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

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Drugs Health Technologies Health Systems

Reimbursement Review

Trametinib: Supplemental Material

Requester: Public Drug Programs
Therapeutic area: Gynecological cancers, low-grade serous ovarian cancer

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Abbreviations

AE adverse event

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

MEK mitogen-activated protein kinase kinase

MID meaningful important difference

Clinical Review Appendices

Appendix 1: Methods of the Clinical Review

Search Strategy

Strategy for Primary Studies (Systematic Review)

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist.[1]

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed by manual deduplication in EndNote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the PICOS framework and research questions. The main search concepts were trametinib and ovarian cancers. An additional search for mitogen-activated protein kinase kinase (MEK) inhibitors and low-grade serous ovarian cancer was also conducted, using the same parameters. The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results.

The initial searches were completed on September 25, 2024. Regular alerts updated the searches until the meeting of the Formulary Management Expert Committee meeting on January 30, 2025.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from Grey Matters: A Practical Tool For Searching Health-Related Grey Literature. Included in this search were the websites of regulatory agencies (US FDA and European Medicines Agency). Google was used to search for additional internet-based materials.

Strategy for Indirect Treatment Comparisons

A focused literature search for indirect treatment comparisons dealing with trametinib or ovarian cancer was run in MEDLINE on September 25, 2024. Retrieval was not limited by publication date or by language.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts.

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946-present)
- Embase (1974-present)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: September 25, 2024

Alerts: Biweekly search updates until project completion

Search filters applied: No filters were applied to limit the retrieval by study type.

Limits:

- Publication date limit: none
- Language limit: none
- Conference abstracts: excluded

Table 1: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*****	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Warning

To conduct a comprehensive search, we may have included antiquated, noninclusive, or potentially stigmatizing terms that may have appeared in past and present literature. We recognize and acknowledge

the inappropriate and harmful nature of terms that may appear in search strategies and include this warning so the reader can determine how they would like to proceed.

The warning is modified from the University of Michigan Library's guidance, Addressing antiquated, non-standard, exclusionary, and potentially offensive terms in evidence syntheses and systematic searches.

Multi-Database Strategy

Embase < 1974 to 2024 September 24 >

Ovid MEDLINE(R) ALL < 1946 to September 24, 2024 >

Trametinib for Ovarian Cancer

1. (mekinist* or trametinib* or Meqsel* or mekinst* or spexotras* or GSK-1120212 or GSK1120212 or JTP 74057 or JTP74057 or snr 1611 or snr1611 or tmt 212 or tmt212 or 33E86K87QN).ti,ab,kf,ot,hw,rn,nm.
2. Ovarian Neoplasms/ or Carcinoma, Ovarian Epithelial/ or Cystadenocarcinoma, Serous/
3. (ovar* adj3 (carcinoma* or cancer* or tumo?r* or neoplas*)).ti,ab,kf.
4. (LGSOC or low-grade serous carcinoma*).ti,ab,kf.
5. *Genital Neoplasms, Female/
6. ((genital* or gyn?ecolog*) adj3 (carcinoma* or cancer* or tumo?r* or neoplas* or oncolog*)).ti,kf.
7. 2 or 3 or 4 or 5 or 6
8. 1 and 7
9. 8 use medall
10. *trametinib/
11. (mekinist* or trametinib* or Meqsel* or mekinst* or spexotras* or GSK-1120212 or GSK1120212 or JTP 74057 or JTP74057 or snr 1611 or snr1611 or tmt 212 or tmt212).ti,ab,kf,dq.
12. 10 or 11
13. Ovary tumor/ or ovary cancer/ or ovary carcinoma/ or cystadenocarcinoma/
14. (ovar* adj3 (carcinoma* or cancer* or tumo?r* or neoplas*)).ti,ab,kf.
15. (LGSOC or low-grade serous carcinoma*).ti,ab,kf.
16. *female genital tract cancer/ or *female genital tract carcinoma/ or *female genital tract tumor/
17. ((genital* or gyn?ecolog*) adj3 (carcinoma* or cancer* or tumo?r* or neoplas* or oncolog*)).ti,kf.
18. 13 or 14 or 15 or 16 or 17
19. 12 and 18
20. 19 not conference abstract.pt.
21. 20 use oemezd
22. 9 or 21

