PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Bevacizumab (Avastin) for Ovarian Cancer

June 4, 2015

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1 GUIDANCE IN BRIEF

1.1 Background

Ovarian cancer is the eighth leading cause of death in Canadian women and fifth leading cause of cancer death[1]. It is most common in peri- or postmenopausal women. Screening strategies in well women have not been found to be effective in diagnosing early stage ovarian cancer when the prognosis is still good[2], and the majority of patients still present with advanced, metastatic disease. The Canadian Cancer Society estimates that, in 2014, 2,700 women in Canada will develop ovarian cancer, with 1,750 deaths due to this disease.

The objective of this review was to evaluate the effectiveness and safety/toxicity of bevacizumab when used in combination with paclitaxel and carboplatin for the front-line treatment of patients who have undergone upfront surgery for epithelial ovarian, fallopian tube or primary peritoneal cancer and who have a high risk of relapse (stage III sub-optimally debulked, stage III unresectable, or stage IV patients).

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

Two randomized controlled trials met the criteria for inclusion in this review. The ICON7 study was an open-label trial that randomized (1:1) 1528 patients who had undergone surgery and had early-stage high-risk disease (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 cancer, or fallopian tube cancer, to receive either carboplatin plus paclitaxel (carbo-pac) (n=764) for six cycles or to receive carboplatin plus paclitaxel plus concurrent bevacizumab (n=764; 7.5 mg/kg for cycles 2-6) followed by bevacizumab maintenance (7.5 mg/kg for up to an additional 12 cycles or until disease progression). Randomization was stratified according to several factors, including FIGO stage and residual disease.[3]

The GOG-218 study was a blinded, placebo-controlled randomized trial that compared carbo-pac 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 for cycles 2-6) followed by placebo maintenance (cycles 7-22; =625) versus carboplatin plus paclitaxel for six cycles plus concurrent bevacizumab (15 mg/kg for cycles 2-6) followed by bevacizumab maintenance (15 mg/kg for cycles 7-22 or until disease progression; n=623). Initially, the study enrolled patients with previously untreated, incompletely resectable (residual disease >1 cm) FIGO stage III (i.e., suboptimally debulked) or any FIGO stage IV epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer. After enrolling 467 patients, the inclusion criteria of the trial were modified to allow patients with incompletely resectable stage III disease and residual lesions ≤1 cm (stage III optimally debulked) to participate.[4]) Of the 1873 patients enrolled in the trial, 40.1% were suboptimally debulked stage III and 25.8% were stage IV.[5]

Efficacy

In the 2010 analysis of the ICON7 trial data, in a pre-planned analysis of the subgroup of 465 patients at high risk for progression (defined as stage III disease with >1 cm of residual disease, or stage IV disease), median overall survival was statistically significantly longer for those who received bevacizumab in combination with carboplatin and paclitaxel compared with those who received carbo-pac alone (36.6 months versus [vs.] 28.8 months;

hazard ratio for death [HR] 0.64, 95% CI 0.48 to 0.85; p=0.002).[3] In an updated analysis conducted in 2013, the subgroup analysis was modified to include an additional 37 patients with non-operated disease (n=502). A statistically significant difference in overall survival in favour of the bevacizumab arm was reported (log-rank test, p=0.03); however, non-proportional hazards were detected (p=0.007). Restricted mean survival times were 39.3 months for patients who received bevacizumab compared with 34.5 months for patients who received the control, and are preferable for use in comparative analysis when non-proportional hazards are detected. Limited health-related quality of life data were available for the ICON7 trial, and were reported for the entire study population, but not for the high risk subgroup separately. 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 no difference in scores between the treatment arms.

Overall survival data were not available for the subgroup of patients at high risk for progression (i.e., stage III disease with residual lesions >1 cm, or stage IV) in the GOG-218 trial. For the subgroup of patients with stage III disease and residual lesions >1 cm, median progression-free survival was statistically significantly improved for the patients who received carboplatin plus paclitaxel plus concurrent and maintenance bevacizumab (n=242) compared with those who received carboplatin plus paclitaxel alone (n=253) (13.9 months vs. 10.1 months; HR 0.78, 95% CI 0.63 to 0.96). Similarly, in the subgroup of patients with stage IV disease, median progression-free survival was also statistically significantly longer for patients who received concurrent plus maintenance bevacizumab compared with those in the control arm (12.8 months vs. 9.5 months; HR 0.64, 95% CI 0.49 to 0.82). Quality of life was assessed, and reported for, all patients in the GOG-218 trial using the Functional Assessment of Cancer Therapy-Ovarian Cancer Trial Outcome Index (FACT-O TOI). The TOI is a summary of the physical and functional outcomes of the FACT-O. A statistically significant improvement in change in TOI scores between the second half of the chemotherapy phase (cycles 4 and 7) and the latter portion of the extended treatment phase (cycles 13 and 21) in favour of the carboplatin plus paclitaxel plus concurrent and maintenance bevacizumab treatment arm compared with the carboplatin plus paclitaxel arm was reported (p=0.0008); however, the change (2.6 points) was less than the minimally important difference of 5 points.

Harms

In both trials, adverse events were not reported separately for the high risk for progression subgroups; instead results were reported for the entire study populations.

In ICON7, four patients in the bevacizumab arm and seven patients in the control arm experienced an adverse events leading to death.[5] A total of 164 patients (22.0%) in the bevacizumab arm and 68 patients (8.9%) in the control arm discontinued treatment due to an adverse event.[5] Non-central nervous system (CNS) bleeding events occurred in 39.4% of patients who received bevacizumab and in 11.0% of patients who received the control treatment.[5] Hypertension also occurred more frequently in patients who received bevacizumab (25.6% vs. 6.4%)[5]. Arterial thrombotic events occurred in 3.5% of patients who received bevacizumab and in 1.6% of patients who received control.[5] Wound healing complications occurred in 4.6% of patients who received bevacizumab and in 1.6% of patients who received the control.[5] Fistulae and abscesses occurred in 1.7% of patients who received bevacizumab and 1.2% of patients who received the control, with GI perforations occurring in 1.3% and 0.4% of patients, respectively.[5]

In GOG-218, four patients in the control arm, nine patients in the concurrent bevacizumab arm, and 14 patients in the concurrent plus maintenance bevacizumab arm experienced an adverse event leading to death.[5] A total of 58 patients (9.7%) in the control arm, 83

patients (13.7%) in the concurrent bevacizumab arm, and 100 patients (16.4%) in the concurrent plus maintenance bevacizumab arm discontinued treatment due to an adverse event.[5] Non-CNS bleeding events occurred in 36.7% of patients who received concurrent plus maintenance bevacizumab, 35.6% of patients who received concurrent bevacizumab, and in 11.0% of patients who received the control treatment.[5] Hypertension also occurred more frequently in patients who received concurrent plus maintenance bevacizumab or concurrent bevacizumab alone (32.2% and 23.6%) than in patients who received the control (13.5%).[5] Arterial thrombotic events occurred in 3.1% of patients in the concurrent plus maintenance bevacizumab and the concurrent bevacizumab alone arms and in 2.3% of patients who received the control.[5] Wound healing complications occurred in a similar proportion of patients in all three arms (range 3.6% to 4.8% of patients).[5] Fistulae and abscesses occurred in 2.0% of patients who received concurrent plus maintenance bevacizumab, in 0.8% of patients who received concurrent bevacizumab alone, and in 1.2% of patients who received the control, with GI perforations occurring in 2.0%, 1.8%, and 0.3% of patients, respectively.[5]

1.2.2 Additional Evidence

pCODR received input on bevacizumab for ovarian cancer from one patient advocacy group, Ovarian Cancer Canada. Provincial Advisory group input was obtained from nine of the nine provinces participating in pCODR.

No supplemental issues were identified during the development of the review process.

1.2.3 Interpretation and Guidance

The overall survival benefit reported from the addition of bevacizumab to chemotherapy in the ICON7 trial, followed by up to 12 cycles of maintenance treatment, is based on analyses of a large subgroup of 465 patients who are at high risk for progression. The original pre-planned analysis for this subgroup of patients demonstrated a statistically and clinically significant difference in overall survival in favour of the bevacizumab arm. In an updated analysis, a similar, but modified high risk for progression subgroup that included an additional 37 inoperable patients demonstrated a significant difference in OS in favour of the bevacizumab arm. A similar treatment effect in the GOG-218 study is supportive of the ICON7 results. Finally, the results are biologically plausible, given the characteristics of the high risk for progression population and the mechanism of action of bevacizumab.

The ICON7 and GOG-218 trials excluded patients treated with neoadjuvant chemotherapy and interval debulking surgery. Many centres in Canada offer neoadjuvant chemotherapy for patients with newly diagnosed advanced ovarian cancer. Neoadjuvant therapy may be delivered for multiple reasons, including restricted timely access to operating rooms and/or extensive disease distribution in poor performance status patients. Given the variety of reasons for delivering neoadjuvant treatment, some being disease or patient related, and others logistical, it is not reasonable to assume that all patients getting interval debulking have high risk for progression. As patients receiving neoadjuvant chemotherapy were excluded from the studies of bevacizumab, the effectiveness and safety in this group of patients is unknown. It is also not known how to select patients for bevacizumab treatment following neoadjuvant chemotherapy and interval debulking surgery. Therefore, at this time there is no evidence to support or refute the use of bevacizumab in women who have received neoadjuvant chemotherapy.

Generally, bevacizumab added to standard carboplatin and paclitaxel was well tolerated and did not significantly increase the common toxicities observed with chemotherapy (myelosuppression, febrile neutropenia, nausea, alopecia, etc.). However, the addition of bevacizumab significantly increased the risk of rare and potentially serious adverse events such as fistulae formation, gastrointestinal bleeding, and thrombosis. All serious adverse events were rare, typically under 4%, and were felt to be both well understood and medically manageable. There was not an obvious dose effect of bevacizumab on the rate of toxicity, with both the 7.5 mg/kg dose and the 15 mg/kg dose levels leading to similar side effect profiles. Treatment-related deaths were rare. Overall, the risk of bevacizumab added to chemotherapy is not significantly increased above baseline; however, careful patient selection and careful informed consent for treatment remain essential.

Advances in the treatment of this disease are needed. Since the addition of paclitaxel to standard therapy in the early 1990's, there have been no major practice changing developments in the treatment of ovarian cancer. Apart from standard treatment with chemotherapy and surgery, there are currently no proven therapies that can prolong overall survival in this patient population.

Quality of life data from the ICON7 trial and the GOG-218 trial suggest that bevacizumab is generally well tolerated and does not measurably erode patient quality-of-life. The magnitude of the clinical benefit is significant, adding a median 9.4 months of overall survival over the control group to the high-risk for progression subgroup in the ICON7 trial. Withdrawals from the trial were rare and no patients were reported to be lost to follow up. At this time, no other treatment beyond chemotherapy has demonstrated an improvement in overall survival in the first-line treatment setting.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to bevacizumab given at 7.5 mg/kg with cycles 2-6 of standard 3-weekly carboplatin- and paclitaxel-based first line chemotherapy, and as maintenance treatment for up to 12 additional 3–weekly cycles in the treatment of advanced stage, high-risk for progression, ovarian cancer (stage III with > 1cm of residual disease, stage IV disease, or unresectable disease). This is based on a large subgroup analysis of a multicenter, randomized controlled trial (ICON7, with 1528 participants, of which 502 belonged to the subgroup of interest) that demonstrated a clinically meaningful improvement in overall survival in favour of the bevacizumab arm. A second randomized phase III trial, also demonstrated a clinically and statistically significant benefit on progression-free survival for the subgroups of patients with a) stage III cancer and residual disease following primary surgery and b) stage IV cancer who were treated with bevacizumab (given concurrently with standard chemotherapy and in the maintenance setting for up to 12 months) when compared to standard chemotherapy alone. Serious adverse events, such as fistulae, GI perforation, and thrombosis were more commonly observed with the use of bevacizumab, but were still relatively rare (<4%).

