Canada's Drug Agency
L'Agence des médicaments du Canada

Reimbursement Review

Review Report

TRAMETINIB

(Non-Sponsored Review)

Therapeutic area: Gynecological cancers, low-grade serous ovarian cancer

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Key Messages

What is Recurrent Low-Grade Serous Ovarian Cancer?

- In 2024, an estimated 3,000 individuals in Canada will be diagnosed with ovarian cancer and 2,000 will die from the disease.
- Low-grade serous cancer of the ovary, fallopian tube, or peritoneum is a rare subtype of epithelial ovarian carcinoma, accounting for about 10% of serous carcinomas and 5% of all epithelial ovarian carcinomas. Compared with high-grade serous ovarian cancer, low-grade serous ovarian cancer is characterized by younger age at diagnosis, advanced stage of disease, poor response to standard chemotherapy, slow progression, and high rates of disease recurrence especially in a metastatic setting.
- Approximately 70% of patients with metastatic low-grade serous ovarian cancer will experience disease recurrence despite standard of care front-line treatment for epithelial ovarian cancers, with poor response (5% to 10%) to subsequent lines of therapy. Symptoms experienced by patients with recurrent low-grade serous ovarian cancer can include bloating, early satiety, urinary urgency, abdominal or pelvic pain, pleural effusion, and bowel obstruction.

What are the Treatment Goals and Current Treatment Options for Recurrent Low-Grade Serous Ovarian Cancer?

- Goals of treatment identified through clinician inputs include prolonging life, delaying disease progression, reducing cancer-related symptoms, and improving patients' health-related quality of life.
- Treatment options for patients with recurrent low-grade serous ovarian cancer mirror that of high grade serous ovarian cancer including 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 plus 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).

What is Trametinib and Why Did We Conduct This Review?

- Trametinib is a drug that is available as an oral tablet. Health Canada has approved trametinib as monotherapy or in combination with dabrafenib for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600 mutation.
- At the request of the participating public drug programs, we reviewed trametinib to inform a recommendation on whether it should be reimbursed for recurrent low-grade serous ovarian cancer in adults.

How Did We Evaluate Trametinib?

- We reviewed the clinical evidence on the beneficial and harmful effects and compared costs of trametinib versus other treatments used in Canada for recurrent low-grade serous ovarian cancer in adults. Letrozole, anastrozole, tamoxifen, carboplatin, cisplatin, carboplatin-paclitaxel (with or without bevacizumab), carboplatin-gemcitabine (with or without bevacizumab), carboplatin-pegylated liposomal doxorubicin (with or without bevacizumab), paclitaxel, pegylated liposomal doxorubicin, topotecan, bevacizumab, and gemcitabine were considered relevant treatments to compare with trametinib.
- The clinical evidence was identified through systematic searches for available studies.

The review was also informed by 1 clinician group submission in response to our call for input and by input from the participating public drug programs around issues that may impact their ability to implement a recommendation. We consulted 2 clinical specialists with expertise in the diagnosis and management of gynecologic cancer as part of the review process.

What Did We Find?

Clinical Evidence

- We reviewed the following clinical evidence:

- 1 randomized controlled trial (GOG 281/LOGS) comparing trametinib with physician's choice of therapy (letrozole, pegylated liposomal doxorubicin, tamoxifen, paclitaxel, or topotecan) in 260 patients with recurrent low-grade serous ovarian cancer

- For the comparison of trametinib versus physician's choice of therapy:
  - There was a statistically significant and clinically important improved progression-free survival and objective response rate. There was some uncertainty in the evidence due to concerns about potential risk of bias, substandard reporting, and lack of control for multiple testing.
  - There was a statistically significant health-related quality of life detriment compared with physician's choice of treatment at week 12. The detriment was not considered clinically important, per the protocol-specified threshold. Between-group differences at other follow-up times were small (1 to 4 points), although between-group differences were not reported past week 24 and statistical testing occurred only at week 12. The results at all follow up times are at high risk of bias due to missing outcomes data and the subjective nature of the outcome. It is unclear how crossovers from the physician's choice group to the trametinib group post-progression may have affected the health-related quality of life results.
  - Symptoms of neurotoxicity were measured but the results were not reported.
  - The evidence was insufficient to demonstrate a statistically significant difference in overall survival. The interpretation of the overall survival results is challenged by many (68%) patients in the physician's choice group crossing over to the trametinib group post-progression, which was allowed per the protocol.
  - There was no evidence to inform how trametinib compares with other available treatments (e.g., anastrozole; bevacizumab; gemcitabine; carboplatin; cisplatin; and, carboplatin-paclitaxel, carboplatin-gemcitabine, carboplatin-pegylated liposomal doxorubicin; all with or without bevacizumab).
  - The safety profile of trametinib was as expected with no new safety signals.

Economic Evidence

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

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Abbreviations

AE	adverse event
CI	confidence interval
CT	computed tomography
DB	double blind
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FACT/GOG-Ntx	Functional Assessment of Cancer Therapy Gynecologic Oncology Group – Neurotoxicity questionnaire subscale
FACT-O TOI	Functional Assessment of Cancer Therapy – Ovarian Cancer Trial Outcome Index
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRQoL	health-related quality of life
ITT	intention to treat
LOCF	last observation carried forward
MEK	mitogen-activated protein kinase kinase
MID	meaningful important difference
MRI	magnetic resonance imaging
PP	per protocol
RCT	randomized controlled trial
RECIST	Response Evaluation Criteria In Solid Tumors
RR	relative risk
SAE	serious adverse event
SD	standard deviation
TEAE	treatment-emergent adverse event
WDAE	withdrawal due to adverse event

BACKGROUND

Introduction

The objective of the Clinical Review is to review and critically appraise the evidence on the beneficial and harmful effects of trametinib, 0.5 mg and 2.0 mg, oral tablets in the treatment of recurrent low-grade serous ovarian cancer in adults. The focus will be placed on comparing trametinib to relevant comparators and identifying gaps in the current evidence. The economic review consists of a cost comparison for trametinib compared with relevant comparators for the same population. The comparators considered relevant to the reviews were 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 plus 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).

Trametinib, 0.5 mg, 1.0 mg, and 2.0 mg tablet, was previously reviewed by CDA-AMC as monotherapy for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation and it was recommended to be reimbursed with clinical criteria and/or conditions (October 2013).[1]

Table 1: Information on the Drug Under Review and on the CDA-AMC Review

Item	Description
Information on the drug under review	
Drug (product)	Trametinib, 0.5 mg and 2.0 mg, oral tablets
Relevant Health Canada indication	Not applicable
Mechanism of action	Selective, reversible inhibitor of MEK1 and MEK2
Data protection status	Expired data protection: July 2021
Status of generic drugs / biosimilars	No current generic on the market or under review by Health Canada No current biosimilar on the market
Information on the CDA-AMC review	
Requestor	Provincial Advisory Group
Indication under consideration for reimbursement	Adults with recurrent low-grade serous ovarian cancer

MEK = mitogen-activated protein kinase kinase.

Sources of Information

The contents of the Clinical Review report are informed by studies identified through systematic literature searches and input received from interested parties.

Calls for patient group, clinician group, and industry input are issued for each Non-sponsored Reimbursement Review. We received 1 clinician group submission from Ontario Health (Cancer Care Ontario) Gynecologic Cancer Drug Advisory Committee (OH [CCO] DAC). OH (CCO) DAC gathered input through conference calls and emails. The full submission received is available in the input document <insert hyperlink or citation>. Input from the clinician group was considered throughout the review, including in the selection of outcomes to include in the Clinical Review and in the interpretation of the clinical evidence. Relevant input from the clinician group is summarized in the Disease Background, Current Management, and Unmet Needs and Existing Challenges sections. No input was received from any patient group nor from industry.

The drug programs provide input on each drug being reviewed through the Reimbursement Review process by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted for this review are summarized and provided to the expert committee in a separate document.

Each review team includes 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. Two gynecologic oncologists with expertise in the diagnosis and management of low-grade serous ovarian cancer participated as part of the review team, with representation from Manitoba and Ontario.

