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:** In combination with paclitaxel and carboplatin for the front-line treatment of epithelial ovarian, fallopian tube or primary peritoneal cancer patients with high risk of relapse (stage III sub-optimally debulked, or stage III unresectable, or stage IV patients)	
Submitted By: Hoffmann-La Roche Limited	**Manufactured By:** Hoffmann-La Roche Limited
NOC Date: N/A	**Submission Date:** November 28, 2014
Initial Recommendation: April 2, 2015	Final Recommendation: June 4, 2015

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding bevacizumab (Avastin) in the front-line treatment of patients with advanced stage ovarian cancer at a high risk of progression, conditional on the cost-effectiveness being improved to an acceptable level. Funding should be for bevacizumab given at a dose of 7.5 mg/kg in combination with carboplatin and paclitaxel in cycles 2-6, and as a maintenance treatment for up to 12 additional cycles or until disease progression, whichever occurs first. This patient population should include those with advanced stage, "high risk for progression" (stage III with >1 cm of residual disease, stage III unresectable, or stage IV) epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer who have good performance status. pERC made this recommendation because it was satisfied that compared to carboplatin and paclitaxel, there is a net clinical benefit based on a clinically meaningful improvement in overall survival, a need for more effective treatment options for this disease, and alignment with patient values. However, the Committee noted that bevacizumab in combination with carboplatin and paclitaxel may not be cost-effective when compared with carboplatin and paclitaxel.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness
Given that pERC was satisfied that there is a net clinical benefit of adding bevacizumab to carboplatin and paclitaxel, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of the regimen to an acceptable level.

Neoadjuvant use not recommended
pERC did not make a recommendation on the use of bevacizumab in those patients who may receive neoadjuvant chemotherapy and interval debulking surgery. pERC agreed with the Clinical Guidance Panel that there is no evidence to support or refute the use of bevacizumab in these patients. Jurisdictions may need to address funding requests for this population on a case-by-case basis if there are constraints on access to surgical procedures which necessitate patients receiving neoadjuvant chemotherapy.

SUMMARY OF pERC DELIBERATIONS

Epithelial ovarian, primary peritoneal or fallopian tube cancer (collectively called ovarian cancer) occurs in approximately 2,700 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 a combination of 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. Unfortunately, these patients have poor outcomes. There has been a dearth of new treatments for women with ovarian cancer for many years. pERC acknowledged that there is a need for additional treatment options that extend survival for patients.

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 two randomized controlled trials (ICON7 and GOG-218) which compared bevacizumab with carboplatin and paclitaxel to carboplatin and paclitaxel alone. The Committee specifically focused on the "high risk for progression" subgroups in each trial since these subgroups were aligned with the funding request for this submission. Despite the inherent limitations of subgroup analyses, pERC noted that the "high risk for progression" subgroup in the ICON7 study demonstrated a statistically significant and clinically meaningful improvement in overall survival (OS) for patients treated with bevacizumab plus carboplatin and paclitaxel compared to carboplatin and paclitaxel alone. They also noted that both studies consistently demonstrated statistically significant and clinically meaningful improvements in progression-free survival (PFS) for patients treated with bevacizumab plus carboplatin and paclitaxel compared to carboplatin and paclitaxel alone. pERC also discussed that in both the ICON7 and GOG-218 studies, no statistically significant improvements in OS for the entire study population were found. pERC considered whether it was biologically plausible that patients with lower risk for disease progression would not experience the same benefit as patients with "high risk for progression" disease. Although the reason for the differing results between the entire study population and the "high risk for progression" subgroup was unclear, pERC accepted the results as reported. pERC discussed the adverse events reported in the ICON7 and GOG-218 studies, and concluded that the adverse events associated with bevacizumab were both expected and manageable. Therefore, pERC concluded that there is a net clinical benefit of bevacizumab plus carboplatin and paclitaxel for the treatment of patients with advanced stage, "high risk for progression" (stage III with residual lesions >1 cm, stage III unresectable or stage IV) epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer because of the clinically meaningful improvement in OS and PFS and that the adverse event profile is expected and manageable.

Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback received from pCODR's Provincial Advisory Group (PAG) which expressed concern about the strength of evidence used to support the Initial Recommendation. PAG was concerned that the net clinical benefit was based on a subgroup analysis from a randomized controlled trial. The Committee re-deliberated upon the strength of the evidence used by pERC to conclude that there is a net clinical benefit of bevacizumab plus carboplatin and paclitaxel compared to carboplatin and paclitaxel alone in patients with ovarian cancer who have a high risk for progression. pERC noted that the subgroup analysis in the ICON7 trial was based on stratification factors determined *a priori* (pre-planned) while the subgroup analysis in the GOG-218 trial was likely to be preplanned, that the size of the high risk for progression subgroups in both trials was large (n=502 in ICON7 and n=406 in GOG-218), and that a statistical test for interaction was statistically significant for the OS results in the ICON7 trial (p=0.011), demonstrating that an interaction effect existed between the treatment and the subgroup variables. In addition, pERC considered that the two trials independently demonstrated concordant PFS results for the subgroup of patients at high risk for progression. Therefore, pERC confirmed that, given the totality of evidence, there is a net clinical benefit of bevacizumab plus carboplatin and paclitaxel compared with carboplatin and paclitaxel in this group of patients.

pERC considered input from one patient advocacy group that indicated patients valued treatment options that extend survival. In addition, more than half of the patients providing input were willing to tolerate

additional adverse events to prolong short term survival (i.e. months versus years). pERC also noted that caregivers reported anxiety, stress and fatigue as being the most significant negative impacts of caring for a loved one with ovarian cancer. pERC concluded that bevacizumab plus carboplatin and paclitaxel aligned with patient values because it provides an additional treatment option with a clinically meaningful improvement in overall survival compared to carboplatin and paclitaxel alone.

pERC noted that the incremental cost-effectiveness estimates provided by the pCODR Economic Guidance Panel (EGP) were similar to the manufacturer's estimates. The Committee observed that the ICER estimates provided by the EGP for this treatment in this patient population may not be cost-effective. Also during their deliberations, pERC expressed concern that assumptions about post-progression survival benefits and potential carry over effects were only partially explored by the EGP and not included in the EGP's reanalyses. pERC recognized that some carry over benefit of bevacizumab is clinically plausible once treatment is stopped; however, there is an absence of clinical evidence to justify the post-progression benefit inherent in the model. Given the uncertainty regarding the true impacts of the post-progression survival benefit and potential carry-over effect, pERC felt that the ICER may be higher than the upper range of the EGP's best estimate. Therefore, pERC concluded that bevacizumab plus carboplatin and paclitaxel may not be cost-effective at the submitted price.

Upon reconsideration of the pERC Initial Recommendation, pERC considered feedback received from the patient advocacy group that patients value treatment with bevacizumab plus carboplatin and paclitaxel and that funding should be provided regardless of its cost-effectiveness. The Committee noted that it is required to make conclusions around cost-effectiveness as part of its Deliberative Framework, and importantly, this allows the provinces to make informed decisions regarding funding relative to other cancer therapies. Therefore, pERC concluded that the original conclusion was still appropriate and, specifically that bevacizumab plus carboplatin and paclitaxel may not be cost-effective at the submitted price. pERC also considered feedback from the manufacturer that the EGP's range of best estimates of the ICER included the manufacturer's best estimate. Notwithstanding this observation, pERC felt that its original conclusion remains valid and that the true ICER may be higher than the upper range of the EGP's best estimate given the uncertainty regarding the post-progression survival benefit and potential carry-over treatment effect. Therefore, pERC concluded that bevacizumab plus carboplatin and paclitaxel may not be cost-effective at the submitted price.

pERC discussed the feasibility of implementing a funding recommendation for bevacizumab plus carboplatin and paclitaxel for women with advanced stage, "high risk for progression" epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. The Committee discussed that since the ICON7 study used a dose of 7.5mg/kg and reported similar outcomes as the GOG-218 study, which used a dose of 15mg/kg, that a dose of 7.5mg/kg is appropriate. Also, pERC noted that since both the ICON7 and GOG-218 studies were designed for women to receive bevacizumab during the initial chemotherapy phase and then continue bevacizumab as a single agent during the maintenance phase, which a similar regimen should be recommended for funding in Canadian practice. Finally, pERC also noted that in many Canadian centres, women are offered neoadjuvant (prior to surgery) chemotherapy for newly diagnosed advanced ovarian cancer for multiple reasons, including restricted timely access to operating rooms or extensive disease distribution in poor performance status patients. Since patients receiving neoadjuvant chemotherapy were not included in the studies of bevacizumab, its effectiveness and safety in this group is unknown, consequently pERC concluded that at this time there is no evidence to support or refute the use of bevacizumab in women who have received neoadjuvant chemotherapy.

