pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

pERC Final Recommendation
This pERC Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Bevacizumab (Avastin)	
Submitted Funding Request: Bevacizumab, in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens.	
Submitted By: Hoffmann-La Roche Limited	**Manufactured By:** Hoffmann-La Roche Limited
NOC Date: September 28, 2015	**Submission Date:** October 29, 2015
Initial Recommendation: March 3, 2016	**Final Recommendation:** May 5, 2016

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding bevacizumab (Avastin) in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior anticancer regimens, conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for bevacizumab given at a dose of 10 mg/kg every 2 weeks when given with pegylated liposomal doxorubicin, paclitaxel, or a 4-week cycle of topotecan (or at a dose of 15 mg/kg every 3 weeks when given with a 3-week cycle of topotecan). Treatment should continue until disease progression or unacceptable toxicity. This patient population should include those with good performance status, no contraindications to bevacizumab, and whose disease is not primary platinum refractory.

pERC made this recommendation because it was satisfied that, compared with chemotherapy alone, there is a net clinical benefit of bevacizumab in combination with chemotherapy based on clinically meaningful improvements in progression-free survival and quality of life. The toxicities of bevacizumab were both expected and manageable.

pERC also noted that bevacizumab aligned with patient values as there is a need for more effective treatment options that improve quality of life and extend survival for patients with platinum-resistant recurrent ovarian cancer.

The Committee noted that bevacizumab in combination with chemotherapy compared with chemotherapy alone could not be considered cost-effective in this population.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Risk of Gastrointestinal (GI) Perforations
Patients in the AURELIA trial were carefully selected to avoid the risk of GI perforations, which can have a considerable detrimental impact on a patient's quality of life. Therefore, pERC felt it very important that physicians provide a fulsome description of the risk of GI perforations with their patients prior to commencing therapy with bevacizumab.

Pricing Arrangements to Improve Cost-Effectiveness
Given that pERC was satisfied that there is a net clinical benefit of adding bevacizumab to chemotherapy, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of the regimen to an acceptable level. Furthermore, given the unknown, but potentially long duration of therapy with bevacizumab compared with chemotherapy alone, a substantial reduction in the price of the drug would be required to improve cost-effectiveness to an acceptable level.

No Prior Use of Anti-Angiogenic Therapy
Given that only a small number of patients in the AURELIA trial (7.2%) had received prior anti-angiogenic therapy (e.g., bevacizumab), pERC concurred with the authors of the AURELIA study that no conclusions could be drawn on the efficacy of bevacizumab in bevacizumab-pretreated patients. Therefore pERC was unable to make a recommendation on the use of bevacizumab for those who had received prior anti-angiogenic therapy.

Time-Limited Need in Prevalent Population
pERC considered that, at the time of implementing a funding recommendation for bevacizumab plus chemotherapy, a time-limited need only would exist for patients with platinum-resistant recurrent ovarian cancer, given that funding for bevacizumab plus chemotherapy for the front-line treatment of advanced ovarian cancer is in place in some jurisdictions and is being considered for funding in remaining jurisdictions.

Definition of Prior Anticancer Regimen
pERC noted a lack of clarity with the definition of "prior anticancer regimen" used in the AURELIA trial. Jurisdictions should consult with provincial tumour groups to determine an appropriate definition for "prior anticancer regimen" in this context. Furthermore, although there may be a benefit of treatment with bevacizumab in combination with chemotherapy for patients with platinum-resistant recurrent ovarian cancer who have received three or more prior lines of therapy, pERC considered that there is a lack of evidence to support or refute the use of bevacizumab in this specific group of patients.

Potential to Use a Lower Dose of Bevacizumab
pERC considered that in other disease settings, including first line treatment of ovarian cancer, bevacizumab has demonstrated a clinical benefit independent of the dose used. However, pERC noted that there is no direct evidence to support or refute a lower dose in women with platinum-resistant recurrent ovarian cancer.

SUMMARY OF pERC DELIBERATIONS

Epithelial ovarian, primary peritoneal or fallopian tube cancer (collectively called ovarian cancer) occurs in approximately 2,800 women in Canada per year, and the majority of patients present with advanced disease. Women diagnosed with metastatic or advanced ovarian cancer are frequently treated with surgery, to resect as much disease as possible, and chemotherapy (combination of a platinum agent and a taxane), the intent of which is to prolong life and reduce symptoms. Eventually, disease recurs in most patients and requires retreatment with platinum-based chemotherapy. When the progression-free interval since the last platinum-based combination chemotherapy is less than six months (i.e., platinum-resistant ovarian cancer), patients then receive non-platinum based chemotherapy regimens (e.g., pegylated liposomal doxorubicin, topotecan, paclitaxel, gemcitabine, etc.). The prognosis of patients with platinum-resistant recurrent ovarian cancer is poor. pERC acknowledged that there is a need for additional treatment options that improve patients' quality of life, provide disease control and extend survival.