Disease Background

In 2024, an estimated 3,000 individuals in Canada will be diagnosed with ovarian cancer (for an age-standardized incidence rate of 12.9 per 100,000 people) and 2,000 will die from the disease.[2] Low-grade serous cancer of the ovary, fallopian tube, or peritoneum is a rare subtype of epithelial ovarian carcinoma, accounting for about 10% of serous carcinomas[3] and 5% of all epithelial ovarian carcinomas;[4] approximately 90% of individuals present with disseminated disease (International Federation of Gynecology and Obstetrics [FIGO] stage II to IV).[5]

Compared to high-grade serous ovarian cancer, low-grade serous ovarian cancer follows a distinct developmental pathway and is commonly characterized by younger age at diagnosis (median of 43 to 57 years of age), advanced stage of disease at presentation, poor response to standard chemotherapy (4%), slow progression, and high rates of disease recurrence.[3,5] Patients with recurrent low-grade serous ovarian cancer may have an asymptomatic abdominal disease or may experience significant symptomatology (bloating, early satiety, urinary urgency, and abdominal or pelvic pain), pleural effusion, or recurrent bowel obstruction in advanced cases.[5] According to the clinical experts consulted for this review, approximately 70% of patients with metastatic low-grade serous ovarian cancer will experience disease recurrence despite standard of care front-line treatment, with poor response (about 5 to 10%) to subsequent lines of therapy. Currently, there is no standard effective second line therapy for recurrent low grade disease.

Current Management

Treatment Goals

Per the clinical experts consulted by CDA-AMC and the input from the clinician group, current treatment goals for patients with recurrent low-grade serous ovarian cancer are to prolong life, delay disease progression, reduce cancer-related symptoms, and improve patients' HRQoL.

Given these treatment goals, the clinical experts expressed that overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and HRQoL could be considered all important relevant outcomes for patients. For PFS and ORR, their rationale was that longer PFS and/or better ORR could result in reduced symptom burden (e.g., large burden of disease may be reduced by shrinking the tumour) and in turn, improved health-related quality of life (HRQoL). They noted that OS may be more challenging to measure in a trial setting due to the protracted disease course expected after disease progression.

Current Treatment Options

Current treatment options for recurrent low-grade serous ovarian cancer mirror that of high-grade serous ovarian cancer including secondary cytoreductive surgery, chemotherapy (e.g., pegylated liposomal doxorubicin, paclitaxel, topotecan), endocrine therapies (e.g., tamoxifen, anastrozole, letrozole), targeted agents such as mitogen-activated protein kinase kinase (MEK) inhibitors (e.g., trametinib) and angiogenesis inhibitors (e.g., bevacizumab), or drugs available via clinical trials (e.g., ribociclib).[5] Selection of therapy is commonly based upon stratifying individuals according to their response to initial platinum-based chemotherapy, as platinum-sensitive (i.e., ≥ 6 months have elapsed between completion of platinum-based therapy and detection of relapse) or platinum-resistant (i.e., < 6 months have elapsed between completion of platinum-based therapy and detection of relapse).[6]

Unmet Needs and Existing Challenges

OH (CCO) DAC reported that patients with recurrent low-grade serous ovarian cancer experience low response to chemotherapy and hormonal therapy, and that response rates are not durable.

The clinical experts indicated that since many patients with low-grade serous ovarian cancer are diagnosed with metastatic disease, there are high recurrence rates and effective treatments are limited, highlighting a significant unmet need for effective treatment options in the metastatic and recurrent setting.

Potential Place in Therapy

Contents within this section have been informed by input from the clinical experts consulted for the purpose of this review and from clinician groups. The following has been summarized by the review team.

Potential Place in Therapy

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.[7] As such, the experts highlighted that trametinib has the potential to cause a shift in the current treatment paradigm where there are few effective therapies in the recurrent setting, by providing a targeted treatment option that modifies the disease process. According to the clinical experts, trametinib is anticipated to be favoured over other systemic therapies in the first-line after recurrence with its unique antineoplastic activity. Additionally, the experts anticipated that trametinib may also be used for patients with progressive disease after standard first-line treatment (i.e., for patients with high burden of disease where surgery is not possible, or for whom surgical debulking was infeasible or unsuccessful).

The clinician group agreed with the experts that trametinib would be an option for patients with low-grade serous ovarian cancer who have received at least 1 platinum-based chemotherapy regimen and have previously received endocrine therapy. Specifically, those who experience disease recurrence or progression after treatment with platinum-based chemotherapy and maintenance endocrine therapy would be best suited for treatment with trametinib.

Patient Population

The clinical experts considered patients with low-grade serous ovarian cancer who experience first disease recurrence after primary treatment with chemotherapy and maintenance hormonal therapy to be best suited for treatment with trametinib; eligible patients would be identified by symptoms suggestive of disease progression followed by confirmatory imaging (e.g., computed tomography [CT] or magnetic resonance imaging [MRI]). While the clinical experts expressed that tumour testing should not be a requirement for access to treatment with trametinib, tumour testing for *KRAS*, *BRAF*, or *NRAS* mutations may be beneficial as patients with mutation-positive tumours may be associated with greater benefit from treatment with MEK inhibitors than those with mutation-negative tumours and may help predict response to treatment.[8-10] Additionally, the experts did not consider a repeat tissue biopsy to be required at time of recurrence to determine treatment eligibility. The experts expressed that patients with recurrent low-grade serous ovarian carcinoma who have not previously received chemotherapy and for whom the risk of adverse events was felt to be unreasonably high would not be suited for treatment with trametinib. Given the types of adverse events (e.g., hypertension, decreased ejection fraction, pneumonitis, QTc prolongation, left ventricular dysfunction) that can occur with trametinib, the experts caution its use among patients with significant cardiovascular and respiratory comorbidities, for whom prescribing and monitoring would be at the discretion of the prescribing clinician.

The clinician group agreed with the experts that tumour testing should not be required to determine treatment eligibility.

Assessing the Response to Treatment

According to the clinical experts consulted for this review, patients undergoing treatment with trametinib may be assessed for treatment response via clinical examination every 3 to 4 weeks and routine diagnostic imaging (e.g., CT scan) every 8 to 12 weeks for the first 15 months, followed by radiological imaging once every 3 months. A clinically meaningful response to treatment was considered by the experts to include clinical and radiologic evidence of disease stability or regression, and stabilization or improvement of patients' symptoms and HRQoL.

The clinician group agreed with the experts that clinical examination and imaging would be used to assess patients' response to treatment.

Discontinuing Treatment

Treatment with trametinib would be discontinued due to evidence of disease progression (via imaging or worsening of signs or symptoms during clinical assessment), significant toxicities (e.g., grade ≥ 3 adverse events including rash, diarrhea, hypertension, nausea, vomiting, fatigue, or anemia), or patient preference, according to the clinical experts.

The clinician group agreed with the experts that treatment with trametinib would be discontinued with disease progression or toxicity.

Prescribing Considerations

The clinical experts consulted for this review expressed that trametinib should be prescribed by clinicians with expertise in the management of gynecologic cancer (e.g., medical oncologists, gynecologic oncologists) supported by multidisciplinary clinicians and administered in a setting where adverse events can be managed (e.g., comprehensive cancer centre, outpatient clinic).

The clinician group indicated that trametinib could be prescribed in ambulatory centres with expertise in handling systemic therapies.

CLINICAL REVIEW

Methods

We conducted a systematic review to identify evidence for trametinib for the treatment of recurrent low-grade serous ovarian cancer. Studies were selected according to the eligibility criteria in Table 2. Also eligible were long-term extension (LTE) studies of included RCTs, indirect treatment comparisons (ITCs) that adhered to the eligibility criteria except for the study design criteria, and studies addressing gaps that did not meet the eligibility criteria but were considered to address important gaps in the Systematic Review evidence.

Relevant comparators included treatments used in clinical practice in Canada in the patient population under review. We selected outcomes (and follow-up times) for review considering clinical expert input, and patient and clinician group inputs. Selected outcomes are those considered relevant to expert committee deliberations. Detailed methods for literature searches, study selection, data extraction, and risk of bias appraisal are in the Working Papers, Appendix 1.