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 groups (Ovarian Cancer Canada)
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- one patient advocacy group (Ovarian Cancer Canada)
- the Submitter (Hoffmann-La Roche Limited)

The pERC initial recommendation was to fund bevacizumab (Avastin) in the front-line treatment of patients with advanced stage ovarian cancer at a high risk of progression, conditional on the cost-effectiveness being improved to an acceptable level.

Feedback on the pERC Initial Recommendation indicated that the manufacture and patient advocacy group agreed in part and pCODR's Provincial Advisory Group disagreed with the initial recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the effectiveness and safety of bevacizumab when used in combination with paclitaxel and carboplatin, as compared to an appropriate comparator, for the front-line treatment of patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer and who have a high risk of relapse (stage III with >1 cm of residual disease, stage III unresectable, or stage IV).

Studies included: Two high quality RCTs

The pCODR systematic review included two randomized controlled trials (RCTs). The first, the ICON7 study was an international open-label RCT, comparing carboplatin plus paclitaxel (n=764) for six cycles to carboplatin plus paclitaxel plus concurrent bevacizumab (n=764; 7.5 mg/kg in cycles 2-6) plus maintenance bevacizumab (7.5 mg/kg up to an additional 12 cycles or until disease progression) in patients who had undergone surgery for early-stage high-risk (International Federation of Gynecology and Obstetrics [FIGO] Stage I or IIA and clear cell or grade 3 tumours) or advanced (FIGO Stage IIB to IV) epithelial ovarian, primary peritoneal, or fallopian tube cancer.

The second, the GOG-218 study was a three-armed blinded, placebo-controlled RCT. The study compared carboplatin plus paclitaxel for six cycles followed by placebo maintenance (cycles 7-22; n=625) versus carboplatin plus paclitaxel for six cycles plus concurrent bevacizumab (15 mg/kg in cycles 2-6) followed by placebo maintenance (cycles 7-22; n=625) versus paclitaxel plus carboplatin for six cycles plus concurrent bevacizumab (15 mg/kg in cycles 2-6) followed by bevacizumab maintenance (15 mg/kg in cycles 7-22 or until disease progression; n=623). The study population included patients with previously untreated, incompletely resectable FIGO Stage III with residual lesions >1 cm (i.e., sub-optimally debulked) or with residual lesions ≤1 cm (i.e., optimally debulked), or any FIGO Stage IV epithelial ovarian, primary peritoneal, or fallopian tube cancer.

Patient populations: Subgroup of patients at "high risk for progression"

pERC noted that both studies included a patient population that was broader than the Submitter's funding request, which was limited to women with disease at "high risk for progression".

ICON7 study: The primary publication reported a pre-planned subgroup analysis of 465 patients with Stage III disease and residual lesions >1 cm or Stage IV disease (called the original "high risk for progression" subgroup) conducted in 2010. In a 2013 abstract publication (Oza, 2013), an additional 37 non-operated stage III patients were included with the original subgroup in a modified subgroup analysis of patients at "high risk for progression" (called the modified "high risk for progression" subgroup).

GOG-218 study: Originally, patients with stage III disease and residual disease >1 cm (i.e., suboptimally debulked) or Stage IV disease were eligible. However, the eligibility criteria for the trial were modified to allow for inclusion of patients with Stage III disease with residual lesions ≤1 cm. Out of a study population of 1,873; 751 patients (40%) were included in a subgroup analysis of patients with Stage III suboptimally debulked disease, and a further 483 patients (26%) were included in a subgroup analysis of patients with Stage IV disease.

Key efficacy results: Clinically meaningful improvement in overall survival

ICON7 study: In the original "high risk for progression" subgroup (2010), the median OS was statistically significantly longer in the carboplatin-paclitaxel-bevacizumab group than in the carboplatin-paclitaxel group (36.6 months versus [vs.] 28.8 months; HR 0.64, 95% confidence interval [CI] 0.48 to 0.85; p=0.002). In the 2013 modified "high risk for progression" subgroup, a statistically significant difference in overall survival in favour of the bevacizumab arm was reported (log-rank p=0.03); however, non-proportional hazards were detected (p=0.007), that is, the survival curves crossed each other at some time during the trial period. The restricted mean survival times, which allow for more reliable statistical representation of the data, were 39.3 months vs. 34.5 months for the bevacizumab vs. control groups, respectively. Median progression-free survival (PFS) was statistically significantly longer in the bevacizumab arm (16.0 months) compared with the control arm (10.5 months; HR 0.73, 95% CI 0.60 to 0.93); however, non-proportional hazards were again detected (p<0.001). The restricted mean survival times at 42 months were 18.1 months in the bevacizumab arm and 14.5 months in the control arm.