The Clinical Guidance Panel also considered that from a clinical perspective:

- There is uncertainty regarding the use of bevacizumab in patients treated with neo-adjuvant chemotherapy who then go on to interval debulking surgery, as this patient population was excluded from these studies.
- Careful patient selection (e.g., good performance status, i.e., ECOG 0-2; no evidence of bowel obstruction; >4 weeks from the time of surgery) and careful informed consent for treatment remain essential.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding Bevacizumab (Avastin) in combination with paclitaxel and carboplatin for the frontline treatment of patients epithelial ovarian, fallopian tube or primary peritoneal cancer patients who are at high risk of relapse. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website,www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding bevacizumab (Avastin) conducted by the gynecological Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review is fully reported in Sections 6. Background Clinical Information provided by the CGP, a summary of submitted patient advocacy group input on bevacizumab (Avastin) and a summary of submitted Provincial Advisory Group input on bevacizumab (Avastin) are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Epithelial carcinoma of the ovary is one of the most common gynecologic malignancies and the fifth most frequent cause of cancer death in women, with 50% of all cases occurring in women older than 65 years.[6] Findings from risk-reducing surgeries in healthy women with *BRCA1* or *BRCA2* mutations have reinforced the hypothesis that many high-grade serous cancers—the most common histologic subtype of ovarian cancer—may arise from precursor lesions that originate in the fimbriae of the fallopian tubes.[7] Common subtypes of ovarian cancer include high grade serous, endometrioid, clear cell, and low grade serous. Ovarian, fallopian and peritoneal carcinomas all share similar histological features, molecular aberrations and clinical behaviour. In addition, histologically similar cancers diagnosed as primary peritoneal carcinomas share molecular findings, such as loss or inactivation of the tumour-suppressors p53 and *BRCA1* or *BRCA2* proteins.[8] In Canada, it is estimated that in 2014, 2,700 women will be diagnosed with ovarian cancer and that an estimated that 1,750 women will die from it.[9]

Traditionally, surgery is the primary treatment for any stage or type of epithelial ovarian, fallopian tube, or primary peritoneal cancer to maximally debulk as much tumour as possible followed by adjuvant combination chemotherapy with a platinum (carboplatin or cisplatin) in combination with a taxane (paclitaxel or docetaxel).

Bevacizumab is a recombinant humanised monoclonal antibody that inhibits angiogenesis by neutralising all isoforms of human vascular endothelial growth factor-A (VEGF-A), and blocking their binding to VEGF receptors.[5] Bevacizumab in combination with platinum (carboplatin or cisplatin) and a taxane (paclitaxel or docetaxel) is a new treatment regimen currently under review for patients with epithelial ovarian, fallopian tube or primary peritoneal cancer.

As the mechanism of action of bevacizumab is angiogenesis blockade by binding to the VEGF receptor, studying its effects in advanced stage ovarian cancer is biologically rational. Advanced stages of ovarian cancer have large tumours requiring independent blood supply, which suggests a greater likelihood of benefit from anti-angiogenesis therapy. Studies have demonstrated that tumours > 2 mm in diameter require their own blood supply[10], hence, patients with residual tumours >10mm after surgery were also included as they has a high risk of relapse and would thus be dependent on new blood vessel formation. Bevacizumab also improves disordered blood vessel proliferation and reduced tumour oncotic pressure, features that could lead to improved chemotherapy delivery to tumour masses.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effectiveness and safety/toxicity of bevacizumab when used in combination with paclitaxel and carboplatin for the front-line treatment of patients who have undergone initial surgery with epithelial ovarian, fallopian tube or primary peritoneal cancer patients at high risk of relapse (stage III sub-optimally debulked, or stage III unresectable, or stage IV patients). Only randomised controlled trials were considered for inclusion. Overall survival, progression free survival, and adverse events associated with both this disease type and monoclonal antibodies like bevacizumab, are outcomes of interest.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

Trial and Patient Characteristics

Two trials met the eligibility criteria for this review. ICON 7[3] is an open-label, 2 arm trial that examined carboplatin plus paclitaxel (carbo-pac) versus carboplatin plus paclitaxel plus concurrent bevacizumab followed by bevacizumab maintenance (carbo-pac-bev) in patients who have undergone surgery and had histologically confirmed, high-risk, early-stage disease (International Federation of Gynecology and Obstetrics [FIGO] stage I or IIA and clear-call or grade 3 tumors) or advanced (FIGO stage IIB to IV) epithelial ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer (based on local histopathological findings). One thousand five hundred twenty eight patients were enrolled but high risk, early stage patients were restricted to 10% of total enrollment. Treatment groups in the ICON 7 study[3] were well balanced with respect to baseline characteristics. The median age was 57 years, and 94% of the patients had an ECOG performance status of 0 or 1; 90% had epithelial ovarian cancer; 9% had high-risk early-stage disease; 30% were at high risk for progression; 21% had FIGO stage III, IIIA, or IIIB disease; 70% had FIGO stage IIIC or IV disease; 69% had a serous histologic type; and 26% had more than 1.0 cm of residual disease after surgical debulking. Bevacizumab dosing was (7.5 mg per kilogram of body weight), given concurrently every 3 weeks for 5 or 6 cycles and continued for 12 additional cycles or until disease progression for the bevacizumab group.

GOG-218[4] is a three arm trial that examined carboplatin plus paclitaxel (carbo-pac), carboplatin plus paclitaxel plus concurrent bevacizumab (carbo-pac-bev), and carboplatin plus paclitaxel plus concurrent bevacizumab followed by maintenance bevacizumab (carbo-pac-bev-maintenance). Eligibility included previously untreated, incompletely resected stage III or any stage IV epithelial ovarian, primary peritoneal, or fallopian-tube cancer histologically confirmed by the Gynecologic Oncology Group (GOG) Pathology Committee after standard abdominal surgery with maximal debulking effort within 12 weeks before study entry; a GOG performance status score of 0 (fully active) to 2 (ambulatory and capable of self-care but unable to work; up and about more than 50% of waking hours); and no history of clinically significant vascular events or evidence of intestinal obstruction. Changes to eligibility were made following start of enrollment to include patients with stage III disease and residual lesions less than 1 cm as well. These patients were initially excluded. Treatment groups were well balanced in the GOG-218 trial[4] with 35% of patients being Stage III, optimally debulked in all three treatment arms, and the proportion of patients with serous histologic type was similar in all three arms (carbo-pac, 86.6%; carbo-pac-bev 83.0%; carbo-pac-bev-maintenance, 84.1%). The proportion of Stage III sub-optimally debulked patients was 40.5%, 41%, and 38.8% in the carbo-pac, carbo-pac-bev, and carbo-pac-bev-maintenance arms respectively. The proportion of stage IV patients was 24.5%, 26.4%, and 26.5% of patients in the carbo-pac, carbo-pac-bev, and carbo-pac-bev-maintenance arms respectively. Bevacizumab dosing was (15 mg per kilogram of body weight) added in cycles 2 through 6 and placebo added in cycles 7 through 22. Carbo-pac-bev-maintenance treatment was chemotherapy with bevacizumab added in cycles 2 through 22. Both overall survival (OS) and progression free survival (PFS) were the main endpoints in the study.

Efficacy

Non-proportional hazards were detected in the 2010 PFS analyses, within the ICON 7 study.[3] Restricted mean values were also reported for PFS and are preferable for use in comparative analysis and decision making when non-proportional hazards are detected. In the ICON 7 study a primary analysis of the high risk for progression subgroup (defined as stage III disease with >1 cm of residual disease following primary cytoreductive surgery, or patients with stage IV disease, N=465) was conducted in February 2010 as well as an updated analysis in November 2010. The subgroup included in the 2010 analyses will be referred to as the "original high risk for progression subgroup" from this point forward. PFS for the original subgroup analysis was significantly extended in the experimental arm with a hazard ratio (HR) of 0.73 and a p-value of p=0.002. Overall survival was also found to be significantly extended in the experimental arm in the original subgroup analysis, with a hazard ratio of HR =0.64 and p=0.002. Non-proportional hazards were not detected in this OS analysis. At the European Cancer Congress in 2013, Oza et al reported an updated analysis of OS for a subgroup of patients at high risk for progression that was modified from the original subgroup as defined in the 2010 analyses (from this point on referred to as the "modified high risk for progression subgroup"). The modified subgroup included an additional 37 patients (n=502) and was defined in the same way as the original subgroup except that it also included non-operated patients, as they were felt to have a high risk of progression. Oza et al reported a statistically significant difference in OS (log-rank test, p=0.03); however, non-proportional hazards were detected (p=0.007). The restricted mean

survival time for the bevacizumab-containing arm was 39.3 months compared to 34.5 months in the chemotherapy-alone arm.

In GOG-218[4] PFS was also reported for Stage III, tumor >1cm and stage IV patients. The hazard ratio for the comparison of the carbo-pac-bev treatment arm with the carbo-pac treatment arm for stage III, >1cm was HR=0.981, and HR =0.923 for stage IV patients (HR<1 favoured carbo-pac-bev). There was no p-value reported in this analysis but the 95% confidence interval did include unity for both subgroups, indicating no significant difference between carbo-pac and carbo-pac-bev treatment arm. Hazard ratios for the comparison of the carbo-pac and carbo-pac-bev-maintenance treatment arms were HR=0.763 and HR =0.698 for Stage III, >1cm patients and stage IV patients, respectively (HR<1 favoured carbo-pac-bev-maintenace). The 95% CIs did not include unity, indicating significant differences in both subgroups between carbo-pac and carbo-pac-bev-maintenance treatment arms. Overall survival was not reported for the high risk subgroup in the GOG-218 study.

Harms

In both trials, adverse events were not reported separately for the high risk for progression subgroups. Results presented below are for safety populations. Overall, in ICON 7 treatment-related ≥ grade 3 adverse events (AE) occurred in 419 (55%) and 791 (64%) of patients in the carbo-pac and carbo-pac-bev arms respectively.[3] Information on the incidence of patients who experienced at least one ≥ grade 3 adverse events was not available for the GOG-218 study.[3, 4]

Gastrointestinal perforations occurred in 0.4%, and 1.3% of patients in the carbo-pac versus carbo-pac-bev arms of ICON 7, while they occurred in 0.3%, 1.8%, and 2.0% in the carbo-pac, carbo-pac-bev, and carbo-pac-bev-maintenance groups respectively in the GOG-218 study.[3, 4]

Fistulae and abscesses were reported in 1.2%, and 1.7% of patients in the control and treatment arms of the ICON 7 study respectively. Similarly, in the GOG-218 study fistulae and abscessed were reported in 1.2, 0.8%, and 2.0% of patients from carbo-pac, carbo-pac-bev, and carbo-pac-bev-maintenance treatment arms, respectively. [3, 4]

Wound healing complications were reported in 1.6%, and 4.6% of patients in carbo-pac versus carbo-pac-bev arms in ICON 7, while they occurred in 4.5%, 4.8%, and 3.6% of patients in carbo-pac, carbo-pac-bev, and carbo-pac-bev-maintenance groups respectively in the GOG-218 study. [3, 4]

Arterial thromboembolic events occurred in 1.6% and 3.5% of patients in the chemotherapy and bevacizumab plus chemotherapy arms respectively in the ICON 7 study. In the GOG-218 study, the incidence was 2.3%, 3.1%, and 3.1% in the carbo-pac, carbo-pac-bev, and carbo-pac-bev-maintenance treatment arms respectively. [3, 4]

Heart failure was reported in 0.4% of patients in both carbo-pac and carbo-pac-bev arms of the ICON 7 study and in 0%, 0%, and 0.5% of patients from carbo-pac, carbo-pac-bev, and carbo-pac-bev-maintenance treatment arms respectively, in the GOG-218 study. [3, 4]

In the ICON7 study, there were 5 deaths related to treatment. Seven (0.9%) and 4(1.5%) adverse events leading to death were reported in the control and

treatment arms, respectively.[3] In the GOG-218 study, four (0.7%), nine (1.5%), and 14 (2.3%) adverse events leading to death were reported for the carbo-pac, carbo-pac-bev, and carbo-pac-bev-maintenance treatment arms respectively.[4] Note that mortality results reflect the entire safety population and not just the high risk subgroup, for both studies.