Table 2: Systematic Review Eligibility Criteria

Criteria	Description
Population	Adults with recurrent low-grade serous ovarian cancer Subgroups: • Number of prior therapies (e.g., 1, 2, or ≥3) • Type of prior therapies (e.g., chemotherapy, and/or hormonal) • Disease stage (e.g., I, II, III, IV, or V) • Presence of mutations (e.g., *KRAS*, *NRAS*, *BRAF*, or none) • ECOG performance status (e.g., 0 or 1)
Intervention	Trametinib Dosage: 0.5 mg and 2.0 mg, oral tablets; 4.7 mg/bottle, powder for oral solution
Comparator	Endocrine therapy: • Letrozole • Anastrozole • Tamoxifen Single-agent platinum-based chemotherapy: • Carboplatin • Cisplatin Platinum-based regimens: • Carboplatin-paclitaxel ± bevacizumab • Carboplatin-gemcitabine ± bevacizumab • Carboplatin-pegylated liposomal doxorubicin ± bevacizumab Single-agent therapies: • Paclitaxel • Pegylated liposomal doxorubicin • Topotecan • Bevacizumab • Gemcitabine
Outcomes	**Efficacy outcomes:** • Overall survival

	• Progression-free survival
	• Objective response rate
	• HRQoL (with preference for disease-specific measures)
	
	Harms outcomes:
	• TEAE, SAE, AE grade ≥3, withdrawal due to AE, death due to AE
	• Adverse events of special interest:
	  ○ Left ventricular dysfunction
	  ○ Retinal pigment epithelial detachment and retinal vein occlusion
	  ○ Interstitial lung disease
	  ○ Skin toxicity
	  ○ Venous thromboembolism
	  ○ Major hemorrhagic events

Study design	Published phase II, III, and IV RCTs

AE = adverse event; ECOG = Eastern Cooperative Oncology Group; HRQoL= health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Clinical Evidence

An information specialist conducted a peer reviewed literature search of key bibliographic databases, trial registries, and grey literature sources. The initial search was completed on September 25, 2024, with alerts maintained until the Formulary Management Expert Committee meeting on January 30, 2025. Refer to the Working Papers document for detailed search strategies.

From the search for primary studies, we identified 148 unique records via the searches of databases and registers, of which we excluded 147 by title and abstract. We screened 1 record by full text and included 1 report of 1 study. We did not identify any potentially relevant records via other sources. No reports of long-term extensions of the included studies or studies addressing gaps were identified.

From the search for ITCs, we identified 115 unique records via the searches of databases and registers, of which none met eligibility by title and abstract.

Systematic Review

Description of Study

Details regarding the interventions and comparators, and relevant outcome measures, are in the Working Papers document in Appendix 2.

The GOG 281/LOGS study[8] was a multicentre (72 hospitals in the US and 12 hospitals in the UK), phase II/III, open-label, RCT that enrolled 260 patients from February 27, 2014, to April 10, 2018. Sources of funding for the trial included the manufacturer (Novartis). Eligible patients were those with recurrent low-grade serous ovarian cancer who were previously treated with at least 1 platinum-based chemotherapy. Patients were randomized in a 1:1 ratio to trametinib or 1 of 5 physician's choice options (letrozole [n = 44], pegylated liposomal doxorubicin [n = 40], tamoxifen [n = 27]), paclitaxel [n = 11], or topotecan [n = 8]. Randomization was stratified by minimization to balance treatment assignment by geographical region (US or UK), number of previous regimens (1, 2, or ≥ 3), performance status (0 or 1), and planned physician's choice treatment (applicable to patients in that group). The primary end point was investigator-assessed PFS, defined as the time from randomization to disease progression or death. Disease progression was defined as at least a 20% increase in the sum of the diameters of target lesions. Secondary end points included: OS, ORR, HRQoL up to 24 weeks (the Functional Assessment of Cancer Therapy – Ovarian Cancer Trial Outcome Index [FACT-O TOI], and the adapted patient-administered Functional Assessment of Cancer Therapy Gynecologic Oncology Group – Neurotoxicity [FACT-GOG-Ntx] subscale questionnaire); and adverse events (AEs). Exploratory end points included PFS and ORR after crossover, and HRQoL beyond 24 weeks.

Key inclusion criteria were age 18 years or older, GOG performance status of 0 or 1, and with recurrent low-grade serous carcinoma following initial diagnosis of ovarian or peritoneal low-grade serous carcinoma or serous borderline tumour. Histology was confirmed by prospective expert pathology review of tissue from the recurrent carcinoma or from original diagnostic specimen. Pathology review included digital tissue review by a panel of pathologists and separate pathologist panels in the US and UK, with confirmation of eligibility confirmed by at least 2 pathologists on the diagnosis of recurrent low-grade serous carcinoma. Patients must have had measurable disease as defined by the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Patients were eligible if they had previously received at least 1 platinum-based chemotherapy regimen (but not all 5 physician's choice options) and could have had an unlimited number of previous therapy regimens (including chemotherapy or hormonal therapy). Key exclusion criteria were patients with serous borderline tumours or tumours containing low-grade and high-grade serous carcinomas, chemotherapy or radiotherapy within 4 weeks of study enrolment, and prior MEK, *KRAS*, or *BRAF* inhibitor therapy.

Patients received trametinib 2.0 mg, oral tablets, once daily or 1 of 5 physician's choice options (paclitaxel, pegylated liposomal doxorubicin, topotecan, letrozole, or tamoxifen), until disease progression or unacceptable toxicity. After disease progression, patients in the physician's choice group could cross over to receive trametinib. Dose modifications of trametinib including treatment interruptions and dose reductions (2 levels; to 1.5 mg or 1.0 mg) were permitted for hematological and other AEs (e.g., hypertension, rash, ejection fraction changes, pneumonitis, diarrhea, liver chemistry, QTc prolongation, visual changes, or other clinically significant toxicities). Trametinib was to be discontinued if a third dose level reduction was required, or if treatment delay was 21 days or longer due to clinically significant toxicities. Patients in the physician's choice group could discontinue therapy after 6 cycles at the investigator's discretion. Dose modifications of treatments in the physicians' choice group were permitted per standard of care at the investigator's discretion; however, the standard of care was not described.

Disease progression and tumour response were evaluated by radiological and clinical review per RECIST v.1.1 criteria. Lesion assessments were measured by contrast CT or MRI at baseline, once every 8 weeks for the first 15 months, and then once every 3 months. HRQoL assessments (FACT-O TOI and FACT-GOG-Ntx) were conducted before cycles 1 and 4 (week 16), 4 weeks after cycle 6 (week 24), and at weeks 36 and 52. Safety assessments were conducted at every study visit, after crossover, and then once every 3 months for 2 years followed by once every 6 months for 3 years, and then annually. All patients were to be followed for 10 years after removal from the study or until death, whichever occurred first.

All randomized patients were included in the intention to treat (ITT) analysis for the efficacy and HRQoL end points. Patients who received at least 1 dose of study treatment were included in the safety analysis and grouped according to their assigned treatment. Patients who completed the baseline assessment and at least 1 follow-up assessment were evaluable for the HRQoL analyses. An interim analysis for futility was prespecified and evaluated by a data monitoring committee. The primary efficacy analyses were conducted at the data cut-off date of July 16, 2019.

Results

Patient Disposition

In the GOG 281/LOGS trial, 427 patients were screened for eligibility. After excluding 167 patients due to missing pathology (n = 96), not meeting eligibility criteria (n = 26), and declining participation (n = 45), 260 patients were randomized to trametinib (n = 130) and the physician's choice group (n = 130). Three of 130 patients (2.3%) in each group did not receive assigned treatment; 1 patient who was randomized to the physician's choice group received trametinib and was included in the safety analysis for the trametinib group. Of those who were treated, 116 of 128 patients (90.6%) in the trametinib group and 120 of 127 patients (94.5%) in the physician's choice group discontinued study treatment. Eighty-eight of 127 (69.3%) patients in the physician's choice group crossed over to receive trametinib post-progression. Reasons for treatment discontinuation in the trametinib and physician's choice group, respectively, were due to disease progression (43.0% and 63.8%), death (1.6% and 0), withdrawal or refusal of treatment (2.3% and 10.2%), and other reasons not specified (7.8% and 7.9%). The number of patients who discontinued treatment due to AEs were 46 of 128 patients (35.9%) in the trametinib group and 16 of 127 patients (13.3%) in the physician's choice group; including those who crossed over to the trametinib group following disease progression, the overall number of patients in the physician's choice group who discontinued study treatment due to AEs were 38 (29.9%). At data cut-off (July 16, 2019), 229 of 260 patients (88.1%) had discontinued study treatment, including 61 patients (46.9%) in the trametinib group and 52 patients (40.0%) in the physician's choice group who had died.