GOG-218 study: Overall survival data for the subgroups of patients with either suboptimally debulked disease or Stage IV disease in the GOG-218 study were not available. For the subgroup of patients with suboptimally debulked disease, median PFS was significantly longer for patients who received carboplatin-paclitaxel in combination with concurrent and maintenance bevacizumab compared with patients who received carboplatin-paclitaxel-placebo (13.9 months in 242 patients vs. 10.1 months in 253 patients; HR 0.78, 95% CI 0.63 to 0.96). For the subgroup of patients with Stage IV disease, median PFS was also significantly longer for patients who received carboplatin-paclitaxel in combination with concurrent and maintenance bevacizumab compared with patients who receive carboplatin-paclitaxel-placebo (12.8 months in 165 patients vs. 9.5 months in 153 patients; HR 0.64, 95% CI 0.49 to 0.82).

Despite the inherent limitations of subgroup analyses, pERC noted the consistency in the results of the ICON7 and GOG-218 studies, which provided them confidence in their conclusion that there were statistically significant and clinically meaningful improvements in OS and PFS for patients with disease at "high risk of progression". pERC also noted that in both the ICON7 and GOG-218 studies, no statistically significant difference in OS for the entire study population was found. pERC considered whether it was biologically plausible that patients with lower risk disease would not experience the same benefit as patients with "high risk for progression" disease. Although the reason for the differing results between the entire study population and the "high risk for progression" subgroup was unclear, pERC accepted the results as reported.

Upon reconsideration, pERC discussed feedback from PAG expressing concern regarding the use of subgroup analyses for the determination of net clinical benefit. pERC noted several factors with the subgroup analyses that increased the Committee's confidence in the strength of the evidence. pERC noted that the subgroup analysis in the ICON7 trial was based on stratification factors determined *a priori* (pre-planned) while the subgroup analysis in the GOG-218 trial was likely preplanned, and that the size of the high risk for progression subgroups in both trials was large (n=502 in ICON7 and n=406 in GOG-218). pERC also noted that a statistical test for interaction was statistically significant for the OS results in the ICON7 trial (p=0.011), demonstrating that an interaction effect existed between the treatment and the subgroup variables, i.e., that the magnitude of the treatment effect in the high risk for progression subgroup is larger than in the subgroup consisting of all other women in the study. In addition, pERC considered that the two trials independently demonstrated concordant PFS results for the subgroup of patients at high risk for progression.

Quality of life: No separate data for the "high risk for progression" subgroup

In both the ICON7 and GOG-218 studies, quality of life (QoL) data were available for the entire study population, but there were no separate analyses of the QoL data for the "high risk for progression" subgroups.

ICON7 study: The mean global health status score from the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ C-30) indicated an improvement in

global quality of life over time, but there was no significant difference in scores between the treatment arms.

GOG-218 study: Quality of life was assessed using the Functional Assessment of Cancer Therapy-Ovarian Cancer Trial Outcome Index (FACT-O TOI).The scores for the period between cycles 4-7 and cycles 12-21 demonstrated a statistically significant improvement in change in scores in favour of the carboplatin-paclitaxel in combination with concurrent and maintenance bevacizumab compared with carboplatin-paclitaxel (2.6 points; p=0.0008); however, this change was less than the clinically minimally important difference of 5 points.

Safety: No separate data for the "high risk for progression" subgroup; no significant increases in toxicities generally associated with chemotherapy

In both the ICON7 and GOG-218 studies safety outcomes were reported for the entire study population and not separately for the subgroup of patients at "high risk for progression". In the ICON7 study, 22.0% of 764 patients who received carboplatin-paclitaxel-bevacizumab discontinued treatment due to an adverse event compared with 8.9% of 764 patients who received carboplatin-paclitaxel. In addition, arterial thrombotic events occurred in a higher proportion of patients who received bevacizumab compared with those who did not (3.5% vs. 1.6%). Wound healing complications (4.6% vs. 1.6%), fistulae formation (1.7% vs. 1.2%), and gastrointestinal (GI) bleeding events (1.3% vs. 0.4%) occurred more often in patients who received bevacizumab; however, no statistical comparisons were reported. Similar safety results were reported for the GOG-218 study. pERC discussed the adverse events reported in the ICON7 and GOG-218 studies, and concluded that the adverse events associated with bevacizumab were both expected and manageable.