Quality of Life

Health related quality of life (HRQoL) was reported by patients using the EORTC QLQc-30 and OV28 questionnaires in the ICON 7 study. The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients. It is a copyrighted instrument, which has been translated and validated into 81 languages and is used in more than 3,000 studies worldwide. Presently QLQ-C30 Version 3.0 is the most recent version and should be used for all new studies. It is supplemented by disease-specific modules which in this study is the Ovarian Cancer Module (EORTC QLQ-OV28). Eighty nine percent of protocol QL data was available for the control arm and 92% for the intervention arm at baseline. Completion rates for each interval were not available. Results indicated improvement in global QOL, for patients in both treatment and control arms, over time. [3]

In the GOG-218 trial quality of life was compared among the three groups with the use of the Trial Outcome Index of the Functional Assessment of Cancer Therapy–Ovary (FACT-O TOI) survey. Only one period analysis found statistical improvements in health related quality of life and that was between the second half of the chemotherapy phase (Cycles 4 and 7) and the latter portion of the extended treatment phase (Cycles 13 and 21). Improvements were found for patients in the carbo-pac-bev-maintenance compared to the carbo-pac arm (p=0.0008).[4]

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team identified Gynecologic Oncology Group Study 262 (GOG-262), preliminarily reported in 2013 by Chan et al.[11] In this trial, 692 evaluable patients with newly diagnosed, stages II-IV ovarian cancer were randomly assigned to receive treatment either with standard-doses of carboplatinum (AUC 6) and paclitaxel (175 mg/m2) given on a 3-weekly schedule, or else standard-dose carboplatinum once every 3-weeks with paclitaxel given weekly at 80 mg/m2 (dose-dense arm). Approximately 70% of patients on this study had stage III disease, and 63% had >1 cm residual post debulking. On both arms of the study patients were treated for up to 6 cycles. The study was designed to determine whether dose-dense chemotherapy may improve patient outcomes. The use of bevacizumab was permitted on both arms of the study, at the discretion of the treating physician, and was given at 15 mg/kg, delivered with chemotherapy and subsequently as maintenance therapy until progression. 83.5% of patients on the standard arm and 84.1% on the investigational arm received bevacizumab. The overall results of the study demonstrated no measurable difference in outcomes on either arm of the study (standard arm, 14.3 versus 14.8 months on the dose-dense arm, hazard ratio = 0.97, 95% confidence interval 0.79e1.18). However, in the subgroup of patients who did not receive bevacizumab (n= 112), a significant difference in PFS was noted between standard drug schedules and dose-dense treatment (10.3 versus 14.2 months, hazard ratio = 0.60, 95% confidence interval 0.37e0.96, P = 0.033).

As both dose-dense chemotherapy and bevacizumab are purported to work by blockade of angiogenesis, it is conceivable that the addition of bevacizumab to the control arm effectively eliminated the possibility of detecting benefit of dose-dense paclitaxel, as both groups had angiogenesis blockade. By contrast, in the subgroup of patients who did not receive bevacizumab, the dose-dense treatment resulted in equivalent outcomes to the overall study population (PFS of ~14 mo).

A tempting conclusion may be that the use of dose-dense paclitaxel with standard-dose carboplatinum can achieve equivalent outcomes to concurrent and maintenance bevacizumab. However, the results of this trial were reported in a preliminary fashion, and the observations are made in a small subgroup of patients. The analysis was conducted in a post hoc manner, and the use of bevacizumab was optional within each arm of the study, hence selection bias and confounders cannot be accounted for.

Dose-dense chemotherapy has been studied in other trials, including the Japanese Gynecologic Oncology Group Trial 3016 (JGOG 3016)[12] which demonstrated a significant improvement in ovarian cancer survival amongst women receiving dose-dense paclitaxel and standard-dose carboplatin compared to those receiving standard 3-weekly dosing of both drugs. However, an Italian Trial (MITO 7) failed to detect a difference in outcomes for patients receiving dose-dense carboplatin and dose-dense paclitaxel (i.e. a different treatment schedule to those used in the GOG-262 and JGOG 3016, studies) over the usually 3-weekly schedule. The topic of dose-dense paclitaxel in ovarian cancer is reviewed in Kumar et al.[13]

Based on the GOG-262 subgroup analysis described above, and the JGOG trial, some jurisdictions, unable to fund bevacizumab for ovarian cancer, may view dose-dense chemotherapy as a more affordable alternative, recognizing that dose-dense chemotherapy has never been directly compared to standard-dose chemotherapy with concurrent and maintenance bevacizumab.

The results of the GOG-262 study do suggest that there is no obvious advantage in using bevacizumab with dose-dense chemotherapy. Standard-dose and standard-schedule platinum-taxane based therapy combined with bevacizumab appears to be equally efficacious, and is the simpler option.

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review

2.1.6 Other Considerations

Patient Advocacy Group Input

One patient advocacy group, Ovarian Cancer Canada (OCC), provided input on bevacizumab (Avastin) 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), and their input is summarized below.

OCC conducted an anonymous online survey which was promoted to women diagnosed with Stage III and IV ovarian cancer and their caregivers through the organization's database, website, social media sites and partners. OCC reported receiving responses from 76 patients with ovarian cancer (Stage III and IV) and 5 caregivers. Of the total 81 respondents, the majority of respondents had been

diagnosed with ovarian or related cancers between 2010-2014. The sample included 10 respondents with fallopian tube cancer, 11 respondents with primary peritoneal cancer and 7 respondents who designated their ovarian cancer as 'other'. Respondents ranged in age from 28 – 76 years, and approximately 79% of respondents were 50 years and older. Responses were predominantly received from Canadian respondents, however there were no respondents from New Brunswick, Newfoundland, Prince Edward Island, Northwest Territories, Nunavut or the Yukon. There were also eight respondents from the United States. A total of six respondents indicated that they had experience with bevacizumab for first-line treatment. Of the respondents who had not used bevacizumab as first-line treatment, it was reported that 62.5% of respondents had at least one if not multiple recurrences. Of those who had used bevacizumab as first-line treatment, it was reported that 50% of respondents had two or more recurrences.

From a patient perspective, the impact of ovarian cancer is significant for women diagnosed with this disease and their caregivers. Because early symptoms can be non-specific and generally there is no screening test, ovarian cancer is usually detected in its later stages resulting in a grim prognosis. Surgery and chemotherapy have been the mainstays of first-line treatment; however, as most women are likely to face a recurrence, OCC believes it is helpful to have a greater spectrum of agents with which to treat this type of cancer. OCC reported that six respondents had direct experience with bevacizumab as a first-line treatment. Three respondents had recurrence with their ovarian cancer; two respondents had two recurrences, one respondent recurred more than 3 times. The primary treatment side effects of bevacizumab included fatigue, bowel problems, neuropathy, hair loss and nausea, which were found to be similar in the larger non-bevacizumab group. It was also reported there was a slightly higher indication of high blood pressure in the bevacizumab group than the group that did not take bevacizumab; however, it was noted that the sample size in the bevacizumab group is small.

PAG Input

Input on for bevacizumab (Avastin) for ovarian cancer was obtained from nine of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From the PAG perspective, the key enablers include familiarity with bevacizumab and it is an add-on to existing therapy with the same dosing schedule. Key barriers to implementation are the high cost of bevacizumab and the additional nursing, lab, physician and pharmacy resources required for safe preparation and administration of bevacizumab.

2.2 Interpretation and Guidance

Burden of the Disease

In 2014 2,700 women in Canada will develop ovarian cancer which is approximately 11 per 100,000 (age standardized rate). Approximately 1,750 women will die as a result of this disease for a mortality rate of 6.4 per 100,000 women[14]. It is the 5th most common cause of cancer-related death in women. As the disease often strikes women in their 50s and 60s, it removes them from the work force and leads to a substantial person-years of life lost. [15]

Effectiveness

The ICON7 trial, as described in detail in section 2.1.3, was an unblinded, phase III, randomized study examining the clinical impact of the addition of bevacizumab to standard first-line systemic therapy with carboplatin and paclitaxel and subsequently as maintenance treatment for up to 12 additional cycles in women with either high risk stage I ovarian cancers or advanced, stages IIB to IV, ovarian cancers.[3] Randomization between the study arms was 1:1. The bevacizumab dose was 7.5 mg/kg given intravenously every 21 days, given concurrently with chemotherapy. Patients having interval debulking surgery were excluded from the study. The primary endpoints of the study were progression-free survival (PFS) and overall survival (OS). The study enrolled 1528 eligible participants.

At first reporting, with a median 28 months of follow up for the entire study population, PFS was significantly longer in the bevacizumab group: 19.8 months vs 17.4 months (HR=0.87;95% CI, 0.77-0.99, P=0.04). Overall survival data were not final. However, a pre-planned analysis of overall survival of women in the original high-risk for progression subgroup (stage III disease with >1 cm of residual disease following primary cytoreductive surgery, or patients with stage IV disease, N=465) demonstrated that the median overall survival of this patient group was improved from 28.8 months to 36.6 months with the addition of bevacizumab [HR for death, 0.64(95% CI 0.48-0.85; P=0.002)].[3]

An updated analysis of this trial was presented by Oza et al., in 2013 in which a "modified high-risk for progression" group was evaluated (defined as above, but also included non-operated patients, as they were felt to have high risk of relapse). In this analysis of 502 patients, Oza et al. demonstrated a 9.4 month improvement in OS (from 30.3 in the standard chemotherapy-only arm to 39.7 mo in the bevacizumab-containing arm) in the modified high-risk for progression subgroup with HR 0.78 (95% CI 0.63-0.97; P=0.03) by Log-Rank test and by the restricted mean survival analysis, a 4.8 mo improvement for the bevacizumab-containing arm as compared to chemotherapy alone (39.3 months vs to 34.5 months).[16]

The GOG-218 trial, as described in Section 2.1.3 above, was a double-blind, 3-arm randomized phase III trial for women newly diagnosed with stage III or IV ovarian cancer. The study compared standard first-line treatment using platinum and a taxane alone, to standard chemotherapy given concurrently with bevacizumab (cycles 2-6), or standard chemotherapy given concurrently with bevacizumab and followed by maintenance bevacizumab (starting at cycle 2 and up to 22 cycles).[3] The dose of bevacizumab was double that used in the ICON7 trial, being 15 mg/kg, intravenously every 21 days. Like ICON7, patients undergoing interval debulking were excluded from the study. The key finding of this study was that the PFS (as assessed by RECIST or CA-125 elevation) was longer in the bevacizumab throughout arm, 10.3 vs 14.1 mo (HR 0.717 (95% CI, 0.625 to 0.824; P<0.001). There was no impact on OS, and the authors felt cross over was a possible contributor to this, as bevacizumab was available for off-label use in the United States during the time of this trial. The pre-planned subgroup analysis demonstrated that patients with "high risk" disease (stage III with > 1cm of residual disease following surgery, and stage IV disease) benefited from the bevacizumab throughout treatment (HR=0.763 and HR =0.698 for Stage III, >1cm patients and stage IV patients, respectively). Subgroup analysis did not demonstrate evidence of benefit from bevacizumab in the initial (with chemotherapy) strategy. There was also no benefit observed in the delivery of bevacizumab (initial or throughout) to the non-serous histological subtypes.

A dose effect of bevacizumab has not been observed. The ICON7 study treated patients with 7.5 mg/kg IV every 3 weeks, while the GOG-218 study used 15 mg/kg IV every 3 weeks. Both trials reported similar clinical benefit on PFS. Based on the ICON7 OS results described herein, the 7.5 mg/kg dose is considered appropriate.

Limitations of the Evidence

The OS benefit reported from the addition of bevacizumab to chemotherapy in the ICON7 trial, followed by up to 12 cycles of maintenance treatment, is based on analyses of a subgroup of 465 patients who are at high risk for progression. The original pre-planned analysis of OS for this subgroup of patients demonstrated a statistically and clinically significant difference in OS in favour of the bevacizumab arm. In an updated analysis, a similar, but modified high risk for progression subgroup that included an additional 37 inoperable patients demonstrated a significant difference in OS in favour of the bevacizumab-containing arm. Subgroup analyses are often viewed as hypotheses generating. However, a similar treatment effect in the GOG-218 study is supportive of the ICON7 results. In addition, the subgroup size is large, at 502 patients. Finally, the results are biologically plausible, given the characteristics of the high-risk for progression population and the mechanism of action of bevacizumab.