23. remove duplicates from 22

MEK Inhibitors for LGSOC

1. ((mek or Mitogen-activated protein kinase) adj2 inhibitor*).ti,ab,kf.
2. ((ovar* adj3 (carcinoma* or cancer* or tumo?r* or neoplas*)) and serous and low-grade).ti,ab,kf.
3. (LGSOC or low-grade serous carcinoma*).ti,ab,kf.
4. 25 or 26
5. 24 and 27
6. 28 use medall
7. *mitogen activated protein kinase kinase inhibitor/
8. ((mek or Mitogen-activated protein kinase) adj2 inhibitor*).ti,ab,kf.
9. 30 or 31
10. ((ovar* adj3 (carcinoma* or cancer* or tumo?r* or neoplas*)) and serous and low-grade).ti,ab,kf.
11. (LGSOC or low-grade serous carcinoma*).ti,ab,kf.
12. 33 or 34
13. 32 and 35
14. 36 not conference abstract.pt.
15. 37 use oemezd
16. 29 or 38
17. remove duplicates from 39

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search -- ovarian | (mekinist* OR trametinib* OR Meqsel* OR mekinst* OR spexotras* OR “GSK 1120212” OR GSK1120212 OR “JTP 74057” OR JTP74057 OR “snr 1611” OR snr1611 OR “tmt 212” OR tmt212)]

WHO International Clinical Trials Registry Platform

International Clinical Trials Registry Platform, produced by the WHO. Targeted search used to capture registered clinical trials.

[Search terms -- ovarian AND (mekinist* OR trametinib* OR Meqsel* OR mekinst* OR spexotras* OR “GSK 1120212” OR GSK1120212 OR “JTP 74057” OR JTP74057 OR “snr 1611” OR snr1611 OR “tmt 212” OR tmt212), (tumour* OR tumour* OR solid) AND (mekinist* OR trametinib* OR Meqsel* OR mekinst* OR spexotras* OR “GSK 1120212” OR GSK1120212 OR “JTP 74057” OR JTP74057 OR “snr 1611” OR snr1611 OR “tmt 212” OR tmt212)]

Health Canada’s Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms -- Mekinist, trametinib, meqsel, mekinst, spexotras, tmt 212, tmt212, GSK1120212, GSK 1120212]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- (mekinist* OR trametinib* OR Meqsel* OR mekinst* OR spexotras* OR “GSK 1120212” OR GSK1120212 OR “JTP 74057” OR JTP74057 OR “snr 1611” OR snr1611 OR “tmt 212” OR tmt212)]

EU Clinical Trials Information System

European Union Clinical Trials Information System, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- mekinist trametinib Meqsel mekinst spexotras “GSK 1120212” GSK1120212 “JTP 74057” JTP74057 “snr 1611” snr1611 “tmt 212” tmt212]

Grey Literature

Search dates: September 12 to 16, 2024

Keywords: trametinib, mekinist, ovarian cancer

Limits: none

Relevant websites from the following sections of the grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

Study Selection

Two reviewers independently selected relevant studies for inclusion in 2 stages, first by titles and abstracts and then by full texts. Any record considered relevant by either reviewer at the title and abstract stage was reviewed by full text. The 2 reviewers agreed on the studies included in the report.

Data Extraction and Critical Appraisal

One reviewer extracted relevant data from the included studies with verification by a second reviewer. One reviewer appraised the internal and external validity of the available evidence in consideration of inputs by the clinical experts, and patient and clinician groups, with input from a methodologist.

Appendix 2: Methods of the Study Included in the Systematic Review

Characteristics of the Included Study

Inclusion and Exclusion Criteria

Table 2: Details of Eligibility Criteria of Study Included in the Systematic Review