Baseline Characteristics

Baseline characteristics of patients were overall similar in the trametinib and physician's choice group in age (median 56.6 years [interquartile range (IQR), 44.6 to 63.3] and median 55.3 years [IQR, 42.4 to 65.6]), enrolment location (79% from the US and 21% from the UK in both groups) and performance status (72% and 28% with performance status of 0 and 1, respectively, in both groups). Most patients' disease was in the ovary (92% and 90%) and classified as stage III (74% and 72%). The mutational status of patients in the trametinib and physician's choice group, respectively, were *KRAS* (12% and 11%), *NRAS* (3% and 5%), *BRAF* (2% and 1%), and any of *KRAS*, *BRAF*, or *NRAS* (17% in both groups); the proportion of patients with no mutation was 37% in the trametinib group and 32% in the physician's choice group. Approximately half of enrolled patients had missing information on mutation status (46% and 51% in the trametinib and physician's choice groups, respectively). Patients in the trametinib and physician's choice group, respectively, had a mean 2.9 (SD, 1.9) and mean 2.9 (SD, 1.7) previous lines of systemic therapy (including chemotherapy and hormonal therapy); nearly half of patients (48% and 49%) had 3 or more previous lines of systemic therapy. The number of previous lines of chemotherapy in the trametinib and physician's choice group, respectively, were 1 (48% and 42%), 2 (25% and 30%), and 3 or more (28% in both groups). The number of previous lines of hormonal therapy in the trametinib and physician's choice group, respectively, were 0 (42% and 43%), 1 (58% and 52%), and 2 (0% and 5%).

Treatment Exposure and Concomitant Medications

The number of treatment cycles for trametinib (n = 127) was median 8 (IQR, 3 to 16). In the physician's choice group, the number of treatment cycles for letrozole (n = 44) was median 10 cycles (IQR, 5 to 16), for tamoxifen (n = 27) was median 4 cycles (IQR, 2 to 6), for pegylated liposomal doxorubicin (n = 40) was median 6 cycles (IQR, 4 to 11), for paclitaxel (n = 11) was median 4 cycles (IQR, 2 to 6), and for topotecan (n = 8) was median 2 cycles (IQR, 2 to 3). Ten of 57 patients (17.5%) who received paclitaxel, pegylated liposomal doxorubicin, or topotecan in the physician's choice group discontinued treatment after 6 cycles, as allowable per protocol.

The relative dose intensity for trametinib was median 75% (IQR, 59% to 91%), letrozole was median 100% (IQR, 96% to 100%), tamoxifen was median 82% (IQR, 64% to 98%), pegylated liposomal doxorubicin was median 100% (IQR, 88% to 100%), paclitaxel was median 100% (IQR, 67% to 100%), and topotecan was median 98% (IQR, 83% to 100%).

Concomitant medications and subsequent therapies were not reported in the GOG 281/LOGS trial.

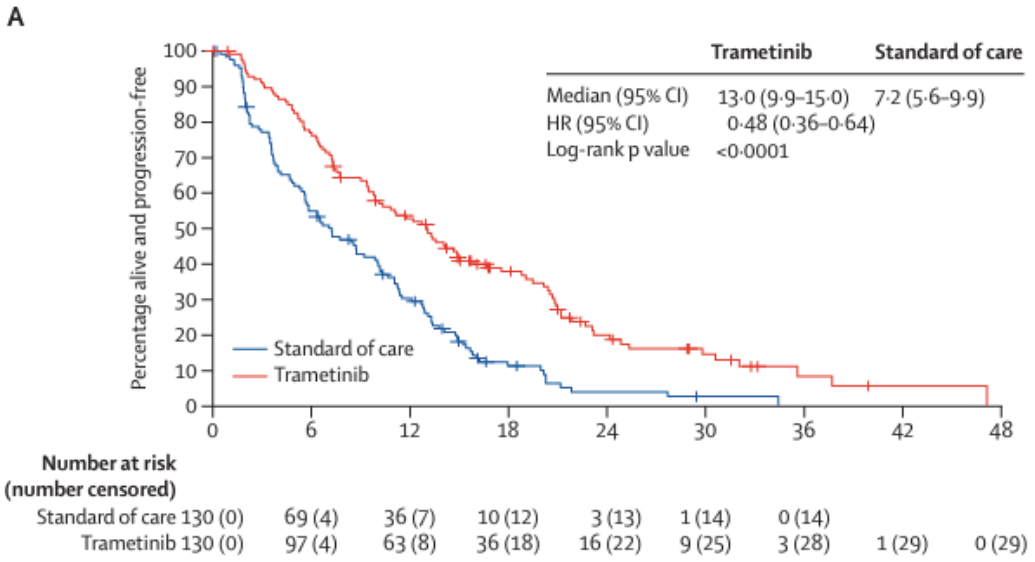
Efficacy

Results for outcomes important to this review are presented in Table 5. Key results include the following:

- Statistically, trametinib was favoured over physician's choice of therapy for investigator-assessed PFS (Figure 1) and ORR.
- Results from subgroup analyses of PFS (geographical region, number of previous regimens, performance status, and planned physician's choice regimen) were overall consistent with the primary analysis.
- The evidence was insufficient to demonstrate a statistically significant difference in OS between the treatment groups (Figure 2). The analysis of OS included 88 patients who received trametinib after crossover from the physician's choice group.
- Between-group differences in the probabilities of PFS and OS at clinically relevant follow-up time points were not reported. Absolute between-group differences with confidence intervals for ORR were also not reported.
- HRQoL was statistically poorer among patients in the trametinib group compared with those in the physician's choice group at week 12. The between-group difference was not clinically important according to trial-specified meaningful important difference (MID). According to the investigators, the evidence was insufficient to show a difference in HRQoL between the treatments at later time points, although the between-groups differences with confidence intervals were not reported. As such, the CDA-AMC review team could not validate this assertion. Point estimates for the differences were smaller than the trial-specific MID.
- Although the authors noted "no differences" in neurotoxicity (per FACT-GOG-Ntx) between groups at any time point, numeric results were not reported. As such, the CDA-AMC review team could not validate this assertion.

Figure 1: Kaplan-Meier Estimate of Investigator-Assessed Progression-Free Survival (ITT Population)

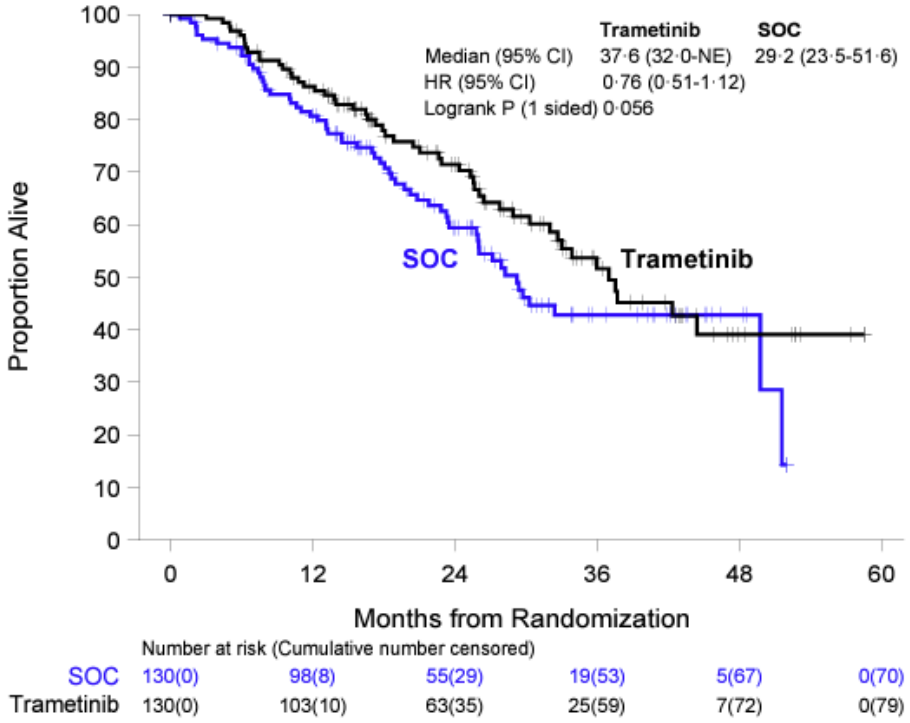
Alt Text: Kaplan-Meier curves of investigator-assessed progression-free survival in the trametinib group (N = 130; red) versus the standard of care group (N = 130; blue) showing early separation at approximately 2 months that was maintained through to nearly 48 months and 34 months for trametinib and standard of care, respectively. The number of patients in the trametinib and standard of care group, respectively, who were at risk dropped significantly by 6 months (97 and 69, respectively), 12 months (63 and 36, respectively), 18 months (36 and 10, respectively), 24 months (16 and 3, respectively), 30 months (9 and 1, respectively), 36 months (3 and 0, respectively), 42 months (1 and 0, respectively), and 48 months (0 and 0, respectively).