The ICON7 and GOG-218 trials excluded patients treated with neoadjuvant chemotherapy and interval debulking surgery. This will limit the generalizability of this data. In real-world practice, many centres in Canada offer neoadjuvant chemotherapy for patients with newly diagnosed advanced ovarian cancer. There are no data available to describe the prevalence of neoadjuvant therapy use in Canada for newly diagnosed ovarian cancer, but some centres are known to treat at least 50% of ovarian cancers with chemotherapy first. Neoadjuvant therapy may be delivered for multiple reasons, including restricted timely access to operating rooms and/or extensive disease distribution in poor performance status patients. Given the variety of reasons for delivering neoadjuvant treatment, some being disease or patient related, and others logistical, it is not reasonable to assume that all patients getting interval debulking have high-risk for progression. As patients receiving neoadjuvant chemotherapy were not included in the studies of bevacizumab, the effectiveness and safety in this group is unknown. It is also not known how to select patients for bevacizumab treatment following neoadjuvant chemotherapy and interval debulking surgery. Therefore, at this time there is no evidence to support or refute the use of bevacizumab in women who have received neoadjuvant chemotherapy. For patients who have >1cm residual disease following interval debulking, it is conceivable, but unproven, that the benefits of maintenance bevacizumab would be similar to the high-risk of progression study population of the ICON7 trial.

As the GOG-218 study demonstrated that the strategy of giving bevacizumab initially, only during the chemotherapy phase, did not improve patient outcomes as compared to standard chemotherapy alone (PFS HR:0.908 (95% CI, 0.795 to 1.040; P = 0.16), it may be argued that the benefit of therapy is derived solely from the maintenance component of the treatment. As ICON7 did not have the same trial design, there are no further data to examine this issue.

There are 5 main types of ovarian cancers (high grade serous carcinoma, endometrioid carcinoma, clear cell carcinoma, mucinous carcinoma and low grade serous carcinoma)[17]. These disease histotypes may conceivably respond differently to anti-angiogenic therapy. In the ICON7 study, 31% of cases were non-serous, but an analysis of outcomes by histology is not available. In the GOG-218 trial, non-serous subtypes represented fewer than 15% of all cases. On subgroup analysis, the non-serous cases did not benefit from bevacizumab, however, the small sample size would limit the interpretation of these results.

In addition, BRCA mutation status of patients was not reported, and are not available from the Submitter, in either the ICON7 or the GOG-218 studies. BRCA mutation carriers are reported to have better 5-yr survival[18], more durable and complete responses to platinum based therapy, and better responses to subsequent treatments[19]. Ensuring balanced randomization of such patients between the standard and interventional arms is important.

Safety

Generally, bevacizumab added to standard carboplatin and paclitaxel was well tolerated and did not significantly increase the common toxicities observed with chemotherapy (myelosuppression, febrile neutropenia, nausea, alopecia, etc.). However, bevacizumab did cause rare and

potentially serious adverse events such as fistulae formation, gastro-intestinal bleeding and thrombosis, which were typically under 4%, and were felt to be both well understood and medically manageable. Other well described toxicities of bevacizumab were observed, at rates comparable to those seen in other tumour types (e.g. colorectal cancer), and typically were </= to Grade 2 (e.g. hypertension, proteinuria, delayed wound healing). There is not an obvious dose effect of bevacizumab on the rate of toxicity, with both the 7.5 mg/kg and 15 mg/kg dose levels leading to similar side effect profiles (Section 6, Table 7).

Treatment related deaths were rare. On the ICON7 trial, 5 patients died due to treatment complication, 1 on the control arm and 4 on the investigational arm. GOG-218 reported fatal adverse events in 6 or 601 (1%) patients in the control group, 10 of 607 (1.6%) patients on the bevacizumab-initiation group, and 14 of 608 (2.3%) in the bevacizumab-throughout group. Overall, the risk of bevacizumab added to chemotherapy is not significantly increased above baseline. However, careful patient selection (e.g. good performance status, no evidence of bowel obstruction, > 4 weeks from the time of surgery) and careful informed consent for treatment remain essential.

Need

There is little doubt that advances in the treatment of this disease are needed. Since the addition of paclitaxel to standard therapy in the early 1990s, there have been no major practice changing developments in ovarian cancer therapeutics.

Apart from standard treatment combining chemotherapy and surgery, there are currently no proven therapies that can prolong overall survival in this patient population.

Quality of life data from the ICON 7 and GOG-218 trials suggest that the drug is generally well tolerated, and does not measurably erode patient quality of life.

The magnitude of the clinical benefit is significant, providing a median of 9.4 months, or a difference in restricted mean survival times of 4.8 months, of overall survival over the control group in the high-risk for progression subgroup in the ICON7 trial. Withdrawals from the trial were rare (3%) and no patients were reported to be lost to follow up. At this time, no other treatment beyond chemotherapy has demonstrated an improvement in OS in the first-line treatment setting, although trials are ongoing in patients known to be carriers of a BRCA mutation.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to bevacizumab given at 7.5 mg/kg with cycles 2-6 of standard 3-weekly carboplatin- and paclitaxel-based first line chemotherapy, and as maintenance treatment for up to 12 additional 3–weekly cycles in the treatment of advanced stage, high-risk for progression, ovarian cancer (stage III with > 1cm of residual disease, stage IV disease, or unresectable disease). This is based on a large subgroup analysis of a multicenter, randomized controlled trial (ICON7, with 1528 participants, of which 502 belonged to the subgroup of interest) that demonstrated a clinically meaningful improvement in overall survival in favour of the bevacizumab arm. A second randomized phase III trial, also demonstrated a clinically and statistically significant benefit on PFS for the subgroups of patients with a) stage III cancer and residual disease following primary surgery and b) stage IV cancer who were treated with bevacizumab (given concurrently with standard chemotherapy and in the maintenance setting for up to 12 months) when compared to standard chemotherapy alone. Serious adverse events, such as fistulae, GI perforation, and thrombosis were more commonly observed with the use of bevacizumab, but were still relatively rare (<4%).

The Clinical Guidance Panel also considered that from a clinical perspective:

- There is uncertainty regarding the use of bevacizumab in patients treated with neo-adjuvant chemotherapy who then go on to interval debulking surgery, as this patient population was excluded from these studies.
- Careful patient selection (e.g., good performance status, i.e., ECOG 0-2; no evidence of bowel obstruction; >4 weeks from the time of surgery) and careful informed consent for treatment remain essential.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Gynecologic Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Ovarian cancer is the eighth leading cause of cancer in Canadian women and fifth leading cause of cancer death[1]. Unfortunately, the death rate is high as most women present with advanced staged disease. According to the Canadian Cancer Society, in 2014 2,700 women in Canada will develop ovarian cancer which is approximately 11 per 100,000 (age standardized rate). Approximately 1,750 women will die as a result of this disease for a mortality rate of 6.4 per 100,000 women[1].

The most common forms of ovarian cancer, originate from epithelial cells of the fallopian tube, peritoneum, or the ovary. Thus, when the term 'ovarian cancer' is used, it is referring to all three possible origins of this disease. Ovarian cancer is also a term used to describe a histologically heterogeneous disease, with 5 common histotypes constituting the majority of cases: 1) high grade serous carcinoma (HGSC), 2) Endometrioid Carcinoma (EC), 3) Clear cell carcinoma (CCC), 4) Low grade serous carcinoma (LGSC), and 5) mucinous carcinoma (MC). All five histotypes have distinct clinical presentations and behavior, molecular signatures and, likely, cellular origins.[17]

Ovarian cancer is most common in the peri- or postmenopausal women. Screening strategies applied to well women, using regular ultrasound and/or CA125 testing have been assessed. Unfortunately these have not been found to be effective in diagnosing early stage ovarian cancer when the prognosis is still good[2]. The majority of patients still present with advanced, metastatic disease.

Approximately 15-20% of women diagnosed with non-mucinous epithelial ovarian cancer have a mutation in the BRCA 1 or 2 gene. Prophylactic removals of the fallopian tubes and ovaries has been shown to be effective in decreasing the risk of ovarian/tubal/primary peritoneal cancer and breast cancer in family members who are subsequently tested and known to carry a BRCA 1 or 2 mutation[20].

3.2 Accepted Clinical Practice

Women diagnosed with metastatic/advanced ovarian cancer are frequently treated with a combination of surgery to resect as much disease as possible (hysterectomy, bilateral salpingo-oophorectomy, omentectomy, tumour debulking) and chemotherapy (combination of a platinum and a taxane). Outcomes appeared similar with either surgery followed by chemotherapy or neoadjuvant chemotherapy with interval surgery[21]. Although initial response to treatment is very good, 5 year survival rates are poor (5-yr survival 44%)[22]. In other words, 70% of women will relapse with this disease and ultimately die of their disease.

Treatment options

The use of intravenous (IV) or intraperitoneal (IP) chemotherapy has shown prolongation of the median survival (HR 0.81, 95%CI 0.72-0.90); however, the included population is limited to those who have minimal or no residual disease after upfront surgery[23]. Weekly dose-dense paclitaxel has also been evaluated with mixed results[24].

More recently the benefits of anti-angiogenic agents (i.e., bevacizumab) in upfront treatment of women with advanced ovarian cancer have been evaluated in combination with chemotherapy and in maintenance phase.[5]

Bevacizumab

Bevacizumab is a monoclonal antibody which targets VEGF receptors. Bevacizumab has shown favourable results in several randomized trials in women with recurrent ovarian cancer. [25, 26]

More recently bevacizumab was evaluated concurrently with chemotherapy followed by a maintenance phase. ICON 7 (International Cooperative Group Neoplasia) was a 2 arm RCT of carboplatin and paclitaxel every 3 weeks versus the addition of bevacizumab 7.5 mg/kg during chemotherapy and maintenance for 12 cycles or until disease progression [9]. The trial included 1528 eligible women with Stage I or IIA clear cell or grade 3 histology, or Stage IIB-IV ECOG 0-2 ovarian cancer. The majority (~69%) had HGSC. At 36 months, the PFS was 20.3 months versus 21.8 months for bevacizumab arm (HR for progression or death 0.81, 95%CI 0.70-0.94, p=0.0041). The interim analysis showed no survival difference between the two arms (58.6 versus 58.0 months, HR 0.99, p=0.85). A preplanned subgroup analysis showed that PFS in stage IV and suboptimally debulked stage III women was 5.4 months. Survival was also better in this subgroup if they received bevacizumab (OS 36.6 months versus 28.8 months, HR 0.64, 95%CI 0.48-0.85, p=0.002). Adverse events in ICON 7 were similar to GOG-218 with rates of hypertension, proteinuria, thromboembolic events and GI perforations being higher in the bevacizumab arm.

GOG-218 was a 3 arm randomized controlled trial (RCT) where all of the treatment arms received paclitaxel and carboplatin. The second and third arms also received bevacizumab at 15 mg/kg. In the second arm, bevacizumab was given for 6 cycles during the chemotherapy treatment (initiation), and the third arm bevacizumab was given for the 6 initial cycles during the chemotherapy treatment and an additional 16 cycles, or until disease progression, after chemotherapy (maintenance). Women with Stage III incompletely resected or Stage IV epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer were included in the trial (N=1873). Approximately 85% of patients had HGSC. Progression-free survival (PFS) was superior in the bevacizumab arm compared to placebo (14.1 months bevacizumab during and after chemotherapy versus 11.2 months in bevacizumab during chemotherapy versus 10.3 months, HR 0.717, p<0.0001). Bevacizumab exposure during chemotherapy only gave a HR 0.908 (95% CI 0.795-1.040, p=0.16) for progression or death compared to bevacizumab through chemotherapy and maintenance (HR 0.717, 95%CI 0.625-0.824, p<0.001). There was no difference in overall survival 39.7 versus 39.3 months (p=0.450) respectively. Maximum curve separation was at 15 months around the completion of the bevacizumab in the maintenance arm. The survival curves converged at 24 months possibly due to the off study use of bevacizumab at recurrence. Quality of life (QOL) was assessed using the Functional Assessment of Cancer Therapy – Ovary (FACT-O) scale just before treatment and on days 4, 7, 13, 22 and then 6 months after completing the study. QOL Scores in the bevacizumab group were slightly lower during chemotherapy compared to the control. Adverse events including hypertension which led to drug discontinuation in 2.4%.