pERC's Deliberative Framework for drug funding recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated upon one randomized controlled trial (AURELIA), which compared bevacizumab plus chemotherapy (i.e., pegylated liposomal doxorubicin, topotecan, or paclitaxel) with chemotherapy alone. The Committee noted a statistically significant and clinically meaningful improvement in progression-free survival (PFS) in favour of patients treated with bevacizumab plus chemotherapy. A similar improvement in PFS for the bevacizumab arm was observed in a subgroup of patients with ascites at baseline. pERC noted that no statistically significant difference in overall survival was demonstrated in the trial; however, the Committee concluded that those results were likely confounded due to the high rate (40%) of crossover of patients from the chemotherapy alone arm, upon disease progression, to receive single-agent bevacizumab and due to the study being underpowered to detect a significant difference in overall survival.

pERC noted that the lower than expected rate of GI perforation events in the bevacizumab plus chemotherapy arm (1.7%) may have been due to the careful patient selection of the AURELIA trial, which may have resulted in the exclusion of patients who are at the greatest risk for GI perforation events. pERC also noted that, given the considerable detrimental impact that these events can have on a patient's quality of life, it is important that women considering treatment with bevacizumab fully understand the potential risks and benefits of this drug. pERC noted several contraindications to bevacizumab, including history of bowel obstruction related to underlying disease; history of abdominal fistula, GI perforation, or intra-abdominal abscess; evidence of tumour in the rectosigmoid; prior radiotherapy to the pelvis or abdomen; and surgery within 4 weeks before starting therapy. pERC felt strongly that physicians should have a detailed discussion about the risks and benefits of bevacizumab with their patients prior to commencing therapy with bevacizumab. pERC noted that the other adverse events reported with the use of bevacizumab were both expected and manageable.

pERC was impressed by the quality of data on patient reported outcomes from the AURELIA trial. The Committee noted the clinically meaningful improvements in patients' health related quality of life (HRQoL) in favour of bevacizumab plus chemotherapy compared with chemotherapy alone. pERC acknowledged that ascites is a common and debilitating side effect for many women with ovarian cancer, and noted that in a subgroup analysis of patients with ascites at baseline, a statistically significant higher proportion of patients in the bevacizumab plus chemotherapy group experienced an improvement in pain and GI symptoms compared with the chemotherapy alone group. Overall, pERC concluded that there is a net clinical benefit of bevacizumab plus chemotherapy for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior anticancer regimens because there was a modest improvement in PFS, manageable toxicity, and an improvement in quality of life.

Upon reconsideration of the Initial Recommendation, the Committee considered feedback from the pCODR Provincial Advisory Group (PAG) requesting a definition for the phrase, "whose disease is not primary platinum refractory." pERC noted the provision of a definition of this phrase by the pCODR Clinical Guidance Panel (CGP) and agreed that this refers to patients whose disease has progressed while on first-line platinum-based chemotherapy.

pERC discussed the definition of "prior anticancer regimen" used in the AURELIA trial, and noted that the Submitter could not provide a clarification to pCODR. The Committee considered that jurisdictions should consult with provincial tumour groups to determine an appropriate definition for "prior anticancer regimen." Furthermore, pERC discussed whether patients with platinum-resistant recurrent ovarian cancer who have received three or more prior anticancer regimens could be considered for treatment with bevacizumab plus chemotherapy. Although differing opinions were expressed, pERC concluded that it could not recommend the use bevacizumab plus chemotherapy in patients with platinum-resistant recurrent ovarian cancer who have received three or more prior anticancer regimens, as there is a lack of evidence to support or refute the use of bevacizumab in this specific group of patients.

Upon reconsideration of the Initial Recommendation, the Committee considered feedback from PAG noting concern over the lack of a definition of "prior anticancer regimen." pERC agreed with PAG that the trial definition was unclear and noted that the Submitter was unable to provide clarification. pERC maintained its original conclusion that it could not recommend the use of bevacizumab plus chemotherapy in patients with platinum-resistant recurrent ovarian cancer who have received three or more prior lines of therapy, as there is a lack of evidence to support or refute the use of bevacizumab in this specific group of patients.

pERC also discussed whether patients with platinum-resistant recurrent ovarian cancer who have received prior anti-angiogenic therapy, could be eligible for treatment with bevacizumab plus chemotherapy. The Committee noted that the AURELIA trial enrolled patients who had received prior anti-angiogenic therapy; however, only 7.2% of the patients had received such therapy. Furthermore, pERC concurred with the authors of the AURELIA trial, that no conclusions can be drawn regarding the efficacy of bevacizumab in patients who have been previously treated with bevacizumab. Therefore, pERC could not conclude that, based on the small number of patients included in the AURELIA trial, the overall trial results are applicable to the population of patients expected in clinical practice who have received prior anti-angiogenic therapy.