Limitations: Subgroups of ICON7 and GOG-218 studies

The submitter's requested funding population represents a subgroup of the trial population for both ICON7 and GOG-218. Although subgroup analyses are generally hypothesis-generating, meaning they are not able to test a scientific question, the large size of the ICON7 subgroup (502 patients out of the total 1,528 patients) as well as the similar PFS results obtained in a similar subgroup of the GOG-218 trial increased pERC's confidence in the results presented for the subgroups.

Comparator information: Carboplatin and paclitaxel

In Canada, women with metastatic or advanced ovarian cancer are frequently treated with a combination of surgery to resect as much disease as possible and combination chemotherapy (a platinum and a taxane, either neoadjuvant or adjuvant). The 5-year survival rate is 44% and approximately 70% of women will relapse and ultimately die as a result of their disease.

Need: New treatment options are required

Patients with advanced or metastatic ovarian cancer have incurable disease and the goal of treatment is to extend their duration of survival and to maintain or improve their quality of life. pERC noted that there are no proven therapies other than the current standard treatment combining chemotherapy and surgery that can prolong overall survival in this patient population. pERC acknowledged that the combination of surgery and chemotherapy with a platinum and a taxane provides only moderate effectiveness and that new treatment options are needed.

PATIENT-BASED VALUES

Values of patients with ovarian cancer: Willing to tolerate adverse effects to extend survival

Input from one patient advocacy group indicated that patients with advanced or metastatic ovarian cancer value prolongation of life expectancy, prevention of recurrence and improvement in quality of life. pERC noted that more than half of the 46 patients who provided input were willing to tolerate additional side effects of treatment for short term benefits measured in months vs. years of improvement.

pERC also acknowledged that there is a considerable caregiver burden with this disease, with the most negative impacts being anxiety, stress and fatigue.

Patient values on treatment: Some positive outcomes and increased side effects

pERC noted that a small number of patients who provided input had experience with bevacizumab as a first-line treatment (n=6). Many patients reported positive outcomes after initial treatment with bevacizumab, and noted that some side effects, such as hypertension, were more acceptable than others (bowel issues).

ECONOMIC EVALUATION

Economic model submitted: Cost-utility analysis

The pCODR Economic Guidance Panel (EGP) assessed a cost-utility analysis that compared carboplatin plus paclitaxel plus bevacizumab to carboplatin plus paclitaxel as a front-line treatment for patients with Stage III suboptimally debulked, Stage III unresectable, or Stage IV epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer. This comparison was based on a modified "high risk for progression" subgroup from the ICON7 study. The submitted model was a partitioned-survival or area under the curve model.

Basis of the economic model: Clinical and economic inputs

Costs considered in the model provided by the submitter included the cost of treatment, administration, and wastage, and the costs associated with adverse events.

The key clinical outcomes considered in the model provided by the submitter were overall survival, progression-free survival, and utilities.

Drug costs: Cost of treatment and administration

At the list price, bevacizumab costs $600.00 per 100mg vial and $2,400.00 per 400 mg vial. At the recommended dose of 7.5 mg/kg every 21 days, and assuming a body weight of 70 kg, bevacizumab costs $[redacted] per day and $[redacted] per 28-day course. At the submitted confidential price, bevacizumab costs [redacted] per 100mg vial and [redacted] per 400mg vial. (*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*)

Carboplatin costs $0.10 per mg. At the dosing regimen of 5 mg/mL/min AUC (900 mg/m^2 on average), every 21 days, carboplatin costs $7.29 per day and $204.00 per 28-day course.

Paclitaxel costs $0.33 per mg. At the dosing regimen of 135-175 mg/m^2 on day 1 every 21 days, and assuming a body surface area of 1.7 m^2, paclitaxel costs $3.63 to $4.70 per day and $101.59 to $131.69 per 28-day course.

Clinical effect estimates: Key drivers were OS, time horizon, and utility values

The EGP's reanalyses estimated the extra clinical effect of carboplatin plus paclitaxel plus bevacizumab to be between 0.317 and 0.424 quality adjusted life-years (QALYs). The factors found to have the greatest influence on the incremental effectiveness were the survival effect of carboplatin plus paclitaxel plus bevacizumab, the time horizon, and the utility values for the both the progression-free and the progressed states.