These 2 trials showed the benefits of bevacizumab use during and after chemotherapy as part of a maintenance strategy especially on the PFS but not the OS. This benefit was most profound in the women with a higher burden of disease. Of note, these two trials differed in their eligibility criteria, the investigational arm, drug dosing, and treatment duration.

ROSiA is an on-going global single arm study designed to assess the safety profile and efficacy of adding bevacizumab to carboplatin and paclitaxel in women with advanced ovarian, fallopian tube or peritoneal cancer (N=1000). The bevacizumab was given until disease progression (i.e., up to 36 cycles)[10].

Summary

Epithelial ovarian cancer tends to affect women in their reproductive years (at an age 10 years younger than the age that other cancers affect the population). With the poor overall survival seen with the use of standard combination chemotherapy, there is interest in access to agents which prolong survival. Bevacizumab provides such an opportunity when added to combination chemotherapy and as maintenance treatment.

3.3 Evidence-Based Considerations for a Funding Population

The currently available evidence supports the use of bevacizumab for women with the following criteria:

Women with upfront surgery and stage III suboptimally debulked or unresectable or stage IV ovarian cancer at the start of systemic treatment. The data do not examine the interaction of histotypes with treatment benefit.

Women are not eligible for treatment with bevacizumab if they have uncontrollable hypertension (BP greater than 150/90), planned interval debulking surgery, granulating wounds (i.e., fascial dehiscence, fistula), recent surgery or radiation (within 8 weeks), traumatic injury (within 4 weeks), bowel obstruction, ASA use of higher than 325mg/day in the last 10 days, tumour involving major blood vessels, active bleeding or known bleeding disorder or coagulopathy, active hepatitis, abnormal urine protein (higher than 1gm per 24hr), heart disease (New York heart classification 2-4),or peripheral vascular disease (grade 2 or higher).

3.4 Other Patient Populations in Whom the Drug May Be Used

This submission addresses the first line use of bevacizumab in women with bulky advanced ovarian cancer and does not address use of bevacizumab in women with recurrent ovarian cancer who have previously not been exposed to bevacizumab.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Ovarian Cancer Canada (OCC), provided input on bevacizumab (Avastin) 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), and their input is summarized below.

OCC conducted an anonymous online survey which was promoted to women diagnosed with Stage III and IV ovarian cancer and their caregivers through the organization's database, website, social media sites and partners. OCC reported receiving responses from 76 patients with ovarian cancer (Stage III and IV) and 5 caregivers. Of the total 81 respondents, the majority of respondents had been diagnosed with ovarian cancer between 2010-2014. The sample included 10 respondents with fallopian tube cancer, 11 respondents with primary peritoneal cancer and 7 respondents who designated their ovarian cancer as 'other'. Respondents ranged in age from 28 – 76 years, and approximately 79% of respondents were 50 years and older. Responses were predominantly received from Canadian respondents, but there were no respondents from New Brunswick, Newfoundland, Prince Edward Island, Northwest Territories, Nunavut or the Yukon. There were also eight (8) respondents from the United States. A total of six (6) respondents indicated that they had experienced with bevacizumab for first-line treatment. Of the respondents who had not used bevacizumab as first-line treatment, it was reported that 62.5% of respondents had at least one if not multiple recurrences. Of those who had used bevacizumab as first-line treatment, it was reported that 50% of respondents had two or more recurrences.

From a patient perspective, the impact of ovarian cancer is significant for women diagnosed with this disease and their caregivers. Because early symptoms can be non-specific and generally there is no screening test, ovarian cancer is usually detected in its later stages resulting in a grim prognosis. Surgery and chemotherapy have been the mainstays of first line treatment; however, as most women are likely to face a recurrence, OCC believes it is helpful to have a greater spectrum of agents with which to treat this type of cancer. OCC reported that six (6) respondents had direct experience with bevacizumab as a first-line treatment. Three (3) respondents had recurrence with their ovarian cancer; two (2) respondents recurred twice, one (1) respondent recurred more than 3 times. The primary treatment side effects of bevacizumab included fatigue, bowel problems, neuropathy, hair loss and nausea, which were found to be similar in the larger non-bevacizumab group. It was also reported there was a slightly higher indication of high blood pressure in the bevacizumab group than the group that did not take bevacizumab; however, it was noted by OCC that the sample size in the bevacizumab group is small.

Please see below for a summary of specific input received from the patient advocacy group. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission and have not been corrected.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Ovarian Cancer

OCC reported that the impact of ovarian cancer is substantial for women diagnosed with this disease and their caregivers. The impacts are severe for the following reasons. Firstly, most women are diagnosed in late stages when their prognosis is grim; secondly, there are few effective treatments; and finally, recurrence is expected.

Respondents were asked to describe overall how their life has been affected by their diagnosis of ovarian cancer. Respondents (n=28/55) reported that they were deeply affected by the fatigue from the disease and treatment. Many described the significant psycho-social impacts, including fear, depression, worry and anxiety. Other negative impacts also included, but were not limited to, hardship in family life, cognition, sleep, loss of fertility, sexual intimacy, and activities of daily living. Some of the key responses recorded were as follows:

- *"My life has been totally shattered with diagnosis."*
- *"My main issue is the constant fear of recurrence. It is with me every day."*
- *"I have not returned to work and experience a lot of anxiety."*
- *"Biggest post cancer symptom is stress as there is no cure and no effective treatments for ovarian cancer."*
- *"My whole life changed when I was diagnosed with ovarian cancer – I had a promising career with an amazing job that I eventually was let go from because my long term benefits ran out and I was still unable to work. I have a young daughter who has had her world thrown upside down; I used to be confident and hold myself in high regard…When my benefits ran out, my family was financially unable to keep up with everything so we had to sell our house and move in with my parents….this rocked both myself and my husband to my core. Cancer changed our entire lives and has robbed us from a lot of years."*
- *"I just get feeling better and then boom recurrence. Due to where the tumour was I am afraid to have sex to restart it. It has upset my kids' lives and needed counselling along with my husband having a mental break down."*

Respondents were also asked to rate the impact of ovarian cancer on their lives on a scale from 1 (no effect) to 5 (extremely negative effect). According to OCC, the question was rated a score of 2 or above by all respondents, indicating an impact on all aspects of their lives. Below were the specific areas where respondents (n=55) rated a score of 4 (very negative) or 5 (extremely negative):

- Sexual relationship = 34
- Work life = 32
- Physical activity = 24
- Sleep pattern = 22
- Level of well-being = 21
- Spiritual life = 16
- Self-esteem = 13
- Family/friend relationships = 12
- Ability to care for family = 7
- Ability to care for oneself = 4

According to OCC, the impact of ovarian cancer on these respondents' lives appeared to be similar between women who did and did not have experience with bevacizumab as first-line treatment.

4.1.2 Patients' Experiences with Current Therapy for Ovarian Cancer

OCC reported that 61 respondents responded to the question on their current therapy. Nine (9) respondents were treated with surgery, seven (7) respondents had chemotherapy and 59 respondents reported receiving both for their front-line treatment (*Note: numbers of responses reflect duplicate responses that were reported*). While it was reported overall that their original treatment had helped to manage their cancer (based on a mean rating of 3 out of 5); OCC

indicated that some comments noted below may demonstrate that their treatment was not as effective as the score would suggest.

- *"The treatment did not control my cancer. It recurred after 9 months…"*
- *"The recurrences discourage me as there seems to be so little available for the treatment of ovarian cancer."*

According to the respondents, their ovarian cancer treatments negatively affected them. Respondents were asked to rate the effect of treatments they received on a scale from 1 (no effect) to 5 (extremely negative effect), on aspects of their life. Respondents (n=51) reported on a number of areas that were rated as having a negative influence on their lives. The areas that the respondents, including caregivers rated as a score of 4 (very negative) or 5 (extremely negative) are noted below:

- Fatigue = 32
- Hair loss = 27
- Neuropathy = 26
- Bowel problems = 21
- Aching joints = 20
- Nausea/vomiting = 15
- Ascites = 10
- Blood problems = 9
- Loss of fertility = 7
- Skin irritations = 5
- High blood pressure = 3

A majority of respondents indicated that fatigue was a major impact. Specifically, 63% of respondents rated their fatigue as having a large effect or extremely large effect on their quality of life.

- *"Fatigue has had the biggest effect. Most days I'm just tired and can't get through the day."*
- *"I am a mother of two and it (ovarian cancer treatment) affected my life in so many ways…my energy level has been cut in half from what it was before."*

Many respondents also commented on the impact of neuropathy.

- *"After 3 years still have neuropathy in hands and feet."*
- *"Tingling pain in fingers and wrists woke me up at night."*

Another key area of impact that was mentioned included bowel issues.

- *"Bowel problems are an ongoing daily concern…"*
- *"…constipation and 'gut infection'…."*
- *"Bowel problems required emergency temporary ileostomy."*

In addition to the above, ascites was also mentioned by those not using bevacizumab as first-line treatment. One respondent stated: *"With my ascites, I was vomiting on a daily basis."*

According to OCC, 11 respondents experienced a reduced ability to deal with activities of daily living.

- *"Can no longer work, treatments have interfered with my ability to think/concentrate which was an integral part of my work."*
- *"My routines have changed only do important every day functions."*

- *"I have trouble memorizing things sometimes…"*

Respondents who had not taken bevacizumab as first-line treatment were asked if they would be willing to tolerate additional side effects if the benefits of the treatment were considered to be short term (e.g. months vs. years of improvement). Out of 46 respondents, 24 respondents answered "yes", 3 respondents answered "no" and 19 respondents were "uncertain".

- *"I would think any ovarian cancer sufferer would do anything to prolong life including tolerate side effects. I would."*

Respondents were asked about the barriers to accessing treatments (e.g. financial difficulties, travel issues, treatment not available in your province/state). According to OCC, respondents (n=43) indicated the following top key barriers as follows:

- Travel = 10
- Finances = 8
- Treatment not available = 5
- Wait time = 1

4.1.3 Impact of Ovarian Cancer and Current Therapy on Caregivers

OCC reported that five (5) caregivers responded to this survey: 2 respondents were a spouse/partner; 1 respondent was a child; and 2 respondents were other family members. OCC indicated that these caregivers have been providing care from one to more than five years for women with Stage III or IV ovarian cancer for 3 – 6 hours most days. All of the patients they cared for had experienced with recurrence. Caregivers reported anxiety, stress and fatigue as being the most significant negative impact, followed by feelings of isolation, sleep issues, diet, physical strain and depression.

Respondents were asked to describe how their life has been affected by ovarian cancer; for instance, to describe how the daily routines, physical functioning, mental state, overall life etc. have been affected. Some of the responses included:

- *"I have dedicated much of my time to determining optimal treatments and dealing with the inadequacies of the cancer system."*
- *"My sister (20 months younger than me) was diag. with late stage III OC one week before her 52nd birthday. We were as close as twins. It changed my life in ways I NEVER wanted to be changed. Th (sic) grieving started with the diagnosis. The impact is horrific. Life as I knew it, would never be the same."*
- *"…fatigued most days - feelings of anger, frustration with health care/diagnosis - feelings of distress when related to the patients inability to cope with physical and emotional manifestations of the disease process."*

All five (5) caregivers indicated that the patients they were caring for did not take bevacizumab as first line treatment for ovarian cancer. Four (4) respondents strongly disagreed that the current treatments managed their loved one's ovarian cancer; on a scale of 1-5, they rated the current treatment's ability to manage the woman's ovarian cancer as a 1, as being no effect. Fatigue was reported to be the most troublesome side effect affecting the patient's quality of life. All respondents thought the person for whom they are providing care would be willing to tolerate additional side effects if the benefits of the treatment were considered to be short term (e.g. months vs. years of improvement).

Caregivers were asked if the patient that they are providing care for was to take bevacizumab, which issues would be important for the treatment to address. The caregivers felt that the drug

should prolong survival, shrink the tumour size, improve quality of life and decrease the fluid build-up.

Caregivers were asked if they thought bevacizumab should be available to patients living with ovarian cancer as first line treatment. All believed it should be available, and their responses are noted below.