CI = confidence interval; HR = hazard ratio; ITT = intention to treat.
Note: In the standard of care group, patients received paclitaxel, pegylated liposomal doxorubicin, topotecan, letrozole, or tamoxifen.
Source: Gershenson et al. Trametinib versus standard of care in patients with recurrent low-grade serous ovarian cancer (GOG 281/LOGS): an international, randomized, open-label, multicentre, phase 2/3 trial. Lancet. 2022 Feb 5;399(10324):541-553. Copyright 2022 by the authors. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02175-9/fulltext. Reprinted in accordance with Creative Commons Attribution 4.0 International License (CC BY 4.0): https://creativecommons.org/licenses/by/4.0/deed.en[8]

Figure 2: Kaplan-Meier Estimate of Overall Survival (ITT Population)

Alt Text: Kaplan-Meier curves of overall survival in the trametinib group (N = 130; black) versus the standard of care group (N = 130; blue). Separation of curves appears at approximately 6 months that is maintained until about 42 months, when the blue curve crosses above, slightly higher than the black curve. The curves remain parallel until just after 48 months when the blue curve crosses the black curve once again, descending vertically and terminating at about 52 months and the black curve terminating at nearly 60 months. The number of patients in the trametinib and standard of care group, respectively, who were at risk dropped by 12 months (98 and 103, respectively), 24 months (55 and 63, respectively), 36 months (19 and 25, respectively), 48 months (5 and 7, respectively), and 60 months (0 and 0, respectively).



CI = confidence interval; HR = hazard ratio; ITT = intention to treat; NE = not estimable; SOC = standard of care.
Note: In the standard of care group, patients received paclitaxel, pegylated liposomal doxorubicin, topotecan, letrozole, or tamoxifen.
Source: Gershenson et al. Trametinib versus standard of care in patients with recurrent low-grade serous ovarian cancer (GOG 281/LOGS): an international, randomized, open-label, multicentre, phase 2/3 trial. Lancet. 2022 Feb 5;399(10324):541-553. Copyright 2022 by the authors. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02175-9/fulltext. Reprinted in accordance with Creative Commons Attribution 4.0 International License (CC BY 4.0): https://creativecommons.org/licenses/by/4.0/deed.en[8]

Table 3: Summary of Key Efficacy Results

Variable	GOG 281/LOGS	
	Trametinib N = 130	Physician's Choice N = 130
Primary End Point: Investigator-assessed progression-free survival[a]		
Median follow-up duration, months (IQR)	31.5 (18.1 to 43.3)	31.3 (15.7 to 41.9)
Number of patients with investigator-assessed PFS events, n (%)	101 (77.7)	116 (89.2)
Disease progression, n (%)	NR	88 (67.7)
Death, n (%)	NR	28 (21.5)
Censored[b], n (%)	29 (22.3)	14 (10.8)
Time to investigator-assessed PFS (months), median (95% CI)	13.0 (9.9 to 15.0)	7.2 (5.6 to 9.9)
Adjusted HR (95% CI)[c]	0.48 (0.36 to 0.64)	Reference
P value[d]	< 0.0001	Reference

Variable	GOG 281/LOGS	
	Trametinib N = 130	Physician's Choice N = 130
Secondary End Points:		
Overall survival[a]		
Number of patients who died, n (%)	51 (39.2)	60 (46.2)
Number of patients censored[e], n (%)	79 (60.8)	70 (53.8)
Time to OS (months), median (95% CI)	37.6 (32.0 to NE)	29.2 (23.5 to 51.6)
HR (95% CI)[c]	0.76 (0.51 to 1.12)	Reference
P value[d]	0.056	Reference
Objective response rate[a]		
Complete response, n (%)	1 (0.8)	1 (0.8)
Partial response, n (%)	33 (25.4)	7 (5.4)
Stable disease, n (%)	77 (59.2)	92 (70.7)
Progressive disease, n (%)	9 (6.9)	22 (16.9)
Response undetermined, n (%)	10 (7.7)	8 (6.2)
Number of patients with ORR, n (%)	34 (26.2)	8 (6.2)
Odds ratio (95% CI)[f]	5.4 (2.4 to 12.2)	Reference
P value[f]	< 0.0001	Reference
FACT-O TOI (total score of 0 to 100; higher scores indicate better health-related quality of life)		
Baseline, number of patients contributing to the analysis, n (%)	100 (76.9)	98 (75.4)
Baseline FACT-O TOI score (points), mean (SD)	74.5 (13.7)	74.5 (16.6)
12 weeks		
Number of patients contributing to the analysis, n (%)	91 (70.0)	91 (70.0)
FACT-O TOI score (points), mean (SD)	70.6 (13.5)	74.2 (16.0)
Difference, FACT-O TOI score (points) at 12 weeks (95% CI)[g]	-3.6 (–6.8 to –0.5)	Reference
P value	0.048	Reference
24 weeks		
Number of patients contributing to the analysis, n (%)	75 (57.7)	68 (52.3)
FACT-O TOI score (points), mean (SD)	73.0 (12.8)	70.2 (15.5)
Difference, FACT-O TOI score (points) at 24 weeks (95% CI)	NR	Reference
P value	NR	Reference
36 weeks		

Variable	GOG 281/LOGS	
	Trametinib N = 130	Physician's Choice N = 130
Number of patients contributing to the analysis, n (%)	66 (50.7)	65 (50.0)
FACT-O TOI score (points), mean (SD)	72.6 (12.8)	69.3 (18.6)
52 weeks		
Number of patients contributing to the analysis, n (%)	58 (44.6)	57 (43.8)
FACT-O TOI score (points), mean (SD)	73.3 (14.3)	72.1 (16.9)

CI = confidence interval; FACT-O-TOI = Functional Assessment of Cancer Therapy – Ovarian Cancer Trial Outcome Index; HR = hazard ratio; IQR = interquartile range; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SD = standard deviation.

[a] This analysis was conducted in the intention to treat population (130 patients in the trametinib group and 130 patients in the physician's choice group).

[b] Patients who were alive and disease-free at the last follow-up visit were censored on the date of their last CT scan.

[c] Based on a Cox proportional hazards model that adjusted for treatment, geographic region (US or UK), performance status (0 or 1), and planned treatment regimen (in the physician's choice arm).

[d] P value based on a log-rank test, stratified by geographic region (US or UK), performance status (0 or 1), and planned treatment regimen (in the physician's choice arm). The alpha has not been adjusted for multiple testing and there is an increased risk of type I error.

[e] Patients who were alive at the last follow-up visit were censored on the date of last contact.

[f] Based on a logistic regression model that adjusted for treatment, geographic region (US or UK), performance status (0 or 1), and planned treatment regimen (in the physician's choice arm).

[g] Based on a linear mixed model with unstructured covariance matrix and adjusted for pretreatment TOI score, age at enrolment, and stratification factors.

Source: Gershenson et al. (2022)[8]

Harms

Detailed results for harms for the included study are in the following publication: Gershenson et al. (2022).[8] Detailed harms data are in the Working Papers, Appendix 3.