Upon reconsideration of the Initial Recommendation, pERC considered feedback from PAG seeking clarification of whether the recommendation applies to patients with mucinous-type ovarian cancer. pERC acknowledged feedback from the CGP that although no patients with mucinous-type platinum-resistant ovarian cancer were enrolled in the AURELIA study, these patients were included in the entry criteria for the trial. The Committee noted the CGP's expert opinion that the study results are generalizable to patients with mucinous-type platinum-resistant ovarian cancer. Furthermore, the Committee noted that the number of women with a mucinous histology eligible for the treatment would likely be very small. pERC concluded that these patients should also be considered eligible for treatment with bevacizumab in combination with chemotherapy.

pERC considered input from one patient advocacy group that indicated that patients value additional treatment options and expect that a new treatment could provide improvements in quality of life, disease control, and overall survival, while having manageable toxicity. The Committee noted that almost half of the 58 respondents to the patient advocacy group's survey would be willing to tolerate the side effects of bevacizumab in order to improve their chance of survival. pERC also noted that patients who had experience with bevacizumab felt that the drug had improved their quality of life. pERC concluded that bevacizumab plus chemotherapy for the treatment of platinum-resistant ovarian cancer aligned with patient values based on a modest improvement in progression-free survival and clinically meaningful improvements in quality of life.

pERC noted that the incremental cost-effectiveness estimates provided by the pCODR Economic Guidance Panel (EGP) were higher than the Submitter's estimates. pERC agreed with the EGP's reanalysis that involved revisions to three assumptions used in the Submitter's model. First, the Submitter's choice of method to model overall survival may have over-estimated the survival benefit associated with bevacizumab. pERC agreed with the EGP's assessment that the Submitter's assumption provides an upper estimate of the survival benefit. pERC also agreed with the EGP's decision to model a lower estimate of the survival benefit by using alternative methods to model overall survival. Secondly, pERC agreed with

the EGP's decision to set the model to provide no difference in clinical benefit between treatment groups in the progressed disease state. Lastly, the Committee agreed with the EGP's decision to use a 4-year time horizon in order to reconcile the lack of fitting of the survival curves that becomes more pronounced as time progresses. The Committee noted that the Submitter's estimate of the incremental cost-effectiveness was only slightly less than the lower estimate of incremental cost-effectiveness provided by the EGP. pERC accepted the EGP's reanalysis estimates and concluded that, at the submitted price for bevacizumab, bevacizumab plus chemotherapy could not be considered cost-effective compared with chemotherapy alone in patients with platinum-resistant recurrent ovarian cancer who have received no more than two prior anticancer regimens.

Upon reconsideration of the Initial Recommendation, pERC considered feedback from the Submitter regarding the range of incremental cost-effectiveness estimates provided by the EGP's reanalysis as well as the overall survival data and time horizon used by the EGP in its re-analysis estimates. pERC acknowledged the Submitter's concerns that a conservative approach was used to model overall survival and their concerns that the time horizon was truncated at 5 years; however, pERC felt that the approach taken by the EGP was reasonable and consistent with previous reviews. In addition, pERC noted that the Submitter's estimate of the incremental cost-effectiveness of bevacizumab plus chemotherapy could not be considered cost-effective compared with chemotherapy alone. Therefore, the Committee reaffirmed its original conclusion, that bevacizumab plus chemotherapy could not be considered cost-effective compared with chemotherapy alone in patients with platinum-resistant recurrent ovarian cancer who have received no more than two prior anticancer regimens.

pERC discussed the feasibility of implementing a funding recommendation for bevacizumab plus chemotherapy in women with platinum-resistant recurrent ovarian cancer. pERC discussed that the need for bevacizumab plus chemotherapy in this group of patients would be time-limited, given that jurisdictions in Canada either currently fund front-line therapy with bevacizumab or are considering funding. pERC noted that the dose of bevacizumab in the AURELIA trial is higher than the dose of bevacizumab used in other trials (e.g. ICON7) and other indications. The Committee acknowledged that there was no direct evidence for or against the use of a lower dose of bevacizumab in patients with platinum-resistant recurrent ovarian cancer. pERC also considered PAG's concern regarding the unknown, but potentially long duration of therapy with bevacizumab compared with chemotherapy alone and concluded that a substantial reduction in the price of the drug would be required to improve cost-effectiveness to an acceptable level.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- input from one patient advocacy group [Ovarian Cancer Canada (OCC)]
- input from pCODR's Provincial Advisory Group

Feedback on the pERC Initial Recommendation was also provided by:

- pCODR's Provincial Advisory Group
- one patient advocacy group (OCC)
- the Submitter (Hoffmann-La Roche Limited)

The pERC initial recommendation was to fund bevacizumab (Avastin), conditional on the cost-effectiveness being improved to an acceptable level, for patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior chemotherapy regimens, with good performance status, no contraindications to bevacizumab, and whose disease is not primary platinum refractory.