- *"It is an outrage that women with ovarian cancer must endure multiple cycles of platinum and taxol, and the damage caused by them when there are targeted therapies like Avastin that could be made available. The targeted therapies such as Avastin are substantially less harsh than standard treatments and can be more effective…for those for whom it doesn't work, it can be stopped and the expense will not be substantial. For those for whom it works, we owe it to them - it should not just be available for those with sufficient financial resources to pay the high price."*
- *"In our experience, the response when taking Avastin as a single agent was almost immediate. Within 3-6 weeks, it was possible to determine that it was working. It didn't just work - it worked dramatically - a number of tumors disappeared and some of those never came back. We were not happy about having to pay the high cost but there is no question - it is an excellent treatment for some ovarian cancers."*
- *"If there is a drug therapy with proven success for advanced stage ovarian cancer where other therapies or surgery has had limited success, why wouldn't we want to provide it as a first line treatment?? I saw the impact of repeated failed treatments (two surgeries, two types of chemotherapy, drug trial treatment) had on my sister's physical and mental state. If a first line treatment with success in advanced stage, treatment resistant ovarian cancer exists, it should be made available to reduce the suffering for cancer patients and their caregivers."*

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences to Date with Bevacizumab

43 respondents who have not been treated with bevacizumab as first-line treatment responded to the survey question on their expectation with the drug under review. The majority of respondents indicated that they would expect the drug to prolong their survival, shrink their tumour, improve their quality of life and reduce their ascites. Below were responses from respondents (n=43) who rated the question as a score of 4 (important) or 5 (very important):

- Prolong survival = 39
- Shrink tumour = 36
- Improve quality of life = 39
- Reduce ascites = 28

The majority of respondents would expect there to be some improvement in their ovarian cancer to consider taking it. 12% of respondents indicated they would consider taking it with *a little* improvement, and 30% of respondents would consider taking it with *modest* improvement in their ovarian cancer. According to OCC, respondents gave this question a rating of 3.91 (out of 5), with 1 being no improvement to 5 being no sign of ovarian cancer.

The majority of respondents were willing to deal with many side effects. The specific side effects that respondents (n=43) were willing to deal with are indicated below:

- Fatigue = 41

- Nausea/poor appetite = 33
- Constipation/diarrhea = 33
- Numbness = 28
- High blood pressure = 21
- Increased risk of bleeding = 20
- Blood problems = 20
- Heart problems = 12

42% of respondents indicated that they would be willing to tolerate the side effects because they want to improve their chance of survival. According to OCC, almost half of the respondents noted that the side effects seemed manageable as there were no notable differences in comparison to their chemotherapy side effects.

- *"If there is a drug that has shown promise in being able to shrink my tumour growth and prolong my life, I would be willing to put up with these side effects. I've had to put up with these side effects with relatively no benefit thus far."*

67% of respondents expect bevacizumab to be effective in prolonging life, controlling the cancer and keeping the cancer in remission.

The majority of the respondents believe that bevacizumab should be available to women diagnosed with ovarian cancer as a first line treatment. Below were some of the responses that were noted:

- *"When you are faced with a diagnosis of advanced stage ovarian cancer, you want all options open to you. I am on an ovarian cancer forum on the internet, and have many American women having some degree of success with Avastin. If there are drugs out there that may be beneficial, they need to be available to all."*
- *"Every woman diagnosed with OC deserves every possible treatment, not just for them but for their family and friends. There hasn't been much progress in our care, Avastin seems so promising, side effects and all."*
- *"I have endured treatments which have almost no proven benefit- but since there has been no new developments on drugs (outside of trial drugs which I have been excluded from) my options are limited. If there is a drug which has a hope of showing promise I would take it in a heartbeat."*

OCC reported that six (6) respondents had direct experience with bevacizumab as a first-line treatment. Three (3) respondents had recurrence of their ovarian cancer; two (2) respondents recurred twice, one (1) respondent recurred more than 3 times. The primary treatment side effects of bevacizumab included fatigue, bowel problems, neuropathy, hair loss and nausea, which were reported to be similar to the larger non-bevacizumab group. In addition, it was noted there was a slightly higher indication that high blood pressure was found in the bevacizumab group compared to the group that did not take bevacizumab, but it was noted that the sample size in the bevacizumab group is small.

The six (6) respondents were asked to rate the extent to which they agreed or disagreed with the following statement: "*My initial treatments for my cancer are (were) able to manage my cancer*." The responses were rated as follows:

- Strongly disagree = 1
- Neither agree nor disagree = 3
- Strongly agree = 2

These respondents (n=6) were also asked as to which factors have the most impact in the initial treatment for ovarian cancer. Responses were recorded as follows:

- Fatigue = 4
- Shrunk tumour size = 3
- Prevented a recurrence = 3
- Prolonged survival = 3
- Fluid build-up = 2
- Improved my prognosis = 2

One respondent noted the positive impact that bevacizumab had on her ascites:

- *"…recently suffered from severe ascites and was having up to 14 litres of fluid drained per week. One treatment of Avastin fully dried up all fluid drained for the last 4 weeks."*

In addition to the above, some of the other responses included:

- *"Treatments stopped cancer growth and spread. Side effects were manageable."*
- *"Shrunk cancer but came back."*

In terms of the side effects with bevacizumab, one respondent indicated that all were acceptable, while one respondent indicated that none were acceptable. A few respondents noted that the following were acceptable side effects: hair loss, neuropathy, nausea, headaches and fatigue. One respondent stated: *"I'm ok with them all as I am alive."*

Two respondents highlighted the side effect of high blood pressure specifically, noting:

- *"High blood pressure was easy enough to manage, with one tiny pill per day."*
- *"The HBP I don't notice."*

Three respondents noted the bowel issues as being not acceptable. Some of the comments include:

- "*All of the side effects stink!"*
- *"You have to accept them. No real choice."*

Regarding barriers, respondents (n=2/6) mentioned finances, and one respondent indicated travel was an issue.

All six respondents indicated that bevacizumab should be a treatment option for women diagnosed with stage III or stage IV ovarian cancer. Reasons given included:

- *"It has shown to be succesful (sic) in many patients even with its cautions."*
- *"It keeps the new tumors from growing as chemo destroys the old ones. No pre-meds needed." "Easy to tolerate."*
- *"It works."*
- *"Avastin kept my numbers low. As soon as I stopped I recurred. I am currently trying again."*
- *"Because the research studies show that women who receive Avastin do better, and survive longer, and I'm living proof of that. Every woman deserves the best chance possible of having a great outcome!"*

4.3 Additional Information

Ovarian Cancer Canada indicated that the low number of respondents (6) who have experienced with bevacizumab should not be deemed as a reflection of the lack of interest

of women living with ovarian cancer to provide feedback on a new treatment. In Canada, there have not been significant numbers of women who have taken bevacizumab as front line treatment for ovarian cancer. Further, the women targeted in this survey are living with metastatic disease, and many may be too ill to participate in a survey of this kind.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca). PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of bevacizumab for ovarian cancer:

Clinical factors:

- The addition of bevacizumab to existing chemotherapies may have additional benefits for certain subgroups of patients.
- Clarification of the most appropriate dose.

Economic factors:

- Small patient population.
- High cost of bevacizumab.

Health System factors:

- Additional resources required to monitor and treat adverse effects.

Please see below for more details.

5.1 Factors Related to Comparators

The current standard of care for metastatic ovarian cancer in most of the provinces is a platinum-based product (i.e. carboplatin or cisplatin) plus paclitaxel and this was the comparator in the clinical trial.

5.2 Factors Related to Patient Population

PAG indicated that this would be a relatively small patient population. The addition of bevacizumab to existing chemotherapy may have additional benefits for certain subgroups of patients. These are enablers to implementation.

5.3 Factors Related to Dosing

PAG noted that the dosing schedule is the same as the existing chemotherapy and that there is no dose adjustments associated with bevacizumab.

PAG would like information on which is the best dose or the most appropriate dose, as the dose in the ICON 7 trial is 7.5mg/kg whereas the dose is 15mg/kg in the GOG218 trial.

5.4 Factors Related to Implementation Costs

There is some concern with drug wastage, although PAG noted that bevacizumab is already funded for metastatic colorectal cancer and vial sharing with this larger patient population can minimize drug wastage in larger cancer centres. Vial sharing is not always possible in smaller outreach centres.

PAG noted that patients already being treated may wish to add bevacizumab to their treatment.

5.5 Factors Related to Health System

PAG noted that bevacizumab is already being used for other tumour sites and there is familiarity amongst health care providers with the preparation, administration and monitoring. The addition of bevacizumab to the current chemotherapy will increase preparation and administration times, although the 30 minute infusion time for bevacizumab is fairly short relative to the infusion times for paclitaxel and the platinum-based product. However, there is additional monitoring for adverse events that is new to this patient population and the higher dosage may lead to more adverse events requiring supportive treatment and additional health care resources.

5.6 Factors Related to Manufacturer

The high cost of bevacizumab would be a barrier to implementation.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effectiveness and safety/toxicity of bevacizumab when used in combination with paclitaxel and carboplatin for the front-line treatment of patients who have undergone upfront surgery for epithelial ovarian, fallopian tube or primary peritoneal cancer and who have a high risk of relapse (stage III sub-optimally debulked, or stage III unresectable, or stage IV patients).

No Supplemental Questions relevant to the pCODR review or to the Provincial Advisory Group (PAG) were identified.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table # 1. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Randomized Controlled trials	Patients who have undergone upfront surgery having front-line 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)	Bevacizumab AND Carboplatin + paclitaxel	Platinum (carboplatin or cisplatin) in combination with a Taxane (paclitaxel or docetaxel) OR Platinum (carboplatin or cisplatin) in combination with a Taxane (paclitaxel or docetaxel) AND Monoclonal antibody	**Overall survival,** progression free survival, **grade 3-4 adverse events**, withdrawal due to adverse events, infusion reactions, hematologic adverse events (e.g., tumour-associated hemorrhage, severe neutropenia), febrile neutropenia, infections, non-hematologic adverse events, **fatigue**, **hypertension**, cardiac events, venous thromboembolism, thrombophlebitis,

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
				heart failure, proteinuria, wound healing, neuropathy, gastrointestinal perforations (GI Fistula), **bowel problems**, nausea, ovarian failure, treatment related deaths, and **quality of life**
GI-Gastrointestinal				

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-March 2015) with in-process records & daily updates via Ovid; EMBASE (1980-March 2015) via Ovid; the Cochrane Central Register of Controlled Trials (2010, Issue 2) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Bevacizumab (Avastin) and Ovarian Cancer.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year. Retrieval was limited to the English language.

The search is considered up to date as of March 5th, 2015.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health - clinicatrials.gov and Ontario Institute for Cancer Research - Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and ESMO were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team

independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review (December 29th, 2014).

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

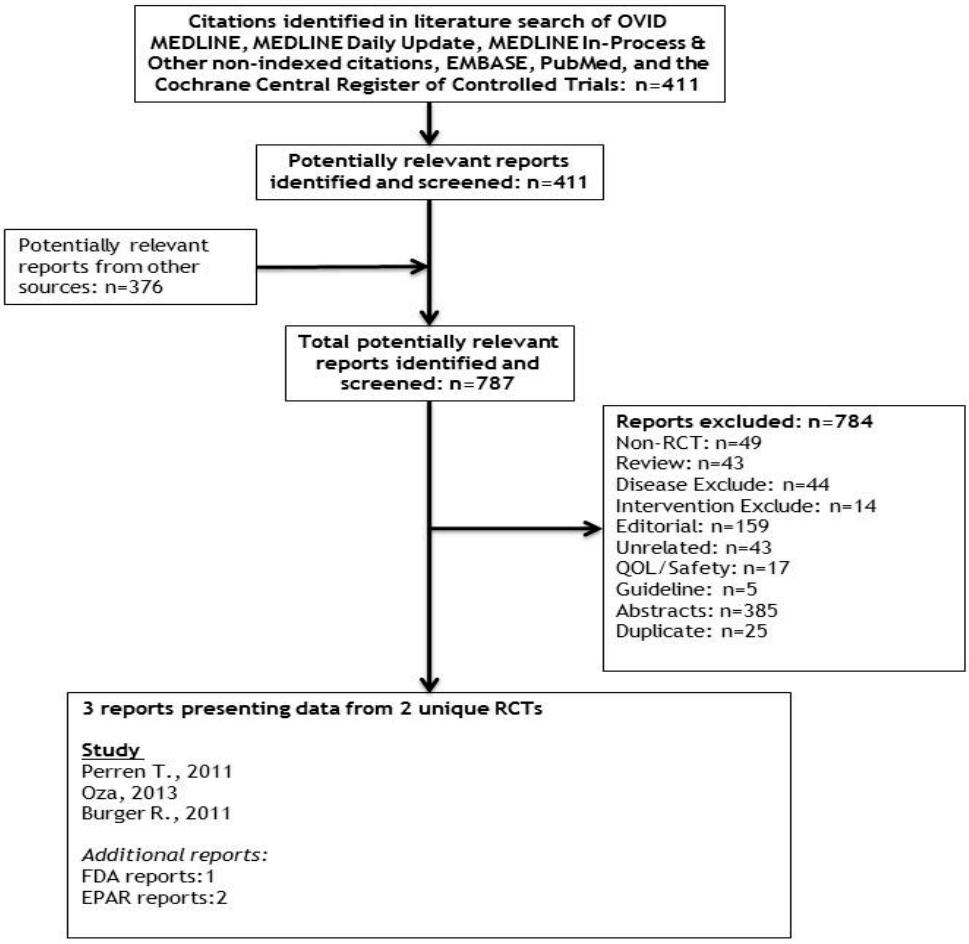
6.3 Results

6.3.1 Literature Search Results

Of the 787 potentially relevant reports identified, 2 studies were included in the pCODR systematic review[3, 4] ; 202 reviews and editorial articles, 5 guidelines, as well as [577] other studies were excluded. Studies were excluded because they were abstracts, were ineligible study design, were unrelated disease type/area, or did not contain eligible intervention.