Key results include the following:

- The overall number of patients with at least 1 TEAE was not reported. TEAEs that occurred in at least 40% of patients in either the trametinib group (n = 128) or the physician's choice group (n = 127), respectively, were fatigue (73% and 58%), nausea (61% and 51%), diarrhea (73% and 34%), anemia (52% and 43%), abdominal pain (45% and 47%), vomiting (46% and 35%), constipation (42% and 39%), acneiform rash (63% and 10%), maculopapular rash (42% and 22%), peripheral edema (49% and 12%), and dry skin (44% and 13%).
- The number of patients with SAEs were 45 of 127 patients (35.4%) in the trametinib group and 43 of 127 patients (33.9%) in the physician's choice group. SAEs that occurred in at least 2% of patients in either the trametinib group or the physician's choice group were small intestinal obstruction (9% and 2%), abdominal pain (2% and 8%), urinary tract infection (5% and 3%), nausea (1% and 4%), thromboembolic event (3% and 1%), anemia (3% and 1%), vomiting (2% and 1%), colonic obstruction (0% versus 3%), and vaginal hemorrhage (0% and 2%).
- Grade 3 or higher AEs that occurred in at least 5% of patients in either the trametinib group (n = 127) or the physician's choice group (n = 127) were anemia (13% and 10%), abdominal pain (6% and 17%), nausea (9% and 11%), small intestinal obstruction (13% and 7%), hypertension (12% and 5%), vomiting (7% and 8%), diarrhea (10% and 3%), fatigue (8% and 4%), acneiform rash (6% and 1%), and maculopapular rash (7% and 0%).
- The number of patients who discontinued treatment due to AEs was 46 of 128 patients (36%) in the trametinib group and 38 of 127 patients (30%) in the physician's choice group; in the physician's choice group, this was inclusive of patients who crossed over to the trametinib group following disease progression.
- No deaths due to AEs were reported.

- Although venous thromboembolism and major hemorrhagic events were considered important for this review, they were not assessed in the included study. AEs of special interest (rash, diarrhea, visual disorders, hepatic disorders, cardiac-related AEs, and pneumonitis) were prespecified in the included study. Ten patients (7.8%) in the trametinib group and 1 patient (0.8%) in the physician's choice group experienced decreased ejection fraction. Two patients (1.6%) in the trametinib group and 1 patient (0.8%) in the physician's choice group experienced grade 3 left ventricular systolic dysfunction. Additional AEs of special interest that occurred in the trametinib group (none occurred in the physician's choice group) were pneumonitis (3 patients [2.3%]), QTc prolongation (2 patients [1.6%]), retinal vascular disorder (2 patients [1.6%]), and retinal tear (1 patient [0.8%]).

Critical Appraisal

Internal Validity

There was low risk of bias in the randomization process. Central randomization likely resulted in adequate allocation concealment and patients were stratified on geographical region, number of previous regimens, performance status, and planned physician's choice regimen (applicable in the physician's choice group). Baseline characteristics of patients were balanced overall between treatment groups.

There was potential risk of bias based on the open-label design of the GOG 281/LOGS trial, as patients and investigators were aware of treatment assignment. Investigators may have been motivated to prematurely ascertain disease progression to allow patients randomized to the physician's choice group to cross over to the trametinib group. Although the study authors indicated this was controlled for in the study (via objective evidence of RECIST criteria-defined progression prior to crossover), the impact of such methods remain unclear. PFS was assessed per investigator, rather than via central review, such that there was an associated degree of subjectivity in the assessment to increase the risk of bias. Such bias would be in favour of trametinib for both PFS and ORR, in addition to some level of subjectivity in ORR assessments (based on radiological assessment and clinical review). Moreover, awareness of allocated treatment may increase risk of bias for subjective outcomes such as patient-reported measures (e.g., HRQoL) and subjective harms.

There were some concerns for risk of bias due to deviations from intended interventions. The rate of treatment discontinuations (due to withdrawal or treatment refusal) was approximately 2% in the trametinib group versus 10% of patients in the physician's choice group to indicate potential bias based on patients' knowledge of assigned treatment. The magnitude and direction of the bias is uncertain.

Patients (n = 88 [68%]) in the physician's choice group who crossed over after disease progression to receive trametinib were not accounted for in analyses of relevant efficacy measures (i.e., OS, HRQoL). For OS, the large proportion of patients crossing over to the trametinib group would likely bias the effect estimate toward the null and likely contributed to the lack of statistical significance for this end point. For HRQoL, the magnitude and direction of bias is unclear, as the timing of the individual crossovers was not reported. It is uncertain whether PFS or ORR are valid surrogates for OS in this patient population and within the context of modern available therapies; however, per the clinical experts OS is difficult to measure in this disease area due to the protracted disease course. As such, both clinical experts suggested that they would rely on PFS and/or ORR as efficacy end points and that a response may result in reduced symptom burden.

For the primary end point of investigator-assessed PFS, treatment effects were estimated from a Cox proportional hazards model with covariates for treatment and stratification factors used in the randomization. Although the proportional hazards assumption for PFS was tested using a time-dependent treatment effect and inspection of the log (-log) survival plots (p = 0.68), this test may not have been sufficiently powered. Based on a visual inspection of the Kaplan-Meier curves, there appeared to be no serious violation of the proportionality assumption for PFS. For OS, the Kaplan-Meier curves appear to converge near the 6-month time point and subsequently crossed at about 42 months to indicate that the proportional hazards assumption may not be valid. As the HR is not constant over time, the estimated HR for OS may be misleading. The primary end point was statistically significant, but there was no adjustment for multiple comparisons, resulting in an increased risk of type I error. The same was true for ORR and statistically significant HRQoL results (i.e., difference in FACT-O TOI at 12 weeks), which were also not adjusted for multiple testing. There was uncertainty related to the stratification factors that were included in analyses of secondary end points due to inconsistent reporting (i.e., number of previous regimens were variably included in descriptions wherever stratification factors were reported).

Subgroup analyses of PFS according to stratification factors (geographical region, number of previous regimens, performance status, and planned physician's choice regimen) demonstrated heterogeneity in treatment effect size by planned physician's choice regimen; excluding the subgroup comparing trametinib with preplanned tamoxifen reduced the subgroup heterogeneity for a treatment effect that was consistent with the primary analysis. However, findings from subgroup analyses were limited in interpretation based on patients not being randomized to the subgroups and analyses that were conducted post-hoc.

Between-group effect estimates of the FACT-O TOI were analyzed using a linear mixed model with unstructured covariance matrix and adjusted for pretreatment TOI score, age at enrolment, and stratification factors. This analysis was specified in the protocol for subgroups of the physician's choice group (by treatment type) and reported in the main publication to be prespecified. There was a risk of bias due to selective reporting as the method of analysis was not defined or detailed in the protocol for the overall population. While findings for the FACT-O TOI indicated a statistically significant decrement at week 12 among patients receiving trametinib compared with physician's choice of therapy, the lower bound of the CI (–6.5%) indicated potential imprecision in the estimate based on the trial's prespecified MID (i.e., 5-point difference).

Evidence of measurement properties for the FACT-O TOI were not identified and a MID was not estimated in the published literature for the FACT-O; however, given the range of possible scores (0 to 100), between-group differences at all time points appeared small (approximately 1 to 4 points). All were smaller than the trial-specified MID; however, no evidence was cited to justify this threshold.

A thorough appraisal of the evidence and interpretation of the results was hindered by substandard reporting. For ORR, the absolute between-group difference with confidence interval was not reported, precluding a judgment about the precision of the estimated effect. For OS and PFS, data on the reasons for censoring were not reported, so an appraisal of informative censoring (e.g., whether the reasons for censoring were related to the risk and timing of the outcome) was not possible. Additionally, between-group differences in event or event-free probabilities at clinically relevant time points were not reported for either OS or PFS. While a sensitivity per-protocol analysis was reported to have been conducted for PFS to account for 3 patients who were censored at time of crossover to trametinib prior to disease progression, the results of this analysis were not reported. The small number of patients is unlikely to significantly impact treatment effects alone.

Concerns for risk of bias were related to several missing data. For ORR, 6% to 8% of patients across groups had responses that were undetermined. The reasons for undetermined responses were not reported, so whether any bias was introduced is uncertain. There were substantial missing data for the FACT-O TOI at baseline (23% to 25% across groups), week 12 (30%), and throughout follow-up, with even greater losses by week 52 (over 50%). No methods were undertaken to account for such missingness (e.g., sensitivity analyses, imputations) and only observed cases were included in analyses. As such, there is high risk of bias due to missing data for the analysis of this end point at all follow-up times reported. Although the analyses of the FACT-O TOI up to week 24 were prespecified, notably the between-group differences at week 24 and the results of any statistical testing were not reported. No data were reported for the FACT-GOG-Ntx. It is possible that the results of these pre-planned analyses were not reported due to the magnitude and/or direction of the effect estimates. The authors indicated that the evidence was insufficient to show a difference between groups in HRQoL at these time points; however, the review team could not verify this assertion in the absence of between-group differences with confidence intervals. Finally, there was a high rate of treatment discontinuation due to harms in the trametinib group (36%) and the physician's choice group (30%); since the comparative effect includes patients in the physician's choice group who crossed over to receive trametinib (permitted per protocol), the direction and magnitude of the potential bias cannot be predicted.