Detail	GOG 281/LOGS

Inclusion criteria	• Aged 18 years and older
	• Initially diagnosed with low-grade serous ovarian or peritoneal carcinoma that recurred as low-grade serous carcinoma (invasive micropapillary serous carcinoma or invasive grade I serous carcinomas as defined by GOG, FIGO, WHO or Silverberg)
	• Initially diagnosed with serous borderline ovarian or peritoneal carcinoma that recurred as low-grade serous carcinoma (invasive micropapillary serous carcinoma or invasive grade I serous carcinomas as defined by GOG, FIGO, WHO or Silverberg)
	• Documented low-grade serous carcinoma with confirmation by prospective pathology review (on tissue from recurrent carcinoma or from original diagnostic specimen) before study entry
	• Measurable disease as defined by RECIST version 1.1; measurable disease was defined as ≥ 1 target lesion that can be accurately measured in ≥ 1 dimension (longest diameter recorded); each lesion must be ≥ 10 mm when measured by CT, MRI, or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest X-ray; lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI; all imaging studies must be performed within 28 days before study registration
	• At least 4 weeks have elapsed since any major surgery (e.g., laparotomy, laparoscopy, thoracotomy, video assisted thorascopic surgery)
	• Prior therapy:
	  ◦ Patients must have recurred or progressed following ≥ 1 platinum-based chemotherapy regimen
	  ◦ Patients may have received an unlimited number of prior therapy regimens
	  ◦ Patients may not have received all 5 choices in the physician's choice arm
	  ◦ Any hormonal therapy directed at the malignant tumour must be discontinued ≥ 1 week before study registration
	• Have a GOG performance status of 0 or 1

Exclusion criteria	• Patients who have had chemotherapy or radiotherapy within 4 weeks before study registration • Use of any investigational drug within 28 days preceding the first dose of study drug. • Not have received prior MEK, *KRAS*, or *BRAF* inhibitor therapy • Current use of non-study anti-cancer or investigational drugs, medications that can prolong Qt interval, or herbal supplements • Patients with known leptomeningeal or brain metastases or spinal cord compression due to poor prognosis and risk of progressive neurologic dysfunction • Patients with a bowel obstruction or other gastrointestinal condition; history of interstitial lung disease or pneumonitis; history or evidence of cardiovascular risk; history, evidence, or risk of retinal vein occlusion

CT = CT; FIGO = Federation of Obstetricians and Gynecologists; GOG = Gynecologic Oncology Group; MEK = mitogen-activated protein kinase kinase; MRI = MRI; RECIST = Response Evaluation Criteria in Solid Tumours; WHO = WHO.

Source: Gershenson et al. (2022)[2]

Interventions and Comparators

Patients in the trametinib group received trametinib 2 mg oral tablets, once daily. Patients in the physician's choice group received 1 of the following:

- paclitaxel 80 mg/m^2 by body surface area, via IV infusion over 1 hour, on days 1, 8, and 15 of every 28-day cycle
- pegylated liposomal doxorubicin 40 mg/m^2 to 50 mg/m^2 by body surface area, via IV infusion over 1 hour, on day 1 every 28 days
- topotecan 4 mg/m^2 by body surface area, via IV infusion over 30 minute, on days 1, 8, and 15 of every 28-day cycle
- letrozole 2.5 mg oral tablets, once daily
- tamoxifen 20 mg oral tablets, twice daily

Treatment continued in both groups until progression of unacceptable toxicity. In the physician's choice group, more than 6 cycles of chemotherapy could be administered at the discretion of the investigator.

Description of Outcomes

Progression-free survival

The primary end point in the GOG 281/LOGS trial was investigator-assessed progression-free survival, defined as time from randomization to disease progression or death. Patients who were alive and disease-free at the last follow-up visit were censored on the date of their last com scan. Patients who crossed over to trametinib from the physician's choice group before progression were censored on their crossover date.

Overall survival

Overall survival was defined as the time from study entry to time of death or date of last contact. Patients who were alive at the last follow-up visit were censored on the date of last contact. Patients were not censored at the time of crossover to the trametinib group from the physician's choice group following disease progression.

Objective response rate

Objective response rate was defined as the proportion of patients with a complete or partial clinical response, in each treatment group. Complete response was the disappearance of all target lesions, and any pathological lymph nodes (target or non-target lesions) must have reduction in short axis to less than 10 mm. Partial response was defined as at least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. Progressive disease was defined as at least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study; in addition, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered a progression. Stable disease was defined as neither sufficient shrinkage to qualify for partial response no sufficient increase to qualify for progressive disease. Best overall (unconfirmed) response was defined as the best time point response recorded from start of treatment until disease progression or recurrence.

Disease progression and tumour response were assessed by radiological and clinical review per investigator, according to RECIST version 1.1 criteria.

