Draft Reimbursement Recommendation

Trametinib

Reimbursement request: For the treatment of recurrent low-grade serous ovarian cancer

Requester: Public drug programs

Draft recommendation: Reimburse with conditions

Summary

The Formulary Management Expert Committee (FMEC) recommends that trametinib be reimbursed for the treatment of adult patients with recurrent low-grade serous ovarian cancer if conditions in Table 2 are met.

FMEC reviewed the GOG 281/LOGS trial identified by CDA-AMC's systematic review of the literature, that compared trametinib to physician's choice of therapy in patients with recurrent low-grade serous ovarian cancer. FMEC also considered input received from external partners, including Ontario Health (Cancer Care Ontario) Gynecologic Cancer Drug Advisory Committee, and public drug programs.

FMEC noted that based on the GOG 281/LOGS trial, treatment with trametinib was associated with a meaningful improvement in progression-free survival and objective response rate when compared with physician's choice of therapy. However, there was some uncertainty in the findings. FMEC concluded that trametinib may address a significant unmet need in the treatment of adult patients with recurrent low-grade serous ovarian cancer, although the clinical value remains uncertain.

The reimbursement of trametinib for the treatment of adults with recurrent low-grade serous ovarian cancer is expected to increase drug acquisition costs.

Therapeutic Landscape

What Is Recurrent Low-Grade Serous Ovarian Cancer?

Low-grade serous cancer of the ovary, fallopian tube, or peritoneum accounts for approximately 5% of all epithelial ovarian carcinomas. Compared to high-grade serous ovarian cancer, low-grade serous ovarian cancer is commonly characterized by younger age at diagnosis, and by advanced stage of disease, and is associated with poor response to standard chemotherapy, slow progression, and disease recurrence. Symptoms of recurrent low-grade serous ovarian cancer can include bloating, early satiety, urinary urgency, abdominal or pelvic pain, and bowel obstruction. These symptoms can result in significant and chronic impairment of quality of life. In 2024, an estimated 3,000 people in Canada were diagnosed with ovarian cancer and 2,000 died from the disease.

What Are The Current Treatment Options?

Treatments for recurrent low-grade serous ovarian cancer include secondary cytoreductive surgery, endocrine therapy (i.e., letrozole, anastrozole, and tamoxifen), single-agent platinum-based chemotherapy (i.e., carboplatin, and cisplatin), combination platinum-based regimens (i.e., carboplatin-paclitaxel, carboplatin-gemcitabine, and carboplatin-pegylated liposomal doxorubicin; all with or without bevacizumab), and single-agent therapies (i.e., paclitaxel, pegylated liposomal doxorubicin, topotecan, bevacizumab, and gemcitabine).

Why Did We Conduct This Review?

Trametinib is a selective, reversible inhibitor of MEK1 and MEK2, with a novel mechanism of action that targets the underlying disease process in recurrent low-grade serous ovarian cancer. BC Gynecology tumour group brought forward a request for a reimbursement review of trametinib. Given that patients with low grade serous ovarian cancer often have a very low response to chemotherapy with high risk for relapse, there is an unmet need for more effective treatment options. Based on emerging evidence and unmet needs as identified by clinicians, public drug plans requested a review of the efficacy and safety of trametinib for the treatment of adults with recurrent low-grade serous ovarian cancer.

Input From Community Partners

- One clinician group, **Ontario Health (Cancer Care Ontario) Gynecologic Cancer Drug Advisory Committee (OH [CCO] DAC)**, advocated that individuals with recurrent low-grade ovarian cancer require access to treatments that prolong life, delay disease progression, reduce cancer-related symptoms, and improve health-related quality of life.

- **Public drug plans** inquired about the evidence for trametinib to inform a recommendation on whether it should be reimbursed for adults with recurrent low-grade serous ovarian cancer. The public drug plans outlined implementation questions related to treatment eligibility and potential costs.

► **Refer to the main report and the supplemental material document for this review.**

Person With Lived Experience

A person with Lived Experience in Ontario and her husband shared her journey living with low grade serous ovarian cancer since her diagnosis in 2009. For years, she struggled with limited treatment options for ovarian cancer, as standard chemotherapy had little effect. Multiple clinical trials and therapies provided only temporary or minimal benefits, and disease progression in 2019 led to additional surgeries, including an ileostomy. In 2022, she started trametinib, which significantly lowered her cancer marker levels and stabilized her condition. Unlike past treatments, she shared that trametinib effectively targeted cancer cells while preserving her quality of life. Though it caused skin sensitivity and worsened lymphedema, she managed these side effects with creams and compression socks. With improved energy and mobility, she now views cancer as a chronic condition rather than a debilitating illness.