Cost-effectiveness estimates: Uncertainty in upper range of Economic Guidance Panel's reanalyses

pERC noted that the incremental cost-effectiveness estimates provided by the pCODR Economic Guidance Panel (EGP) were similar to the manufacturer's estimates. The Committee observed that the ICER estimates provided by the EGP for this treatment in this patient population may not be cost-effective. Also during their deliberations, pERC expressed concern that assumptions about post-progression survival benefits and potential carry over effects were only partially explored by the EGP and not included in the EGP's reanalyses. pERC recognized that some carry over benefit of bevacizumab is clinically plausible once treatment is stopped; however, there is an absence of clinical evidence to justify the post-progression benefit inherent in the model. Given the uncertainty regarding the true impacts of the post-progression survival benefit and potential carry-over effect, pERC felt that the ICER may be higher than the upper range of the EGP's best estimate. Therefore, pERC concluded that bevacizumab plus carboplatin and paclitaxel may not be cost-effective.

pERC considered feedback received from the manufacturer that the EGP's range of best estimates of the ICER included the manufacturer's best estimate. Notwithstanding this observation, the Committee felt that pERC's original conclusion remains valid and that the true ICER may be higher than the upper range of the EGP's best estimate given the uncertainty regarding the post-progression survival benefit and potential carry-over treatment effect.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Small population and high drug cost
pERC discussed the feasibility of implementing a funding recommendation for bevacizumab plus chemotherapy for women with advanced stage, "high risk for progression" (stage III with >1 cm of residual disease, unresectable stage III or stage IV), epithelial ovarian cancer, primary peritoneal cancer or fallopian tube cancer. They noted that the funding request represents a small patient population. The Committee discussed that since the ICON7 study used a dose of 7.5mg/kg and reported similar outcomes to the GOG-218 study which used a dose of 15mg/kg, a dose of 7.5mg/kg is appropriate.

pERC noted that the potential for budget impact of bevacizumab in this setting is affected by the prevalence of ovarian cancer, the probability of suboptimal surgical debulking, the proportion of patients covered by a public plan, and the proportion of patients with Stage III or Stage IV ovarian cancer. pERC noted that the number of women who would be eligible for treatment is likely small.

Also, pERC noted that since both the ICON7 and GOG-218 studies were designed for women to receive bevacizumab during the initial chemotherapy phase and then continue treatment in the maintenance phase, a similar regimen should be recommended for funding in Canadian practice.

pERC also noted that in many centres in Canada women are offered neoadjuvant chemotherapy for newly diagnosed advanced ovarian cancer for multiple reasons, including restricted timely access to operating rooms and extensive disease distribution in poor performance status patients. As patients receiving neoadjuvant chemotherapy were not included in the studies of bevacizumab, its effectiveness and safety in this group of patients is unknown, consequently, pERC concluded that at this time there is no evidence to support or refute the use of bevacizumab in women who have received neoadjuvant chemotherapy.

Finally, pERC discussed the potential for drug wastage with bevacizumab and concluded that 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 7.5 mg/kg of body weight administered intravenously every three weeks
Cancer Treated	• Epithelial Ovarian, Fallopian Type or Primary Peritoneal Cancer Patients with High-Risk of Relapse (stage III sub-optimally debulked, or stage III unresectable, or stage IV patients)
Burden of Illness	• In 2014, 2,700 women in Canada will develop ovarian cancer which is approximately 11 per 100,000 (age standardized rate • Ovarian cancer is the eighth leading cause of cancer in Canadian women and fifth leading cause of cancer death • Approximately 1,750 women will die as a result of this disease for a mortality rate of 6.4 per 100,000 women
Current Standard Treatment	• The combination of a platinum and taxane chemotherapy (i.e. cisplatin/carboplatin + paclitaxel) • Cisplatin is often replaced with carboplatin due to the latter's better toxicity profile
Limitations of Current Therapy	• Poor overall survival seen with the use of standard combination chemotherapy • Apart from standard treatment combining chemotherapy and surgery, there are currently no proven therapies that can prolong overall survival in this patient population

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:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Matthew Cheung, Oncologist
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Wasney, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Tallal Younis, Oncologist
Dr. Kelvin Chan, Oncologist

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

- Drs. Scott Berry and Mario De Lemos who were not present for the meeting
- Drs. Bill Evans, Paul Hoskins and Kelvin Chan who were excluded from voting due to a conflict of interest
- Carole McMahon who did not vote due to her role as a patient member alternate

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

- Dr. Scott Berry who was not present for the meeting
- Drs. Bill Evans, Paul Hoskins and Kelvin Chan who were excluded from voting due to a conflict of interest
- Carole McMahon who did not vote due to her role as a patient member alternate

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 Ovarian Cancer through their declarations, seven members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, and three of these members were excluded from 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

This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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