External Validity

No sites in Canada were included in the GOG 281/LOGS trial and it was unclear if the enrolled patients in trial are representative of the racial or ethnic diversity of patients with low-grade serous ovarian cancer in Canada, of whom nearly 90% were White. The clinical experts consulted for this review indicated no serious concerns with the baseline characteristics of patients. However, approximately 70% of patients had a performance status of 0 which appeared overly high to the experts for patients who have recurrent disease. The experts felt that more than 50% of patients, as observed in the trial, would be expected to have previous hormonal therapy given that it is a standard of care in this disease indication. In contrast, the experts noted that the enrolled patients were highly pretreated (nearly half had had 3 or more lines of systemic therapy) and expressed that trametinib would be used optimally after a single line of therapy (e.g., as second-line treatment). The clinical experts indicated that study eligibility was overall consistent with patients observed in clinical practice and reasonable for who would be considered for treatment with trametinib,

although some criteria were noted to be stringent (e.g., perspective pathology review, short access of 10mm rather than a 15mm cut-off for lymph nodes may be used) to potentially result in a highly selected population that may limit generalizability. The experts expressed that the population was relatively heterogeneous (e.g., number and types of prior treatments) and aligned with patients with recurrent low-grade serous ovarian cancer.

Dose modifications of trametinib including treatment interruptions, dose reductions up to 2 levels (1.5 mg or 1.0 mg), and treatment discontinuation were considered by the experts to align with clinical practice. Patients in the physician's choice group could discontinue therapy after 6 cycles at the investigator's discretion. This appears to be aligned with 6 cycles of chemotherapy as standard clinical practice, according to the experts, acknowledging that treatment duration of 6 cycles is not based on clinical evidence and that treatment may be shorter due to toxicities or longer in the recurrent setting for maximum response (e.g., if visible disease remains on imaging).

Preselected physician's choice treatments in the trial (paclitaxel, pegylated liposomal doxorubicin, topotecan, letrozole, or tamoxifen) are used in Canada; however, the clinical experts also noted additional therapies to be used in practice including endocrine therapy (e.g., anastrozole), single-agent therapies (i.e., bevacizumab, gemcitabine), single-agent platinum-based chemotherapy (i.e., carboplatin, cisplatin) and combination platinum-based regimens (i.e., carboplatin plus paclitaxel, carboplatin-gemcitabine, carboplatin-pegylated liposomal doxorubicin; all with or without bevacizumab). Concomitant and subsequent treatments were not reported so whether these were aligned with clinical practice in Canada is unknown.

Patients were required to have measurable disease per RECIST criteria; the clinical experts considered this to be reasonable since tumour markers (e.g., CA125) are unreliable markers of low-grade disease and clinicians routinely rely on radiological and clinical assessments to assess treatment effectiveness. In the GOG 281/LOGS trial, efficacy was measured using CT or MRI lesion assessments every 8 weeks for 15 months and then every 3 months thereafter. According to the experts, imaging assessments to determine response to therapy would not be as frequent as was employed in the trial (i.e., every 8 to 12 weeks for the first 15 months, followed by radiological imaging once every 3 months).

The primary end point of PFS was a clinically relevant outcome, according to the clinical experts, and more applicable than OS since patients with recurrent low-grade serous ovarian cancer have a long, protracted disease course (and in this trial specifically, the interpretation of results for OS are challenged by protocol-allowable crossovers to the trametinib group). Given that the indicated population experiences poor response to currently available standard therapies, the experts expressed that PFS and ORR are important outcomes, particularly if they are associated with a reduction in symptom burden and improvement in HRQoL. While HRQoL was included in the GOG 281/LOGS trial, the experts weighed in that assessments of patients' quality of life was not routinely conducted using formal outcome measures.

Discussion

Efficacy

Clinicians indicated that patients with low-grade serous ovarian cancer need more efficacious treatment options in the metastatic or recurrent disease setting to improve survival, delay disease progression, reduce symptom burden, and improve HRQoL. The clinical experts consulted for this review expressed that trametinib is a novel treatment for low-grade serous ovarian cancer that would target the underlying disease process.

Findings from the GOG 281/LOGS trial demonstrated that treatment with trametinib may result in a statistically significant increase in PFS when compared to physician-selected chemotherapy or endocrine therapy. There was some uncertainty in the results due to potential risk of bias, lack of adjustment for multiple testing, and substandard reporting (non-reporting of censoring reasons and event or event-free probabilities at relevant follow-up time points). There was insufficient evidence to demonstrate a statistically significant treatment effect for OS; the interpretation of these results is challenged by many (68%) protocol-allowable crossovers from the physician's choice group to the trametinib group following disease progression and potential violation of the proportional hazards assumption. Findings demonstrated that treatment with trametinib may result in a statistically significant increase in ORR when compared with physician's choice therapy. Findings for ORR were clinically meaningful to the experts who highlighted that observed improvements in the number of patients with partial responses were important in a disease setting with few treatment

options available. There were 7% of patients with responses that were undetermined. It is uncertain how this may have affected the results, as the reasons for undetermined responses were not reported. Relative to physician's choice of therapy, treatment with trametinib demonstrated a statistically significant deterioration in HRQoL as measured on the FACT-O TOI at 12 weeks. This result was at increased risk of type 1 error. The point estimate for the between-group difference was not clinically meaningful according to a threshold prespecified by the authors; however, no methodological or clinical rationale was provided for the threshold. Results at later time points were not tested statistically and beyond 24 weeks, between-group differences with confidence intervals were not reported. At all time points, the results were at high risk of bias due to missing outcomes data and the subjective nature of the outcome.

Median follow-up was approximately 30 months in the trial with 77% to 85% of patients across groups experiencing a PFS event that indicated treatment duration was sufficient to capture the key outcome of interest. While longer follow-up of patients with recurrent low-grade serous ovarian cancer may be informative for OS and HRQoL, the available evidence suggests that findings for OS may be uninterpretable due to crossovers and results for HRQoL may be challenged by increasing attrition. Formal assessments of treatment effects on HRQoL beyond 12 weeks was another identified gap in the evidence. Neurotoxicity was measured in the trial via the FACT-GOG-Ntx, but the results were not reported. As such, the effect of trametinib compared with physician's choice of treatment on symptoms of neurotoxicity is not known. The comparative efficacy and harms of trametinib compared with other currently available treatments (e.g., anastrozole; bevacizumab; gemcitabine; carboplatin; cisplatin; and, carboplatin-paclitaxel, carboplatin-gemcitabine, carboplatin-pegylated liposomal doxorubicin; all with or without bevacizumab) is unknown in the absence of evidence.

Harms

While the overall number of patients with TEAEs was not reported, common TEAEs occurring in 20% to 40% of patients were numerically higher among those receiving trametinib compared to those receiving physician's choice therapy. The overall proportion of patients with 1 or more SAEs were similar between treatment groups. However, compared to the physician's choice group, more patients in the trametinib group experienced specific SAEs including small intestinal obstruction, urinary tract infection, thromboembolic event, anemia, and vomiting. Similarly, more patients in the trametinib group experienced AEs of grade 3 or higher including anemia, small intestinal obstruction, hypertension, diarrhea, fatigue, acneiform rash, and maculopapular rash. Nevertheless, the clinical experts expressed that the AEs were considered manageable. No new safety signals were observed. The clinical experts cautioned that patients with significant cardiac or respiratory conditions may not be suitable for treatment with trametinib given the increased risk of related AEs (e.g., hypertension, decreased ejection fraction, QTc prolongation, left ventricular dysfunction[7]).

Conclusion

Clinicians advocate for patients with recurrent low-grade serous ovarian cancer to have more efficacious treatment options to prolong overall survival, improve response rates, prolong progression-free survival, and improve patients' HRQoL. Evidence from a randomized, phase II/III, open-label trial (GOG 281/LOGS) that included 260 adult patients with recurrent low-grade serous ovarian cancer demonstrated that compared with physician's choice of therapy, treatment with trametinib resulted in a statistically significant and clinically important improvement in PFS and ORR; there was some uncertainty in the findings based on potential risk of bias, substandard reporting, and lack of control for multiple testing. Treatment with trametinib may result in a statistically significant deterioration in HRQoL at 12 weeks. Between-group differences at later time points were small and not tested statistically. The results were at risk of bias due to missing data and the subjective nature of the outcome, and the result at 12 weeks is at increased risk of type 1 error. The trial was insufficient to demonstrate a difference between trametinib and physician's choice therapy in OS. The safety profile of trametinib was as expected with no new safety signals. The long-term follow-up for OS and HRQoL and safety of trametinib compared with available treatments is unknown in the absence of evidence.