While feedback on the pERC Initial Recommendation from pCODR's Provincial Advisory Group, the Submitter, and the OCC patient advocacy group indicated that all three stakeholder groups agreed with the initial recommendation, the Submitter and pCODR's Provincial Advisory Group provided feedback on the initial recommendation that required reconsideration by pERC.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of bevacizumab in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens.

Studies included

The pCODR systematic review included one fully published randomized controlled trial, AURELIA, which randomized patients with recurrent platinum-resistant (disease progression within <6 months of platinum therapy) epithelial ovarian, fallopian tube, or primary peritoneal cancer, who received no more than two prior anticancer regimens, to receive bevacizumab plus physician's choice of chemotherapy (paclitaxel, topotecan, or pegylated liposomal doxorubicin; n=179) or to physician's choice of chemotherapy without bevacizumab (n=182). Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent. pERC noted that the dosing schedule of bevacizumab used in the AURELIA trial was matched with the backbone chemotherapy: a dose of bevacizumab of 10 mg/kg every 2 weeks was used in combination with either pegylated liposomal doxorubicin, paclitaxel or a 4-week cycle of topotecan, and a dose of bevacizumab of 15 mg/kg every 3 weeks was used in combination with a 3-week cycle of topotecan. pERC noted that the 40% of patients in the chemotherapy alone arm were permitted to receive single-agent bevacizumab after disease progression (i.e., patients crossed over).

pERC noted that the definition of "prior anticancer regimen" used in the AURELIA trial was unclear and that the Submitter could not provide a clarification to pCODR of how it was defined in the trial. The Committee noted the need to appropriately define "prior anticancer regimen" with respect to patients with platinum-resistant recurrent ovarian cancer and that jurisdictions should consult with provincial tumour groups in order to determine an appropriate definition.

pERC considered feedback from PAG noting concern over the lack of a definition of "prior anticancer regimen." The Committee agreed that the definition used in the AURELIA was unclear and that the Submitter was unable to provide a clarification.

pERC noted that the pCODR Clinical Guidance Panel (CGP) provided an opinion that a lower dose of bevacizumab may have similar efficacy in this patient population. The Committee noted that CGP based its opinion on evidence generalized from other disease settings, where bevacizumab has consistently shown a clinical benefit independent of the dose used. Furthermore, pERC noted that the ICON7 trial, investigating the use of bevacizumab as a front-line treatment for advanced ovarian cancer, used a lower dose of bevacizumab than that used in the AURELIA trial. Overall, pERC agreed that there was a consistent demonstration of efficacy with lower doses of bevacizumab in other disease settings and, despite the lack of direct evidence for a lower dose of bevacizumab in this specific patient population, the Committee considered that a lower dose of bevacizumab may also provide a clinical benefit in patients with platinum-resistant recurrent ovarian cancer who have received no more than two prior chemotherapy regimens.

pERC noted feedback from PAG requesting a definition for the phrase, "whose disease is not primary platinum refractory." The Committee noted that the CGP provided a definition of this as patients whose disease has progressed while on first-line platinum-based chemotherapy.

Patient populations: carefully selected patient population

Baseline characteristics were balanced between treatment arms. Investigator selection of the chemotherapy options was evenly distributed (pegylated liposomal doxorubicin, n=126; paclitaxel, n=115; topotecan, n=120). The median age was 62 years in the bevacizumab plus chemotherapy arm and 61 years in the chemotherapy alone arm. Approximately 57% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 35% had an ECOG performance status of 1, and 6.4% had an ECOG performance status of 2. In addition, 46% of patients had received two prior chemotherapy regimens and 31% had ascites at baseline.

pERC noted that patients in the AURELIA study were carefully selected. The study excluded patients with: a history of bowel obstruction; history of abdominal fistula, GI perforation, or intra-abdominal abscess; evidence of rectosigmoid involvement; prior radiotherapy to the pelvis or abdomen; surgery within 4 weeks before starting study therapy; untreated central nervous system (CNS) disease or symptomatic CNS metastasis; history or evidence of thrombotic or hemorrhagic disorders within 6 months of first study treatment; uncontrolled hypertension; active clinically significant cardiovascular disease; or non-healing wound, ulcer, or bone fracture.

pERC noted feedback from PAG seeking clarification of whether the Initial Recommendation applies to patients with mucinous-type platinum-resistant ovarian cancer. The Committed noted that the response from the CGP that, although no patients with mucinous-type platinum-resistant ovarian cancer were enrolled in the AURELIA study, these patients were included in the entry criteria for the trial. Furthermore, pERC noted the CGP's expert opinion that the study results are generalizable to patients with mucinous-type platinum-resistant ovarian cancer. The Committee also discussed that the number of women with a mucinous histology who would be eligible for treatment with bevacizumab would likely be very small.