Deliberation

FMEC deliberated using the following 5 domains of value:

- **Clinical Value:** The value that patients derive from a health technology in terms of its effect on their health and health-related quality of life. The determination of the clinical value of a health technology requires the measurement of its clinical benefits and harms and an assessment of the impact of these effects on patients. Clinical benefits and harms are assessed against relevant comparators.
- **Unmet Clinical Need:** Morbidity and/or mortality arising from a condition or symptom that is not addressed effectively by available treatments.
- **Distinct Social and Ethical Considerations:** The social and ethical implications of health technologies not already assessed in the other domains, and how they affect patients, caregivers, populations, and the organization of health systems. This includes nonclinical needs, which are the social, psychological, and logistical factors affecting the appropriateness, accessibility, and acceptability of the technology beyond its direct clinical outcomes. It also examines broader ethical considerations in the design, evaluation, and implementation of health technologies.
- **Economic Considerations:** Economic evidence to inform the financial, human or other resource implications associated with the technology under review, and whether it is worthwhile to allocate resources to the technology under review given its expected clinical benefits. Considerations may include the potential resource or cost impacts of the technology under review versus relevant comparator(s).
- **Impacts on Health Systems:** Two distinct but interrelated components: organizational feasibility of adoption is the ease with which the health technology can be implemented in the health system while realizing its clinical value, and economic feasibility of adoption examines how the adoption of a health technology will economically impact the payer or budget holder.

Decision Summary

Table 1 outlines the key discussion points FMEC considered, organized by the five domains of value.

Table 1: Summary of Deliberation

Domain	Discussion point(s)
Clinical Value 	**FMEC concluded that the clinical value of trametinib was uncertain for adults with recurrent low-grade serous ovarian cancer versus relevant comparators in the Canadian setting.** **FMEC discussed that while no patient groups provided input**, the presentation from the person with lived experience highlighted that patients seek effective treatments with tolerable and manageable toxicity. Further, the committee discussed that while progression-free survival is important to patients, it may be weighed and valued differently across patients when considered in combination with or amongst other outcomes (e.g., patients may not prefer a treatment that negatively affected their quality of life while improving progression-free survival but not overall survival). **FMEC members** highlighted the following discussion points: • Based on the GOG 281/LOGS trial, time to investigator-assessed progression-free survival was median 13.0 months for trametinib versus median 7.2 months for physician's choice of therapy (i.e., letrozole, pegylated liposomal doxorubicin, tamoxifen, paclitaxel, or topotecan), respectively (hazard ratio = 0.48; 95% CI, 0.36 to 0.64; P value < 0.0001). The proportion of patients who achieved an objective response rate was 26% of patients for trametinib versus 6% of patients for physician's choice of therapy, respectively (odds ratio = 5.4; 95% CI, 2.4 to 12.2; P value < 0.0001). FMEC considered the results to demonstrate a likely benefit of trametinib in delaying disease progression and improving treatment response. • However, FMEC discussed some uncertainty regarding the importance of progression-free survival as an end point in recurrent low-grade serous ovarian cancer, and whether improvements in progression-free survival translated to benefits in overall survival or health-related quality of life. FMEC highlighted that compared with physician's choice of therapy, treatment with trametinib did not demonstrate improvement in overall survival, acknowledging that findings were challenging to interpret due to the high proportion of patients (68%) who crossed over from the physician's choice group to the trametinib group during the study. Further, treatment with trametinib may be associated with deterioration in health-related quality of life at 12 weeks with no between-group differences thereafter; however, these findings were uncertain. Nevertheless, considering the prolonged survival and impactful symptoms among patients with recurrent low-grade serous ovarian cancer, FMEC recognized the need for treatments to delay disease progression and reduce symptoms. The guest specialists reported that based on the hypothesized disease pathophysiology, trametinib's mechanism of action potentially targets the underlying disease.