Health-related quality of life

Health-related quality of life was assessed using The Functional Assessment of Cancer Therapy – Ovarian Cancer Trial Outcome Index (FACT-O TOI). No published literature was identified reporting on the measurement properties of the FACT-O TOI; however, a literature search identified measurement properties for the FACT-O (version 4) comprising 5 subscales totaling 38 items: physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), functional well-being (7 items), and Ovarian Cancer (11 items).[3] Each item is score using a 5-point scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much), with negative statements reversed for calculation, for a total score of 0 to 100 (higher score indicates better quality of life). Based on a consecutive series of outpatients with epithelial ovarian cancer, the measurement properties of the FACT-O were described as follows:

- convergent and divergent validity with the Functional Living Index – Cancer (quality of life, r = 0.28 to 0.75 for the subscales and 0.73 for the total score), Memorial Symptom Assessment Scale (2 physical symptom subscales, r = –0.56 to –0.70 for 3 subscales and –0.65 for the total score), State-Trait Anxiety Inventory (anxiety, r = –0.73 for emotional well-being and –0.55 for the total score), Center for Epidemiologic Studies Depression scale (depression, r = –0.69 for emotional well-being and for the total score), Family Environment Scale (family functioning, r = 0.24 for emotional well-being, 0.48 for social well-being, and 0.36 for the total score on Cohesion; r = 0.23 for emotional well-being, 0.35 for social well-being, and 0.22 for the total score on Expressiveness; and r = −0.17 for emotional well-being, –0.35 for social well-being, and –0.26 for the total score on Conflict), Marlowe-Crowne Social Desirability Scale (social-desirability, r = 0.09 to 0.28 for the subscales and 0.24 for the total score)
- criterion validity: patients with advanced disease (n = 170) had lower scores on the subscales but there was no difference between early stage (n = 63) and advanced disease on the total score; patients with performance status of 2 or 3 (n = 48) had lower scores on the subscales and total score compared with patients with performance status of 0 (n = 108) or 1 (n = 65); and, patients receiving active treatment (n = 107) had lower scores on subscales and total score compared with those receiving post-treatment surveillance (n = 113),
- internal consistency (n = 225 to 232 (depending on the subscale); Cronbach's alpha = 0.74 to 0.88 for the subscales and 0.92 for the total score),
- test-retest reliability, for tests 1 week apart (n = 225 to 232 (depending on the subscale); Cronbach's alpha = 0.72 to 0.88 for the subscales and 0.81 for the total score),
- responsiveness (n = 98; change in performance status was associated with changes on the subscales [P = 0.014] and total score [P = 0.002]). For patients whose performance status improved, remained stable, and declined, mean (standard deviation) changes in the total score were 5.98 (14.34), –0.37 (12.17), and –11.00 (12.53), respectively.

An estimated meaningful important difference (MID) was not identified in the literature for the FACT-O. In the GOG 281/LOGS trial, a 5-point difference between the trametinib group and the physician's choice group was considered the MID for the FACT-O TOI. The authors provided no supporting evidence for the MID.

The Functional Assessment of Cancer Therapy Gynecologic Oncology Group – Neurotoxicity questionnaire subscale (FACT/GOG-Ntx) comprises 11 items measuring chemotherapy-induced peripheral neuropathy (sensory, motor, and hearing neuropathy; and dysfunction associated with neuropathy);[4,5] each item is scored using the same 5-point scale as the FACT-O TOI, for a total score of 0 to 16 (higher scores indicate worse neuropathy).[4,5] Based on a 12-month longitudinal study of cancer patients (N = 343; 13% gynecological and 5% urinary tract) who were assessed at up to 10 time points after starting chemotherapy, the FACT/GOG-Ntx demonstrated floor effects (28% to 51% rated the lowest score FACT/GOG-Ntx subscales), internal consistency (Cronbach's alpha = 0.82 to 0.89; r = 0.26 to 0.76), and small-to-moderate sensitivity to change (r = 0.17 to 0.37).[4] A meaningful clinically important difference was estimated from a distribution-based method to range from 1.38 to 3.68.[4] Based on a study of patients with advanced endometrial cancer treated with doxorubicin/cisplatin/paclitaxel for up to 7 cycles (N = 116), the 11-item FACT/GOG-Ntx demonstrated reliability and validity, and a reduced subscale of 4 sensory items accounted for 80% of treatment differences and 63% of longitudinal changes in the subscale score to indicate it may be a less burdensome alternative to measuring neuropathy toxicity.[5] In the GOG 281/LOGS trial, an adapted self-administered 4-item version of the FACT/GOG-Ntx was used; a 1-point difference between the trametinib group and the physician's choice group was considered the MID. The authors provided no supporting evidence for the MID.