Key efficacy results: clinically meaningful improvement in PFS; confounded OS

pERC noted that the AURELIA trial demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS; primary study endpoint) in favour of bevacizumab plus chemotherapy. Median PFS was 6.7 months for bevacizumab plus chemotherapy compared with 3.4 months for chemotherapy alone (HR 0.48; 95% confidence interval [CI] 0.38 to 0.60; p<0.001). pERC noted that in a subgroup of 113 patients with ascites at baseline (59 in the bevacizumab plus chemotherapy group and 54 in the chemotherapy alone group), the median PFS was 5.6 months in 59 patients in the bevacizumab plus chemotherapy group compared with 2.5 months in 54 patients in the chemotherapy alone group (HR 0.40; 95% CI 0.26 to 0.60; p<0.001).

Overall survival was a secondary endpoint of the trial, where median overall survival was 16.6 months for patients who received bevacizumab plus chemotherapy compared with 13.3 months for patients who received chemotherapy alone; however, this difference was not statistically significant (HR 0.85, 95% CI 0.66 to 1.08; p<0.174). pERC also noted that at the time of the analysis, 40% of patients in the chemotherapy alone arm who experienced disease progression, crossed over to receive single-agent bevacizumab, which likely confounded the results.

Quality of life: improvement in HRQoL

Health-related quality of life (HRQoL) was assessed at baseline and every two or three cycles until disease progression, using the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Ovarian Cancer Module (QLQ-Ov28) and the Functional Assessment of Cancer Therapy-Ovarian Cancer symptom index (FOSI). The primary HRQoL endpoint was that a higher proportion of patients in the bevacizumab plus chemotherapy arm would achieve at least a 15% (≥15-point) absolute improvement on the QLQ-OV28 abdominal/GI symptom subscale at week 8/9 from baseline. At week 8/9, a higher proportion of patients in the bevacizumab plus chemotherapy arm had achieved a ≥15% improvement in QLQ-OV28 abdominal/GI symptom scores compared with the chemotherapy arm (21.9% versus [vs.] 9.3%, respectively; difference 12.7%, 95% CI 4.4 to 20.9; p=0.002). pERC also noted that in a subgroup analysis of 99 evaluable patients with ascites at baseline who were expected to have considerable pain and GI symptoms, 44% of patients who received bevacizumab plus chemotherapy experienced a ≥15% improvement in pain and GI symptoms compared with 4.1% in the chemotherapy alone arm (difference 39.9%, 95% CI 23.9% to 55.9%; p<0.001). pERC was impressed by the effort in the data collection and reporting of HRQoL from the AURELIA trial.

Safety: expected but manageable toxicity

pERC discussed the safety profile of bevacizumab and agreed that the toxicity associated with bevacizumab plus chemotherapy was both expected and manageable. In the AURELIA study, a total of nine patients in the bevacizumab plus chemotherapy arm and six patients in the chemotherapy alone arm died due to adverse events. Grade 2-5 GI perforation events were reported in three (1.7%) patients who received bevacizumab plus chemotherapy and in one (0.6%) patient who received chemotherapy alone. pERC noted that the trial had very specific selection criteria which may have been the reason for the low rates of serious adverse events, especially GI perforation events.

Burden and Need: more effective treatment options required

Patients with platinum-resistant recurrent ovarian cancer have incurable disease and the goals of treatment are to control disease symptoms, delay time to subsequent progression, improve quality of life and extend survival. pERC noted that the treatment options for platinum-resistant recurrent ovarian cancer are quite limited and that currently available regimens (e.g., paclitaxel, pegylated liposomal doxorubicin, topotecan, oral etoposide and gemcitabine) have shown only modest response rates between 15% and 20%. Prolonged responses are uncommon and the median progression-free interval in the platinum-resistant setting is generally between 2 to 5 months, with median overall survival rarely exceeding 12 months. Therefore, pERC concluded that there is a need for new therapies that prolong survival and improve quality of life and disease control in patients with platinum-resistant recurrent ovarian cancer.

PATIENT-BASED VALUES

Values of patients with platinum-resistant recurrent ovarian cancer: QoL, disease control and survival

Patient advocacy group input indicated that the impact of ovarian cancer is significant to patients and caregivers. Patients expressed that ovarian cancer had negatively impacted their work life, sleep, cognition, sexual intimacy, and activities of daily living. Patients expressed the importance of having new therapies that improve quality of life and disease-related symptoms, control tumour progression, and extend survival. Patients indicated that treatments for ovarian cancer negatively affected their quality of life. Patients commonly experienced fatigue, bowel problems, hair loss, neuropathy, aching joints, nausea/vomiting, blood problems, ascites, skin irritations, and loss of fertility. Of 58 respondents to a survey conducted by the patient advocacy group of patients and caregivers of patients with advanced ovarian cancer, 42% indicated that they would be willing to tolerate the side effects of bevacizumab in order to improve their chance of survival. Additionally, almost half noted that the side effects were manageable and that they seemed no different than the side effects of previously received chemotherapy. Of nine respondents with platinum-resistant ovarian cancer, five reported that they would be willing to tolerate additional side effects if the benefits of treatment were considered to be short term (e.g., months versus years of improvement). Of 69 patients with ovarian cancer, 30.4% experienced significant or extremely significant financial difficulties and 29.0% experienced significant or extremely significant travel requirements for treatment.