Domain	Discussion point(s)
	• FMEC discussed significant concerns regarding the conduct of the trial. Specifically, there was uncertainty in the findings due to the open-label study design, methods of assessment and analysis, missing data, and substandard reporting. • FMEC raised questions about the alignment of the studied comparators with clinical practice in Canada, noting that there are other available treatments used in Canada that were not included in the comparator arm of the GOG 281/LOGS trial (i.e., anastrozole, bevacizumab, carboplatin, cisplatin, or combination platinum therapy).
Unmet Clinical Need	**FMEC concluded that trametinib addresses a significant unmet clinical need with an acceptable level of certainty in clinical value among patients with low-grade serous ovarian cancer who have recurrent disease.**  **FMEC members** highlighted the following discussion points: • FMEC noted that low-grade serous ovarian cancer represents about 5% of ovarian carcinomas and there may be challenges in generating robust clinical trial evidence in this relatively rare tumour subtype. Given these challenges, FMEC agreed that there should be greater allowance for uncertainty in the clinical evidence. The guest specialists reported that many patients with low-grade serous ovarian cancer are diagnosed with advanced or metastatic disease, and experience high rates of disease recurrence and poor response to available treatments (including standard of care chemotherapy). • Compared with physician's choice of therapy, more patients receiving trametinib experienced adverse events of grade 3 or higher and discontinued treatment due to adverse events. FMEC discussed concerns with the toxicity of trametinib, acknowledging that the safety profile of trametinib was considered by the guest specialists to be manageable, noting the risk of decreased ejection fraction and retinal disorders to necessitate adequate monitoring and appropriate dose adjustments.
Distinct Social and Ethical Considerations	**FMEC considered trametinib as an oral drug to potentially offer some advantages.** **FMEC discussed that while no patient groups provided input**, oral drugs offer some advantages for patients. However, oral drugs may not be funded for all populations.  **FMEC members** highlighted the following discussion points: • FMEC discussed that trametinib as an oral treatment option may offer advantages over non-oral therapies for patients (e.g., ease of administration and access across care settings and geographical locations). • FMEC noted that equity considerations are important but there is a lack of available information for the committee to deliberate. In addition, FMEC highlighted that it is difficult to determine whether there is any historically disadvantaged or equity-deserving group among this population to warrant further discussion.
Economic Considerations	**FMEC noted that the reimbursement of trametinib for the treatment of first recurrence low-grade serous ovarian cancer is generally expected to increase drug acquisition costs, except when compared to the higher-dose carboplatin-paclitaxel-bevacizumab regimen. Furthermore, for patients experiencing multiple recurrences, trametinib reimbursement is also anticipated to increase drug acquisition costs.**

Domain	Discussion point(s)
	**FMEC members** highlighted the following discussion points: • FMEC noted that while there is some evidence suggesting trametinib may be more effective in terms of PFS and ORR than some current standard treatments, it is also associated with higher costs compared to all but one comparator. No evidence was identified regarding the cost-effectiveness of trametinib relative to endocrine, platinum-based and non-platinum-based therapies for the treatment of low-grade serous ovarian cancer, and therefore, estimates of cost-effectiveness were not available to the committee. FMEC discussed that a cost-effectiveness analysis would be valuable to fully inform the reimbursement recommendation. • Given the uncertainty surrounding trametinib's incremental clinical benefit compared to all current standard treatments available in Canada, combined with the expected increase in drug acquisition costs upon reimbursement, FMEC recommended a price reduction to address these concerns. • FMEC further emphasized that a pricing condition alone would not resolve the uncertainty stemming from gaps in the clinical evidence, nor address the lack of data on the cost-effectiveness of trametinib compared to endocrine, platinum-based, and non-platinum-based therapies in Canada.
Impacts on Health Systems 	**FMEC considered trametinib as an oral therapy may reduce health system resources.** **FMEC members** highlighted the following discussion points: • FMEC agreed that there may be health system savings with an oral therapy but raised concerns regarding equitable access to oral therapies in Canada since oral drugs are not covered by all public drug plans for patients younger than 65 years of age. • FMEC discussed that treatment with trametinib may require additional consultations or resources (e.g., cardiac and/or ophthalmologic assessments prior to treatment with trametinib or for adverse event management) in select centres or jurisdictions. FMEC noted that according to the guest specialists, cardiology and ophthalmology consultations would not be required routinely for all patients given the low incidence of related serious adverse events.

FMEC = Formulary Management Expert Committee

Full Recommendation

With a vote of 7 to 1, FMEC recommends that trametinib, for the treatment of recurrent low-grade serous ovarian cancer, be reimbursed if the conditions presented in Table 2 are met.

