab- lenvatinib; pMMR = proficient mismatch repair; PS = performance status.

Description of the Provisional Funding Algorithm

Microsatellite Instability-High or Mismatch Repair Deficient

In adult patients with primary advanced or recurrent mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) endometrial cancer, their first-line options include platinum-based chemotherapy or dostarlimab plus platinum-based chemotherapy. For patients who have received platinum-based chemotherapy as the first-line option, the second-line option is pembrolizumab. Patients may also receive multiple prior lines (e.g., not limited to the second line only) if the eligibility criteria are met. For patients

who have received dostarlimab plus platinum-based chemotherapy as the first-line option, the subsequent second-line option can be single-drug chemotherapy. Patients receiving dostarlimab must not have a first recurrence within 6 months of completing neoadjuvant or adjuvant systemic anticancer therapy, prior therapy with an anti-PD-1, anti-PD-L1 or anti-PD-L2 drug and uncontrolled brain metastases. Dostarlimab plus platinum-based chemotherapy is under review for funding.

Microsatellite Instability–Low, Mismatch Repair, or Proficient Mismatch Repair

In adult patients with advanced endometrial carcinoma that is microsatellite instability-low (MSI-L), mismatch repair (MMR) or proficient mismatch repair (MMR), their first-line option is platinum-based chemotherapy, followed by a second-line option with pembrolizumab plus lenvatinib. Adult patients who have received platinum-based chemotherapy in the neoadjuvant or adjuvant setting and have disease progression within 6 months may receive pembrolizumab plus lenvatinib in the metastatic setting, followed by single-drug chemotherapy. Note that to receive pembrolizumab plus lenvatinib, patients must have disease progression following platinum-based chemotherapy.

Additional Remarks

For patients with HER2-positive serous disease, trastuzumab with platinum-based chemotherapy may be funded in some jurisdictions.

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