Patient values on treatment: extend survival, improve QoL, manageable toxicity profile
Patients indicated that they expected bevacizumab to offer longer survival with similar side effects as chemotherapy. A total of 16 patients with ovarian cancer reported having direct experience with bevacizumab; however, only 14 of those patients actually had experience with bevacizumab as a treatment for ovarian cancer. Six patients reported that bevacizumab caused additional side effects while five indicate that there were no additional side effects. Commonly reported side effects from 10 patients included high blood pressure (n=2), fatigue (n=2), bleeding (n=2) and heart problems (n=1). Eight of 15 patients agreed or strongly agreed that bevacizumab improved their quality of life compared to previous treatments, with two patients indicating they neither agreed nor disagreed and four stating they did not know. Sixteen patients rated the top three issues that bevacizumab has better managed with respect to their disease. The issues rated as number one were that bevacizumab was better than their previous treatment at shrinking their tumour (n=11) and at prolonging their survival (n=11). The issues rated number two were improved prognosis (n=5) and managing fatigue (n=5). The third highest rated issues were managing fluid build-up (n=8) and preventing recurrence (n=7). pERC noted that data from the AURELIA trial for patients with ascites, a significant disease-related symptom, indicates that pain and GI symptoms are significantly improved with bevacizumab plus chemotherapy. pERC concluded that the modest improvement in progression-free survival and the improvement in HRQoL demonstrated in the AURELIA trial aligns with patient values.

ECONOMIC EVALUATION

Economic model submitted: cost-utility analysis
The pCODR Economic Guidance Panel assessed a cost-utility analysis comparing bevacizumab in combination with chemotherapy (paclitaxel, topotecan, pegylated liposomal doxorubicin, or gemcitabine) with chemotherapy without bevacizumab in patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than two prior chemotherapy regimens (defined as number of lines of therapy/treatment since diagnosis with ovarian cancer).

Basis of the economic model: uncertainty in OS data due to crossover
Costs included were the cost of treatment and administration, adverse events management costs (including cost of paracentesis), resource utilization costs, costs of post-progression treatment and terminal care costs.

Key clinical effects considered in the analysis included PFS, OS and utilities. pERC noted that there exists uncertainty in the overall survival results from the AURELIA trial due to the fact that over 40% of patients on the control arm crossed over to receive single-agent bevacizumab upon disease progression and considered that the overall survival results of the AURELIA trial are confounded. Furthermore the fact that the trial was not adequately powered to detect a difference in overall survival between treatment arms, also contributes to uncertainty in the overall survival data. pERC accepted the Submitter's use of rank-preserving structural failure time to adjust the survival curves for crossover at disease progression, but noted that there remains uncertainty in those results due to limitations surrounding the assumption of a constant and equal reduction in time to death for all patients before and after progression. Furthermore, the adjustment did not use information on patient covariates which may have affected the probability of crossover.

Drug costs: high cost of bevacizumab
Bevacizumab costs $[redacted] per 100 mg vial or $[redacted] per 400 mg vial; at the recommended dose of 15 mg/kg once every 21 days, the cost per three week cycle, without vial sharing, as used in the model is $[redacted]. (*The cost of bevacizumab is based on a confidential price submitted by the manufacturer and cannot be disclosed to the public according to the pCODR Disclosure of Information Guidelines*.) The disclosable price of bevacizumab is $600 per 100 mg vial and $2,400 per 400 mg vial.

Paclitaxel costs $8.25 per 25 mL vial or $16.50 per 50 mL vial; at the recommended dose of 175 mg/m^2 every 21 days, the cost per three week cycle, without vial sharing, as used in the model is $156.75.

Topotecan costs $28.20 per 1 mL vial or $112.80 per 4 mL vial; at the recommended dose of 1.5 mg/m^2 for 5 consecutive days every 21 days, the cost per three week cycle, without vial sharing, as used in the model is $2,397.00.

Pegylated liposomal doxorubicin costs $341.50 per 10 mg vial or $1,707.50 per 50 mg vial; at the recommended dose of 40 mg/m^2 every 21 days, the cost per three week cycle, without vial sharing, as used in the model is $2,390.50.

Gemcitabine costs $0.06 per 1 mg; at the recommended dose of 1000 mg/m^2 twice every 21 days, the cost per three week cycle, without vial sharing, as used in the model is $210.55.