Figure 1. Quorum Diagram

QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

Two randomized trials met the inclusion criteria and were selected for inclusion. ICON 7[3] is an open-label, 2 arm trial that examined carboplatin plus paclitaxel (carbo-pac) versus carboplatin plus paclitaxel plus concurrent bevacizumab followed by bevacizumab maintenance (carbo-pac-bev) in patients who have undergone surgery and had histologically confirmed, high-risk, early-stage disease (International Federation of Gynecology and Obstetrics [FIGO] stage I or IIA and clear-call or grade 3 tumors) or advanced (FIGO stage IIB to IV) epithelial ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer (based on local histopathological findings). High risk, early stage patients were restricted to 10% of total enrollment.

GOG-218[4] is a blinded placebo design with 3 arms that examined carboplatin plus paclitaxel (carbo-pac)versus carboplatin plus paclitaxel plus concurrent bevacizumab (carbo-pac-bev) versus carboplatin plus paclitaxel plus concurrent bevacizumab followed by maintenance bevacizumab (carbo-pac-bev-maintenance) in patients with newly diagnosed stage III (incompletely resectable) or stage IV epithelial ovarian cancer who had undergone debulking surgery) Optimally debulked stage III patients needed to have macroscopic residual disease.

Further information was also available from EPAR reports, information that comes from the trials noted above but that is not found in the primary publication. Even further information was found in the assessment reports completed by the FDA.

6.3.2.1 Detailed Trial Characteristics

Table 2. Summary of Trial characteristics of the included Study

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
ICON 7, 2011[3] Two arm, open label, randomized Control trial N=1528 Funded by: Hoffman LaRoche	Patients who have undergone initial surgery and who have: • High risk early-stage disease (FIGO I or IIA and clear cell or grade 3) Restricted to 10% of the total study • Advanced disease (FIGO stage IIb to IV) 73% optimally debulked • ECOG performance status 0 to 2	Carboplatin (area under the curve of 5 or 6) plus paclitaxel (175 mg per square meter of body-surface area), given every 3 weeks for 6 cycles (standard-chemotherapy group). **VS.** Carboplatin (area under the curve of 5 or 6) plus paclitaxel (add does) plus bevacizumab (7.5 mg per kg of body weight), given concurrently every 3 weeks for 5 or 6 cycles and continued for 12 additional cycles or until disease progression (Bev group)	Primary: Progression-free survival and overall survival. Secondary: response to therapy, toxicity, and quality of life.
Trial Design	**Key Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
GOG-218, 2011[4] Three arm, open label, randomized Control trial N=1800 Funded by: National Cancer Institute and Genentech	All patients undergoing standard abdominal surgery • included previously untreated, incompletely resectable stage III or any stage IV epithelial ovarian, primary peritoneal, or fallopian-tube cancer histologically confirmed by the Gynecologic Oncology Group (GOG) Pathology Committee after standard abdominal surgery with maximal debulking effort within 12 weeks before study entry • GOG performance status score of 0 (fully active) to 2 (ambulatory and capable of self-care but unable to work • up and about more than 50% of waking hours • no history of clinically significant vascular events or evidence of intestinal obstruction. • Optimally debulked stage III patients needed to have macroscopic residual disease. • Patients with bowel obstruction, pSBO excluded	Carboplatin (area under the curve of 6) plus paclitaxel (175 mg per square meter of body-surface area) by intravenous infusion on day 1, every 3 weeks for cycles 1-6, followed by placebo for cycles 2-22. **VS.** Carboplatin plus paclitaxel (administered as in control arm above) every 3 weeks for cycles 1-6, plus bevacizumab during initial treatment (15 mg per kg of body weight) added in cycles 2 - 6, followed by placebo in cycles 7-22. **VS.** Carboplatin plus paclitaxel (administered as in control arm above) every 3 weeks for cycles 1-6, plus bevacizumab throughout (15 mg per kg of body weight) every 3 weeks for cycles 2-22.	Primary: PFS, OS, Secondary: Safety, QOL
OS=overall survival; PFS=progression-free survival; QOL=quality of life.			

a) Trials

Two randomized control trials were found for this review.[3, 4] ICON 7[3]is a two arm, open label comparative superiority trial. Patients were randomized on a 1:1 basis performed centrally using an interactive telephone or Web-based system, with stratification according to GCIG group, FIGO stage and residual disease (i.e., FIGO stages I to III and ≤1 cm of residual disease, stages I to III and >1 cm of residual disease, or stage III [inoperable] or IV), and planned interval between surgery and initiation of chemotherapy (≤4 weeks or >4 weeks). Primary outcomes for the trial were PFS and OS. Progression was defined as date of randomization to the date of the first indication of disease progression or death, whichever occurred first.

GOG-218[4] is a three arm trial in which patients were randomized to CP + control, CP + Bev during initial therapy, and CP + Bev throughout therapy. Progression-free survival and overall survival were calculated from the date of enrollment. Progression-free survival was considered to have ended at the time of cancer progression as shown on radiography, according to the Response Evaluation Criteria in Solid Tumors criteria, or an increase in the CA-125 level according to Gynecologic Cancer InterGroup criteria, global deterioration of health, or death from any cause.

This study began as a blinded trial but following changes to primary outcomes investigators and clinicians were provided with treatment information to determine how to proceed following progression.

b) Populations

ICON 7 enrolled 1528 patients at 263 centers in the United Kingdom, Germany, France, Canada, Australia, New Zealand, Denmark, Finland, Norway, Sweden, and Spain. Treatment groups were well balanced with respect to baseline characteristics. The median age was 57 years, and 94% of the patients had an ECOG performance status of 0 or 1; 90% had epithelial ovarian cancer; 9% had high-risk early-stage disease; 30% were at high risk for progression; 21% had FIGO stage III, IIIA, or IIIB disease; 70% had FIGO stage IIIC or IV disease; 69% had a serous histologic type; and 26% had more than 1.0 cm of residual disease after surgical debulking.[3] In 2011, Perren et al reported results for OS and PFS for a subgroup of patients with a high risk of progression (defined as stage III disease with >1 cm of residual disease following primary cytoreductive surgery, or patients with stage IV disease, N=465).[3] In 2013, Oza et al reported updated results of OS for a modified subgroup of patients with a high risk of progression. The modified subgroup included an additional 37 patients (N=502) and was defined in the same way as the original subgroup except that non-operated patients were also included, as they were felt to have a high risk of progression. [16] The 2011 subgroup analysis will be further referred to as the "original high risk for progression subgroup" and the 2013 modified subgroup analysis will be referred to as the "modified high risk for progression subgroup."

GOG-218 enrolled 1873 women in 336 institutions in the United States, Canada, South Korea, and Japan.[4] Eligibility criteria were broadened in July 2007 to include patients with stage III disease and no residual lesions greater than 1 cm. At this time a total of 467 patients had enrolled. In October 2008 the primary end point was changed to progression-free survival and at this point 1299 patients had enrolled. A total of twenty nine patients were determined to be ineligible following enrollment, due to tumor characteristics. These patients were included in analysis.[4]

Table 3. Patient Characteristics GOG-218

	Control	**Carbo-pac-bev**	**carbo-pac-bev-maintenance**	**All Patients**
	(n = 625)	(n = 625)	(n = 623)	(n = 1873)
Disease Stage				
Stage III optimally debulked	219 (35.0%)	204 (32.6%)	216 (34.7%)	639 (34.1%)
Stage III sub optimally debulked	253 (40.5%)	256 (41.0%)	242 (38.8%)	751 (40.1%)
Stage IV	153 (24.5%)	165 (26.4%)	165 (26.5%)	483 (25.8%)

EPAR[5]

Table 4. Patient Characteristics ICON 7

FIGO Stage	**Carbo-pac*(Control)* n=(764)**	**Carbo-pac-bev *(n=764)***
IA	16 (2%)	15 (2%)
IB	5 (<1%)	5 (<1%)
IC	44 (6%)	34 (4%)
IIA	10 (1%)	13 (2%)
IIB	30 (4%)	21 (3%)
IIC	40 (5%)	49 (6%)
IIIA	32 (4%)	22 (3%)
IIIB	44 (6%)	45 (6%)
IIIC	432 (57%)	438 (57%)
III	14 (2%)	18 (2%)
IV	97 (13%)	104 (14%)

EPAR[5]

c) Interventions

In ICON 7 patients received carboplatin (area under the curve of 6) & paclitaxel (175 mg per square meter of body-surface area), given every 3 weeks for 6 cycles (standard-chemotherapy group), plus bevacizumab (7.5 mg per kilogram of body weight), given concurrently every 3 weeks for 5 or 6 cycles and continued for 12 additional cycles or until disease progression for the bevacizumab group. Progression-free survival was calculated from the date of randomization to the date of the first indication of disease progression or death, which ever occurred first. Disease progression was defined according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines on the basis of radiologic, clinical, or symptomatic indicators of progression and did not include isolated asymptomatic progression on the basis of CA-125 levels. [3]

More than 90% of the women in both groups received 6 cycles of chemotherapy (91% in the carbo-pac group and 94% in the carbo-pac-bev group). It was noted that patients starting chemotherapy greater than 4 weeks after initial surgery received a slightly higher median number of chemotherapy cycles than those who began chemotherapy < 4 weeks after surgery (17 vs. 16).[3]

In GOG-218 three study regimens comprised 22 3-week cycles with intravenous infusions on day 1, with the first 6 cycles consisting of standard chemotherapy with carboplatin at an area under the curve of 6 and paclitaxel at a dose of

175 mg per square meter of body-surface area. Control treatment (carbo-pac) was chemotherapy with placebo added in cycles 2 through 22; carbo-pac-bev was chemotherapy with bevacizumab (15 mg per kilogram of body weight) added in cycles 2 through 6 and placebo added in cycles 7 through 22. Carbo-pac-bev-maintenance treatment was chemotherapy with bevacizumab added in cycles 2 through 22 or until disease progression or unacceptable toxic effects. Bevacizumab or placebo was initiated at cycle 2, rather than cycle 1, to reduce the risk of wound-healing complications.

Nineteen percent of patients overall (16%, 17%, and 24% in the carbo-pac, carbo-pac-bev, and the carbo-pac-bev-maintenance group, respectively) completed the planned treatment, and 15% overall were still receiving treatment (in the extended-therapy phase) at the time of the database lock. [4]

d) Patient Disposition

Five deaths related to treatment or to treatment and disease were reported: one in the carbo-pac group (due to central nervous system ischemia) and four in the carbo-pac-bev group (one each from gastrointestinal perforation, intracerebral hemorrhage, recurrent bowel perforation and ovarian cancer, and neutropenic sepsis and ovarian cancer).[3]

Fatal adverse events were reported in 6 of 601 patients (1.0%) in the carbo-pac group, in 10 of 607 patients (1.6%) in the carbo-pac-bev group, and in 14 of 608 patients (2.3%) in the carbo-pac-bev-maintenance group.[4]

Neither study indicated these were high risk only.

e) Limitations/Sources of Bias

ICON 7

I. In ICON 7 non-proportional hazards were detected for progression free survival. In an updated overall survival analysis they were also identified. The Difference in restricted means was reported but no testing was completed that would determine statistically significant difference. Comparative testing should be interpreted with caution due to lack of information on hazard ratio analysis and general lack of information on testing for proportionality.