Adverse events

An adverse event (AE) was defined as any untoward medical occurrence associated with the use of a drug, regardless of whether it was considered related to the drug. A serious AE was any AE that is life-threatening, resulted in inpatient hospitalization or prolongation of existing hospitalization for 24 hours or more, resulted in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly or birth defect, or death. Prespecified AEs of special interest included rash, diarrhea, visual disorders (e.g., visual impairment), hepatic disorders, cardiac-related AEs (e.g., left ventricular ejection fraction), and pneumonitis. AEs, including AEs of special interest, were described according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 preferred terms and system organ class classifications; severity of each AE was assessed according to the grading system (grade 1 to 5) and tabulated according to the maximum severity.

Appendix 3: Results of the Study Included in the Systematic Review

Detailed Harms Results

Table 3: Summary of Harms Results (Safety Population)

Adverse events	GOG 281/LOGS	
	Trametinib (N = 128)	Physician's Choice (N = 127)
Most common TEAEs in ≥ 20% of patients, n (%)		
Fatigue	93 (73)	74 (58)
Nausea	78 (61)	65 (51)
Diarrhea	93 (73)	43 (34)
Anemia	67 (52)	54 (43)
Abdominal pain	57 (45)	60 (47)
Vomiting	59 (46)	44 (35)
Constipation	54 (42)	49 (39)
Acneiform rash	8 1(63)	13 (10)
Maculopapular rash	54 (42)	28 (22)
Peripheral edema	62 (49)	15 (12)
Hypertension	50 (39)	27 (21)
Dyspnea	45 (35)	28 (22)
Dry skin	56 (44)	17 (13)
Hypomagnesemia	41 (32)	29 (23)
Oral mucositis	45 (35)	23 (18)
Peripheral sensory neuropathy	36 (28)	28 (22)
Increased aspartate aminotransferase	47 (37)	15 (12)
Hypoalbuminemia	43 (34)	16 (13)
Anorexia	34 (27)	24 (19)
Hyperglycemia	32 (25)	25 (20)
Headache	27 (21)	24 (19)
Decreased white blood cell count	28 (22)	21 (17)
Urinary tract infection	29 (23)	18 (14)
Increased alkaline phosphatase	32 (25)	11 (9)
Hypokalemia	26 (20)	16 (13)
Increased alanine aminotransferase	28 (22)	13 (10)
Increased creatinine	26 (20)	10 (8)
Serious adverse events, n	**127**	**127**
Patients with ≥ 1 SAE, n (%)	45 (35.4)	43 (33.9)

Adverse events	GOG 281/LOGS	
	Trametinib (N = 128)	Physician's Choice (N = 127)
Most common SAEs in ≥ 2% of patients, n (%)		
Small intestinal obstruction	11 (8.7)	2 (1.6)
Abdominal pain	2 (1.6)	10 (7.9)
Urinary tract infection	6 (4.7)	4 (3.2)
Nausea	1 (0.8)	5 (3.9)
Thromboembolic event	4 (3.2)	1 (0.8)
Anemia	4 (3.2)	1 (0.8)
Vomiting	3 (2.4)	1 (0.8)
Colonic obstruction	0	4 (3.2)
Vaginal hemorrhage	0	3 (2.4)
Patients with grade ≥ 3 AE, n (%)	NR	NR
Anemia	16 (13)	12 (10)
Abdominal pain	7 (6)	22 (17)
Nausea	12 (9)	14 (11)
Small intestinal obstruction	16 (13)	9 (7)
Hypertension	15 (12)	6 (5)
Vomiting	10 (7)	10 (8)
Diarrhea	13 (10)	4 (3)
Fatigue	10 (8)	5 (4)
Acneiform rash	8 (6)	1 (1)
Maculopapular rash	9 (7)	0
Patients who stopped treatment due to adverse events, n (%)	**46 (36)**	**38 (30)[a]**
Deaths, n	**127**	**127**
Patients who died, n (%)	51 (40)	60 (47)
Adverse events of special interest, n (%)		
Decreased ejection fraction	10 (7.8)	1 (0.8)
Left ventricular systolic dysfunction	2 (1.6)	1 (0.8)
Pneumonitis	3 (2.3)	0
QTc prolongation	2 (1.6)	0
Retinal vascular disorder	2 (1.6)	0
Retinal tear	1 (0.8)	0

AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a]The number of patients in the physician's choice group who discontinued treatment due to AEs includes patients who had crossed over to the trametinib group following disease progression.

Source: Gershenson et al. (2022)[2]

Economic Review Appendices

Appendix 4: Cost Comparison Table

The comparators presented in Table 4 have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on Provincial Cancer Care Drug programs and validated by clinical experts. If discrepancies in dosing between the monograph and Canadian clinical practice exist, the dose specified by clinical experts was used. Pricing for comparator products was based on publicly available list prices.[6]

The recommended dose of trametinib is 2 mg daily (Table 4). At $342.13 per 2 mg tablet, the treatment acquisition cost of trametinib is $342.13 daily, or $9,580 per patient per year. The incremental cost of trametinib compared with the platinum-based regimens and the non-platinum-based monotherapies range from $712 to $8,859 per patient every 28-day cycle. Results may differ by jurisdiction depending on individual list prices for the drug under review compared to those presented in Table 4.

Table 4: CDA-AMC Cost Comparison Table for Recurrent Low-Grade serous Ovarian Cancer

Treatment	Strength	Form	Price ($)	Recommended dosage	Daily cost ($)	28-day cycle cost ($)	Incremental Cost ($)
Trametinib	**2 mg**	**Tablet**	**342.1270[a]**	**2 mg daily**	**342.13**	**9,580**	**Reference**
Endocrine Therapy							
Anastrozole	1 mg	Tablet	0.9522[a]	1 mg daily	0.95	27	9,553
Letrozole	2.5 mg	Tablet	1.3780[a]	2.5 mg daily	1.38	39	9,541
Tamoxifen	10 mg 20 mg	Tablet	0.1750[a] 0.3500[a]	20 to 40 mg daily	0.35 to 0.70	10 to 20	9,560 to 9,5670
Single-agent Platinum-based Therapies							
Carboplatin	50 mg 150 mg 450 mg 600 mg	Solution for IV infusion (10 mg/ml)	70.0000 210.0000 600.0000 775.0000	4 to 6 AUC on Day 1 of each 21-day cycle	35.24 to 53.57	987 to 1,500	8,080 to 8,593
Cisplatin	50mg 100mg 200mg	Solution for IV infusion (1 mg/ml)	135.0000 270.0000 540.0000	50 to 75 mg/m^2 on Day 1 of each 21-day cycle	12.86 to 19.29	360 to 540	9,040 to 9,220
Platinum-based Regimens							
Carboplatin + Gemcitabine							
Carboplatin	50 mg 150 mg 450 mg 600 mg	Solution for IV infusion (10 mg/ml)	70.0000 210.0000 600.0000 775.0000	4 AUC on Day 1 of each 21-day cycle	35.24	987	N/A
Gemcitabine	1,000 mg 2,000 mg	Lyophilized powder for IV infusion	270.0000 540.0000	1,000 mg/m^2 on Day 1 and 8 of each 21-day cycle	51.43	1,440	