Cost-effectiveness estimates: not cost-effective, uncertainty in cost-effectiveness due to crossover

pERC discussed the EGP's best estimate of the incremental cost-effectiveness ratio in patients with platinum-resistant, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than two prior anticancer regimens. pERC accepted the EGP's re-analysis estimates and concluded that bevacizumab is not cost-effective.

pERC discussed the uncertainty in the overall survival data used to inform the model. pERC agreed with the EGP's use of alternative overall survival curves (i.e., lower 95% confidence interval of Kaplan-Meier curve for the trial follow-up period with a gamma parametric curve to extrapolate beyond the trial follow-up period) to estimate a likely lower bound for the incremental clinical effectiveness and, therefore, to estimate an upper incremental cost-effectiveness ratio. Furthermore, pERC agreed with the EGP's assessment that no incremental gains in clinical benefit should occur for bevacizumab plus chemotherapy compared with chemotherapy alone in the progressed state as there is no clinical evidence to support such a benefit. Lastly, pERC discussed the choice of time horizon used in the model and the differences between the Kaplan-Meier curves and the predicted model curves, differences which become more pronounced as time increases. pERC agreed with the EGP's use of a 4-year time horizon, which truncates the model results at a point where there is no further accrual of benefit, in order to reconcile the lack of fitting of the curves.

pERC noted feedback from the Submitter regarding the range of incremental cost-effectiveness estimates provided by the EGP's reanalysis as well as the overall survival data and time horizon used by the EGP in its reanalysis estimates. pERC acknowledged the Submitter's concerns that a conservative approach was used to model overall survival and their concerns that the time horizon was truncated at 5 years. The Committee felt that the approach taken by the EGP was reasonable and consistent with previous reviews. In addition, pERC noted that the Submitter's estimates of the incremental cost-effectiveness of bevacizumab plus chemotherapy could not be considered cost-effective compared with chemotherapy alone.

pERC noted that the range of estimates provided by the EGP was wide, and coupled with the high cost of bevacizumab and unknown treatment duration (treatment is until disease progression or unacceptable toxicity), pERC agreed that a substantial price reduction would be needed for bevacizumab to be considered cost-effective. Overall, pERC accepted the EGP's re-analysis estimates and concluded that, at the submitted price for bevacizumab, bevacizumab plus chemotherapy is not cost-effective relative to chemotherapy alone in patients with platinum-resistant, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who have received no more than 2 prior anticancer regimens. Furthermore, pERC noted that the Submitter's estimate of incremental cost-effectiveness was only slightly less than the EGP's lower estimate of incremental cost-effectiveness, and therefore, the Committee concluded that bevacizumab plus chemotherapy could still not be considered cost-effective at the submitted price for bevacizumab.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: time-limited need; high drug cost

pERC discussed the implementation of a funding recommendation for bevacizumab plus chemotherapy in patients with platinum-resistant recurrent ovarian cancer. The Committee noted that funding for bevacizumab plus chemotherapy as a front-line therapy for advanced ovarian cancer is in place in some jurisdictions and being considered for funding in remaining jurisdictions. Therefore, pERC considered that there would be only a time-limited need for funding of bevacizumab plus chemotherapy in patients with platinum-resistant recurrent ovarian cancer.

pERC discussed the careful selection of patients in the AURELIA trial to avoid the risk of GI perforations, which can have a considerable detrimental impact on a patient's quality of life. Therefore, pERC felt it important that physicians provide a fulsome description of the risk of GI perforations with their patients prior to commencing therapy with bevacizumab so that patients fully understand the potential risks and benefits of this drug.

pERC noted that the dose of bevacizumab used in the AURELIA trial is higher than the dose of bevacizumab used in other trials (e.g. ICON7) and other indications and that, in other disease settings, bevacizumab has demonstrated a clinical benefit independent of the dose used. However, the Committee acknowledged that there was no direct evidence for or against the use of a lower dose of bevacizumab in patients with platinum-resistant recurrent ovarian cancer. Furthermore, the Committee discussed the use of two different doses and schedules in the AURELIA trial and noted that this was done in order to match the schedule of administration of bevacizumab with the backbone chemotherapy regimen. pERC noted that this may increase the potential for administration errors and that treatment centres will need to carefully monitor the appropriate dose and schedule of bevacizumab in relation to the backbone chemotherapy agent.

pERC discussed whether patients with platinum-resistant recurrent ovarian cancer who have received three or more prior lines of therapy could be considered for treatment with bevacizumab plus chemotherapy. Given the unclear definition of "prior anticancer regimen" used in the AURELIA trial, the Committee was not confident that these patients had been included in the AURELIA trial. pERC concluded that there is a lack of evidence to support or refute the use of bevacizumab in patients with platinum-resistant recurrent ovarian cancer who have received three or more prior lines of therapy.