Table 2: Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult patients with low-grade serous ovarian cancer following an initial diagnosis of ovarian or peritoneal low-grade serous carcinoma or serous borderline tumour who: 1.1. previously received at least 1 platinum-based chemotherapy regimen, and 1.2. could have previously received an unlimited number of chemotherapy or hormonal therapy regimens.	Evidence from the GOG 281/LOGS trial demonstrated that treatment with trametinib resulted in a clinical benefit in patients with these characteristics. In the GOG 281/LOGS trial, patients in the physician's choice group received at least 1 of the following regimens (but not all 5): letrozole, pegylated liposomal doxorubicin, tamoxifen, paclitaxel, or topotecan.	Eligibility for treatment with trametinib among patients with recurrent low-grade serous ovarian cancer who have significant cardiovascular or respiratory comorbidities may be at the discretion of the prescribing clinician. Based on discussion with the guest specialists, the standard of care for the first-line setting (i.e., platinum-based chemotherapy) may change shortly.
2. Patients should have good performance status.	Patients with a GOG performance status of 0 or 1 were included in the GOG 281/LOGS trial.	Patients should have good performance status as determined by the treating clinician.
Discontinuation and renewal		
3. Trametinib should be discontinued in the event of disease progression or significant toxicity.	Consistent with clinical practice, patients in the GOG 281/LOGS trial discontinued treatment upon disease progression or unacceptable toxicity.	—
4. Patients should be monitored for disease progression and tumour response.	In the GOG 281/LOGS trial, patients were monitored for disease progression and tumour response by CT or MRI at baseline, once every 8 to 12 weeks for the first 15 months, and then once every 3 months.	Patients should be monitored for clinical response and safety per standard local practice.
Prescribing		
5. Trametinib should be prescribed by clinicians with expertise in the diagnosis and management of gynecologic cancer.	This will ensure that treatment is prescribed for appropriate patients, and adverse events are optimally managed.	Patients may be initially prescribed trametinib by clinicians with expertise in the diagnosis and management of gynecologic cancer. Patients treated with trametinib may receive ongoing care at any oncology clinic.

Reimbursement condition	Reason	Implementation guidance
		Note that the use of trametinib is contraindicated in pregnant individuals and those of childbearing age due to its risk of teratogenicity.
6. Trametinib should be used as monotherapy.	There is no evidence from the GOG 281/LOGS trial to support the use of trametinib in combination with other drugs.	—
Pricing		
7. A reduction in the price of trametinib may be required.	The reimbursement of trametinib for the treatment of adults with recurrent low-grade serous ovarian cancer is expected to increase drug acquisition costs, except when compared with the carboplatin-paclitaxel-bevacizumab regimen. No evidence was identified regarding the cost-effectiveness of trametinib relative to endocrine, platinum-based, and non-platinum-based therapies for the treatment of low-grade serous ovarian cancer in Canada. Therefore, estimates of cost-effectiveness were not available to the committee. A cost-effectiveness analysis would be needed to determine whether trametinib is cost-effective. Additionally, the GOG 281/LOGS trial included only 5 of the relevant comparators available to patients with low-grade serous ovarian cancer in Canada. In the absence of comparative clinical evidence against all relevant comparators for low-grade serous ovarian cancer, a price reduction may be required.	

CT = computed tomography; MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumours.

Feedback on Draft Recommendation

<to be updated after the feedback period>

FMEC Information

Members of the committee: Dr. Emily Reynen (Chair), Dr. Zaina Albalawi, Dr. Hardit Khuman, Ms. Valerie McDonald, Dr. Bill Semchuk, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, and two non-voting guest specialists from Ontario and Manitoba. Note that the guest specialists also acted as the clinical experts for the Clinical and Pharmacoeconomic Combined Report.

Meeting date: January 30, 2025

Conflicts of interest: None

Special thanks: Canada's Drug Agency (CDA-AMC) extends our special thanks to the individuals who presented directly to FMEC on behalf of people with lived experience and to patient organizations representing the community of those living with Ovarian Cancer, specifically Cailey Crawford, Luda Syvokin, Viktor Syvokin, and Alexandria Tadman.

Note: CDA-AMC makes every attempt to engage with people with lived experience as closely to the indication and treatments under review as possible; however, at times, CDA-AMC is unable to do so and instead engages with individuals with similar treatment journeys or experience with comparators under review to ensure lived experience perspectives are included and considered in Reimbursement Reviews. CDA-AMC is fortunate to be able to engage with individuals who are willing to share their treatment journey with FMEC.

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