Treatment	Strength	Form	Price ($)	Recommended dosage	Daily cost ($)	28-day cycle cost ($)	Incremental Cost ($)
Carboplatin + Gemcitabine (regimen)					**86.67**	**2,427**	**7,153**
Carboplatin + Paclitaxel							
Carboplatin	50 mg 150 mg 450 mg 600 mg	Solution for IV infusion (10 mg/ml)	70.0000 210.0000 600.0000 775.0000	2 AUC on Day 1, 8, and 14 of each 21-day cycle	60.00	1,680	N/A
Paclitaxel	30 mg 100 mg 300 mg	Solution for IV infusion (6 mg/ml)	300.0000 1,196.8000 3,740.0000	60 to 80 mg/m^2 on Day 1, 8, and 15 of each 21-day cycle	213.83 to 256.69	5,987 to 7,187	
Carboplatin + Paclitaxel (regimen)					**273.83 to 316.69**	**7,667 to 8,867**	**712 to 1,912**
Carboplatin + Paclitaxel + Bevacizumab							
Carboplatin	50 mg 150 mg 450 mg 600 mg	Solution for IV infusion (10 mg/ml)	70.0000 210.0000 600.0000 775.0000	4 to 6 AUC on Day 1 of each 21-day cycle	35.24 to 53.57	987 to 1,500	N/A
Paclitaxel	30 mg 100 mg 300 mg	Solution for IV infusion (6 mg/ml)	300.0000 1,196.8000 3,740.0000	135 to 165 mg/m^2 on Day 1 of each 21-day cycle	142.55 to 156.84	3,991 to 4,391	
Bevacizumab	100 mg 400 mg	Solution for IV infusion (25 mg/ml)	347.0000 1,388.0000	7.5 to 15 mg/kg on Day 1 of each 21-day cycle	99.14 to 181.76	2,776 to 5,089	
Carboplatin + Paclitaxel + Bevacizumab (regimen)					**276.93 to 392.17**	**7,754 to *10,981***	**1,825 to *-1,401***
Carboplatin + pegylated liposomal Doxorubicin							
Carboplatin	50 mg 150 mg 450 mg 600 mg	Solution for IV infusion (10 mg/ml)	70.0000 210.0000 600.0000 775.0000	4 to 6 AUC on Day 1 of each 28-day cycle	26.43 to 40.18	740 to 1,125	N/A
Pegylated Liposomal Doxorubicin	20 mg 60 mg	Lyophilized powder for IV infusion	360.3700 1,081.1000	30 to 40 mg/m^2 on Day of each 28-day cycle	25.74	721	
Carboplatin + pegylated liposomal doxorubicin (regimen)					**52.17 to 65.92**	**1,461 to 1,846**	**7,734 to 8,119**
Monotherapies							
Paclitaxel	30 mg 100 mg 300 mg	Solution for IV infusion (6 mg/ml)	300.0000 1,196.8000 3,740.0000	60 to 80 mg/m^2 on Day 1, 8, 15 and 22 of each 28-day cycle	213.83 to 256.69	5,987 to 7,187	2,392 to 3,592

Treatment	Strength	Form	Price ($)	Recommended dosage	Daily cost ($)	28-day cycle cost ($)	Incremental Cost ($)
Pegylated Liposomal Doxorubicin	20 mg 60 mg	Lyophilized powder for IV infusion	360.3700 1,081.1000	40 to 50 mg/m^2 on Day 1 of each 28-day cycle	25.74	721	8,859
Topotecan	1 mg 4 mg	Lyophilized powder for IV injection	138.7500 555.0000	1.25 to 1.5 mg/m^2 on Day 1 to 5 of each 21-day cycle	99.11	2,775	6,805
Bevacizumab	100 mg 400 mg	Solution for IV infusion (25 mg/ml)	347.0000 1,388.0000	7.5 to 15 mg/kg on Day 1 of each 21-day cycle	99.14 to 181.76	2,776 to 5,089	4,490 to 6,804
Gemcitabine	1,000 mg 2,000 mg	Lyophilized powder for IV infusion	270.0000 540.0000	800 to 1,000 mg/m^2 on Day 1, 8 and 15 of each 21-day cycle	77.14	2,160	7,420

AUC = area under the curve; N/A = not applicable

Note: All prices are from IQVIA Delta Price Advisor (accessed October 2024), unless otherwise indicated, and do not include dispensing fees nor assume vial-sharing. Recommended doses for all comparators are from Cancer Care Ontario and validated by clinical experts unless otherwise indicated.[6,7] If discrepancies in dosing between the monograph and Canadian clinical practice exist, the dose specified by clinical experts was used. For the purposes of dosage calculation, the average patient was assumed to weigh 67.5 kg, have a body surface area of 1.71 mg^2 (based on clinical expert feedback) and included wastage of unused medication in vials.

[a]Ontario Drug Benefit Formulary (accessed November 2024)[8]

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