pERC considered feedback from PAG noting concern over the lack of a definition of "prior anticancer regimen." The Committee agreed that the definition used in the AURELIA trial was unclear and that the Submitter was unable to provide a clarification. pERC again noted that there is a lack of evidence to support or refute the use of bevacizumab plus chemotherapy in patients with platinum-resistant recurrent ovarian cancer who have received three or more prior lines of therapy.

pERC considered whether patients with platinum-resistant recurrent ovarian cancer who have received prior anti-angiogenic therapy could be eligible for treatment with bevacizumab plus chemotherapy. The Committee noted that the AURELIA trial enrolled patients who had received prior anti-angiogenic therapy; however, only 7.2% of the patients had received such therapy. pERC concurred with the conclusions of the authors of the AURELIA trial, that no conclusions can be drawn regarding the efficacy of bevacizumab in patients who have been previously treated with bevacizumab. Therefore, based on the small number of patients included in the AURELIA trial, pERC could not conclude that the overall trial results are applicable to the population of patients expected in clinical practice who have received prior anti-angiogenic therapy.

pERC considered the feasibility of implementing a funding recommendation for bevacizumab plus chemotherapy. pERC noted the Provincial Advisory Group's concern about the unknown, but potentially long duration of therapy with bevacizumab compared with chemotherapy alone and concluded that a substantial reduction in drug price would be required to improve cost-effectiveness to an acceptable level.

The Committee noted that the potential for budget impact of bevacizumab in this setting is affected by the prevalence of ovarian cancer, the proportion of patients with platinum-resistant recurrent disease, and the proportion of women who would be suitable candidates for treatment with bevacizumab.

Finally, pERC discussed the potential for drug wastage with bevacizumab and concluded that, except in small treatment centres, this was not likely to be a concern due to the different vial sizes available, the possibility for extended stability to 48 hours once reconstituted and the ability to share partially used vials given that there are patients with other cancers who are treated with bevacizumab.

DRUG AND CONDITION INFORMATION

Drug Information	• Monoclonal antibody that targets VEGF receptors • 100mg and 400mg vials (25 mg/mL) • Recommended dosage of 10 mg/kg of body weight every 14 days or 15 mg/kg every 21 days
Cancer Treated	• Platinum resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior chemotherapy regimens
Burden of Illness	• 2,800 Canadians diagnosed and ~1,750 died of ovarian cancer in 2015 • Platinum resistant recurrent ovarian cancer carries a poor prognosis. Median survival less than 12 months.
Current Standard Treatment	• Paclitaxel • Topotecan • Pegylated liposomal doxorubicin • Gemcitabine Oral etoposide
Limitations of Current Therapy	• Modest response rates of 15% to 20% • Median progression-free interval of 2 to 5 month • Median overall survival rarely exceeds 12 months

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

pERC Membership During Deliberation of the Initial Recommendation

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Kelvin Chan, Oncologist
Dr. Matthew Cheung, Oncologist
Dr. Craig Earle, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Don Husereau, Health Economist
Dr. Anil Abraham Joy, Oncologist
Karen MacCurdy-Thompson, Pharmacist
Valerie McDonald, Patient Member-in-Training
Carole McMahon, Patient Member Alternate
Dr. Catherine Moltzan, Oncologist
Jo Nanson, Patient Member
Danica Wasney, Pharmacist

Dr. Maureen Trudeau chaired the meeting in her capacity as Vice-Chair of pERC. All members participated in deliberations and voting on the initial recommendation except:

- Carole McMahon, who was the designated non-voting patient member alternate for this meeting
- Valerie McDonald who did not vote due to her role as a patient member-in-training
- Dr. Paul Hoskins who was not present for the meeting

pERC Membership During Deliberation of the Final Recommendation

Dr. Anthony Fields, Oncologist (Chair)	Don Husereau, Health Economist
Dr. Maureen Trudeau, Oncologist (Vice-Chair)	Dr. Anil Abraham Joy, Oncologist
Dr. Scott Berry, Oncologist	Karen MacCurdy-Thompson, Pharmacist
Dr. Kelvin Chan, Oncologist	Valerie McDonald, Patient Member Alternate
Dr. Matthew Cheung, Oncologist	Carole McMahon, Patient Member
Dr. Craig Earle, Oncologist	Dr. Catherine Moltzan, Oncologist
Dr. Allan Grill, Family Physician	Jo Nanson, Patient Member
Dr. Paul Hoskins, Oncologist	Danica Wasney, Pharmacist

All members participated in deliberations and voting on the final recommendation except:

- Valerie McDonald, who was the designated non-voting patient member alternate for this meeting
- Dr. Allan Grill who was not present for the meeting
- Dr. Paul Hoskins, who was not present for the discussion, deliberations and voting due to a conflict of interest

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of bevacizumab (Avastin) for platinum-resistant ovarian cancer through their declarations, five members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, one of these members was excluded from deliberations and voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. Hoffmann-La Roche Limited as the primary data owner, did not agree to the disclosure of economic information, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

Use of this recommendation

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