Economic Review

The economic review consisted of a cost comparison for trametinib compared with endocrine, platinum-based and non-platinum-based therapies for adults with recurrent low-grade serous ovarian cancer.

Based on public list prices, trametinib is expected to have a per patient cost of $9,580 per 28-day cycle (Table 4). Clinical experts consulted by CADTH identified that the comparators most likely to be displaced if trametinib is reimbursed for recurrent low-grade serous ovarian cancer differ for those with first recurrence and those with multiple recurrences. A comprehensive comparison of treatment costs for all comparators is provided in Table 4.

For those with first recurrence, platinum-based combination regimens were identified as being most likely to be displaced. Platinum-based combination regimens are expected to have a per patient 28-day cost ranging from $1,461 to $10,981 (Table 4). Therefore, for those with first recurrence the incremental cost of trametinib per patient per 28-day cycle ranges from $7,734 to $8,119 compared to carboplatin with pegylated liposomal doxorubicin, $7,153 compared to carboplatin with gemcitabine, and $712 to $1,912 compared to carboplatin with paclitaxel. For carboplatin-paclitaxel with bevacizumab, trametinib costs $1,825 more than the lower-dose regimen but results in cost savings of $1,401 when compared to the higher-dose regimen over 28-days. As such, the reimbursement of trametinib for the treatment of first recurrence of low-grade serous ovarian cancer is generally expected to increase overall drug acquisition costs, apart from the comparison with the carboplatin-paclitaxel with bevacizumab higher dose regimen.

For those with multiple recurrences, non-platinum monotherapies were identified as being most likely to be displaced. Non-platinum monotherapies are expected to have a per patient 28-day cost ranging from $721 to $7,187 (Table 4). Therefore, for those with multiple recurrences, the incremental cost of trametinib per patient per 28-day cycle ranges from $2,392 to $3,592 compared to paclitaxel, $6,805 compared to topotecan, $4,490 to $6,804 compared to bevacizumab, $7,420 compared to gemcitabine, and $8,859 compared to pegylated liposomal doxorubicin. As such, the reimbursement of trametinib for the treatment of low-grade serous ovarian cancer is expected to increase overall drug acquisition costs for those with multiple recurrences.

Additional items for consideration are provided in the following bullets:

- Evidence from the GOG 281/LOGS trial demonstrated that, compared with physician's choice of therapy, treatment with trametinib resulted in improvements in PFS and ORR.[8] The trial was insufficient to demonstrate a difference in OS between trametinib and physician's choice of therapy. Additionally, treatment with trametinib may result in a deterioration in HRQoL at 12 weeks.[8] Although AEs were manageable, experts noted potential limitations for patients with cardiac or respiratory conditions.
- The GOG 281/LOGS trial included only five of the listed comparators (paclitaxel, pegylated liposomal doxorubicin, topotecan, oral letrozole, and oral tamoxifen). As a result, the comparative effectiveness of trametinib against the remaining relevant comparators (Table 2)is unknown. This limits the ability to evaluate trametinib's relative efficacy and safety across all relevant treatment options available in Canada.
- Some comparators lack a defined maximum treatment duration as specified in their product monographs. Medications such as trametinib, paclitaxel, pegylated liposomal doxorubicin, topotecan and gemcitabine are recommended to treat until disease progression or unacceptable toxicity. Differences in treatment durations which would impact total treatment costs associated with trametinib and comparators, are not captured in the cost comparison.
- As of December 6, 2024, trametinib is only available as a brand-name product in Canada and there are no current generic products under review at Health Canada.[11]
- No healthcare resource use outcomes were included in the clinical trial.[8]
- According to the literature and clinical expert input received for this submission, there may be need for increased monitoring and management due to potential AEs associated with the use of trametinib versus comparators, such as cardiac or respiratory events, which may place additional demands on the healthcare system.
- No cost-effectiveness studies conducted in Canada were identified based on a literature search conducted on September 25, 2024. One cost-effectiveness study, conducted from a US payer perspective, was identified. The study was based on the GOG 281/LOGS trial, which compared trametinib to physician-selected chemotherapy or endocrine therapy for recurrent low-grade

serous ovarian cancer.[12] The study concluded that trametinib is more effective and more costly compared with physician-selected therapy. However, the conclusions were limited by the relatively short duration of follow-up.

Conclusion

The reimbursement of trametinib for the treatment of adults with recurrent low-grade serous ovarian cancer is expected to increase overall drug acquisition costs. Based on the clinical review conclusions, trametinib may provide some clinical benefits, including improvements in PFS and ORR compared to physician's choice of therapy.

Given that trametinib is associated with increased drug acquisition costs and incremental benefits in terms of PFS and ORR, a cost-effectiveness analysis would be required to determine the cost-effectiveness of trametinib relative to endocrine, platinum-based and non-platinum-based therapies. As this was not available, the cost-effectiveness of trametinib relative to endocrine, platinum-based and non-platinum-based therapies for the treatment of recurrent low-grade serous ovarian cancer could not be determined.

References

1. pan-Canadian Oncology Drug Review Committee (pERC) final recommendation: trametinib (Mekinist - GlaxoSmithKline). Ottawa (ON): CDA-AMC; 2013 Oct 22: https://www.cda-amc.ca/sites/default/files/pcodr/pcodr-mekinist-mm-fn-rec.pdf. Accessed 2024 Nov 28.
2. Brenner DR, Gillis J, Demers AA, et al. Projected estimates of cancer in Canada in 2024. *Can Med Assoc J.* 2024;196(18):E615-E623.
3. Moujaber T, Balleine RL, Gao B, Madsen I, Harnett PR, DeFazio A. New therapeutic opportunities for women with low-grade serous ovarian cancer. *Endocr Relat Cancer.* 2021;29(1):R1-R16.
4. Kulkarni A, Cooke C, Fazelzad R, Fung-Kee-Fung M, May T, Zigras T. Treatment of Recurrent Low-grade Serous Ovarian Cancer With MEK Inhibitors: A Systematic Review. *Am J Clin Oncol.* 2024;47(1):11-16.
5. Gershenson DM, Birrer MJ. Management of low-grade, serous carcinomas of the ovary. In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2024: https://www.uptodate.com/. Accessed 2024 Sep 6.
6. Birrer MJ, Fujiwara K. Medical treatment for relapsed epithelial ovarian, fallopian tube, or peritoneal cancer: Platinum-resistant disease. In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2024: https://www.uptodate.com/. Accessed 2024 Sep 6.
7. Mekinist (trametinib): 0.5 mg and 2 mg oral tablets, 4.7 mg/bottle (0.05 mg/mL after reconstitution) powder for oral solution [product monograph]. Montreal (QC): Novartis Pharmaceuticals Canada Inc.; 2024 Jan 16: https://pdf.hres.ca/dpd_pm/00074274.PDF. Accessed 2024 Nov 28.
8. Gershenson DM, Miller A, Brady WE, et al. Trametinib versus standard of care in patients with recurrent low-grade serous ovarian cancer (GOG 281/LOGS): an international, randomised, open-label, multicentre, phase 2/3 trial. *Lancet.* 2022;399(10324):541-553.
9. Kaldawy A, Segev Y, Lavie O, Auslender R, Sopik V, Narod SA. Low-grade serous ovarian cancer: A review. *Gynecol Oncol.* 2016;143(2):433-438.
10. Zwimpfer TA, Tal O, Geissler F, et al. Low grade serous ovarian cancer – A rare disease with increasing therapeutic options. *Cancer Treat Rev.* 2023;112:102497.
11. Health Canada. Generic submissions under review. 2024; https://www.canada.ca/en/health-canada/services/drug-health-product-review-approval/generic-submissions-under-review.html. Accessed 2024 Dec 18.
12. Piao H, Wu M, Qin S, et al. Trametinib for patients with recurrent low-grade serous ovarian cancer: A cost-effectiveness analysis. *Gynecol Oncol.* 2023;168:17-22.