II. ICON 7 is an open label RCT. Being open label, there is no blinding of investigators or participants. This can lead to introduction of bias in investigators and reduces validity of trial results.

III. In ICON 7 Subgroups may not have been powered to detect differences. Information regarding subgroups should be used with caution in making conclusions about subgroup efficacy.

IV. There was no independent assessment of progression in PFS. This may have biased results in this trial.

GOG-218

I. In the GOG-218 study analysis of progression-free survival data for patients with increased CA-125 levels were removed from the analysis. This may reduce the hazard ratio of treatment arm versus control arm, increasing significance and influencing survival analysis.

II. Cross over from CP to CP Bev in GOG-218 did occur and therefore results of OS could be underestimating true effect. No information was available regarding the number of patients who crossed over to bevacizumab treatment.

III. GOG-218 changed eligibility criteria to include Stage III, sub-optimally debulked patients after 7 months of excluding these patients. This reduces generalizability of trial results to high risk patients.

IV. GOG-218 changed the primary endpoint from OS to PFS. In changing the primary outcome investigators were unblinded to treatment after patients had progressed. This could influence response or progression results which could also then influence treatment decisions which may introduce bias.

V. GOG-218 did not conduct analysis of proportional hazards and did not produce alternative survival analysis for consideration along even though they discuss convergence of curves. This creates uncertainty regarding validity of HR results. Based upon visual review and experience in ICON 7, there could be non-proportionality which may affect how results are interpreted.

VI. GOG-218 there were 29 patients that were misclassified and were later deemed ineligible based upon staging type. These patients were included in analysis as though they were eligible. Although this would have a small effect on overall results it may have artificially reduced or increased hazard ratio.

VII. Bevacizumab dosing and treatment time very was different between trials. No information was presented on dose response relationship and comparative analysis should include that information.

VIII. Long term results are not yet available making it difficult to identify benefits for patients who have survived for longer periods. Further follow-up and reporting would provide results for long term survivors.

IX. There was no independent assessment of progression in PFS. This may have biased results in this trial.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Table 5. Efficacy Outcomes – ICON 7

Efficacy Outcomes Progression Free Survival (PFS) High risk subgroup						
	Primary Analysis *Feb 2010 Cut-off*		**Updated Analysis** *Nov 30 2010 Cut-off*		**Final Analysis** Presented September 29, 2013	
Outcome	**carbo-pac**	**carbo-pac-bev**	**carbo-pac**	**carbo-pac-bev**	**carbo-pac**	**carbo-pac-bev**
PFS (high risk for progression) # Patients Median PFS (mo's) HR 95%CI P-value	N=158 10.5	N=173 15.9 HR=0.68 0.55 - 0.85 p<0.0001	N=196 10.5	N=190 16.0 HR=0.73 0.60 - 0.93 P=0.002	NA	NA
PFS (high risk for progression) # Patients Median PFS Restricted Mean(mo) @ 36 months @ 42 months	N=158 10.5 mo 13.1 NA	N=173 15.9 mo 16.5 NA	N=196 10.5 mo 14.1 14.5	N=190 16 mo 17.6 18.1	NA	NA
PFS - Stage III Suboptimally debulked # Patients in subgroup Median PFS HR (95% CI)	NA	NA	154 10.1 mo	140 16.9 mo 0.67 (0.52 - 0.87)	NA	NA
PFS - Stage IV # Patients in subgroup Median PFS HR (95% CI)	NA	NA	97 10.1 mo	104 13.5 mo 0.74 (0.55 - 1.01)	NA	NA
OS - High Risk for progression (n=465) # Deaths,	NA	NA	109 28.8 mo	79 36.6 months HR=0.64, 0.48-0.85	174 34.5 months	158 39.3 months log-rank p = 0.03,

Median Survival Hazard Ratio, HR 95%CI, p-Value				P = 0.002		P-H test = 0.007

Perren 2011[3], EPAR [5]

Table 6. Efficacy Outcomes – GOG-218

Efficacy Outcomes GOG-218		
	Primary Analysis	
Subgroup	**(carbo-pac-bev)vs. Control HR** (number of patients in analysis=510)	**carbo-pac-bev-maintenance vs. Control HR** (number of patients in analysis=496)
Stage III, Suboptimally debulked (residual lesions >1cm)	0.981 (95% CI includes 1)	0.763 (95%CI does not include 1)
Stage IV	0.923 (95% CI includes 1)	0.698 (95%CI does not include 1)
Burger, 2011[4]		
Progression Free Survival (PFS) (Not censored for Non-Protocol Therapy nor censored for ca-125) as of Feb 25, 2010 and as reported in the EPAR		
	(carbo-pac-bev)vs. Control HR (95% CI)	**carbo-pac-bev-maintenance vs. Control HR (95% CI)**
Stage III, Suboptimally debulked (residual lesions >1cm) Median PFS (months) Hazard ratio (95% CI)	10.9 vs. 10.1 0.93 (0.77 to 1.14) **(n=256 vs. n=253)**	13.9 vs. 10.1 0.78 (0.63 to 0.96) **(n=242 vs. 253)**
Stage IV Median PFS (months) Hazard ratio (95% CI)	10.4 vs. 9.5 0.90 (0.70 to1.16) **(n=165 vs. n=153)**	12.8 vs. 9.5 0.64 (0.49 to 0.82) **(n=165 vs. n=153)**
EPAR[5]		

Efficacy Outcomes

Progression Free Survival (PFS)

In the ICON 7 study there was a median follow-up of 19.4 months, disease progression or death occurred in 759 patients (392 in the standard-therapy group and 367 in the bevacizumab group). In the updated analysis, for the original high risk for progression subgroup, the median progression free survival was 10.5 months in the standard therapy group and 16.0 months in the carbo-pac-bev. Using unadjusted log rank test a significant difference was found. The hazard ratio (95% CI) was 0.73 (0.60-0.93). Testing for proportional hazards was completed and there was clear evidence of nonproportional hazards (test of proportional hazards, P<0.001). Restricted mean values were reported as an alternative due to non-proportional hazards. These values were reported at 36 month and 42 month follow up, but differences were not tested. In the updated analyses, at 36 months the restricted mean values were reported to be 14.1 versus 17.6 months in the carbo-pac versus Bevacizumab arms respectively. At 42 months the same values were 14.5 months and 18.1 months.
Testing for interactions suggests that the size of the effect of bevacizumab differed between patients at high risk for progression and the rest of the study population. (P = 0.06)[3]

In the GOG-218 study, for patients with stage III disease and residual lesions >1 cm (n=751), at the time of the data cut-off (February, 2010), the median PFS was 10.1, 10.9, and 13.9 months for the carbo-pac alone arm, carbo-pac-bev arm, and carbo-pac-bev-maintenance arm, respectively. For patients with stage IV disease (n=483), the median PFS was 9.5, 10.4, and 12.8 months, respectively. Statistically significant differences were noted for the carbo-pac-bev plus carbo-pac-bev-maintenance arm compared with the carbo-pac alone arm for the subgroup of patients with stage III disease with residual lesions >1 cm (PFS HR 0.78; 95% CI 0.63 to 0.96) and for the subgroup of patients with stage IV disease (HR 0.64; 95% CI 0.49 to 0.82).[4, 5]

Overall Survival (OS)

Overall survival results from the ICON 7 study were not available at the time of the primary analysis because results were not final. At the time of the updated analysis a hazard ratio and 95% confidence interval of 0.64 and 0.48 – 0.85 was reported for the original high risk for progression subgroup in the carbo-pac-bev treatment arm, versus the control arm. In contrast to the data for progression-free survival, there was no evidence of nonproportional hazards.[3]
Tests of interaction found that the size of effect of bevacizumab on overall survival differs between the patients at high risk for progression and the rest of the women studied (P = 0.011).[3]

At the European Cancer Congress in 2013, Oza et al reported an updated analysis of OS for a subgroup of patients at high risk for progression that was modified from the original subgroup as defined in the 2010 analyses (from this point on referred to as the "modified high risk for progression subgroup"). The modified subgroup included an additional 37 patients (n=502) and was defined in the same way as the original subgroup except that it also included non-operated patients, as they were felt to have a high risk of progression. Oza et al reported that non-proportional hazards were detected (p=0.007). The restricted mean survival time for the bevacizumab-

containing arm was 39.3 months compared to 34.5 months in the chemotherapy-alone arm.[16]

In GOG-218 study results for the subgroup of patients at high risk for progression were not reported. Total population median overall survival was 39.3, 38.7, and 39.7 months for the carbo-pac arm, the carbo-pac-bev arm, and the bevacizumab throughout group, respectively. As compared with the control arm, the hazard of death was 1.036 (95% CI, 0.827 to 1.297; P = 0.76) in the carbo-pac-bev group and 0.915 (95% CI, 0.727 to 1.152; P = 0.45) in the carbo-pac-bev-maintenance group. [4]

Harms Outcomes

*******Safety Outcomes reported for full study populations. Safety data was not available for the high risk for progression subgroup. We have not conducted analyses for risk of bias, but it should be noted that the results presented below may communicate a lower incidence of AE's and death compared to what is found in a high risk population.***

System organ classes gastrointestinal disorders (abdominal pain, constipation, diarrhea, nausea, vomiting), nervous system disorders (headache, peripheral sensory neuropathy), general disorders and administration site conditions (fatigue), skin and subcutaneous tissue disorders (alopecia), and musculoskeletal and connective tissue disorders (myalgia) were most commonly occurring AE's in both studies.[5]

The most frequently occurring Grade of AE in study GOG-218 was Grade 4 events (range 60.9%–66.0% across treatment groups) whereas the majority of patients in study ICON 7 reported Grade 3 events (range 45.2–54.6% across treatment groups). The number of patients who experienced an adverse event leading to death (Grade 5 AEs) was 27 patients in GOG-218 and 11 patients in study ICON 7.[5]

Patient Deaths

At the time of the safety data cut-off in the ICON 7 trial patient deaths were similar between treatment groups with 131 deaths occurring in the control arm carbo-pac and 107 occurring in the carbo-pac-bev arm. The lower number of deaths in the Bev arm is reflective of the lower number of patients who died as a result of disease progression, in this arm. As well, seven patients in the control arm and four patients in the Bevacizumab arm were reported to have AE's leading to death. [5]

In study GOG-218, 27 patients were reported to have an adverse event leading to death. Nine and 14 deaths were reported in the Bev initial and Bev throughout arms respectfully. Four deaths resulting from AE's were reported in the control arm. Adverse events included neutropenic infections and gastrointestinal perforations observed during the period that bevacizumab was combined with chemotherapy. [5]

Table 7 – Adverse events (AE's), AE's leading to discontinuation or death, Patient Deaths

	ICON 7		GOG-218		
	carbo-pac	**carbo-pac-bev**	**carbo-pac**	**carbo-pac-bev**	**carbo-pac-bev-maintenance**
Any AE n (%)	755 (99.0)	746 (100)	600 (99.8)	607 (100)	607 (99.8)
Grade 3-5 AE with lab data n (%)	NA	NA	559 (93.0)	577 (95.1)	574 (94.4)
Grade 3-5 AE w/o lab data n (%)	414 (54.3)	482 (64.6)	274 (45.6)	307 (50.6)	337 (55.4)
adverse events leading to death (Grade 5 AEs) n (%)	7 (0.9)	4 (0.5)	4 (0.7)	9 (1.5)	14 (2.3)
any serious adverse events n (%)	179 (23.5)	281 (37.7)	128 (21.3)	144 (23.7)	157 (25.8)
Deaths as a result of any cause n (%)	131 (17.2)	107 (14.3)	145 (24.1)	148 (24.4)	131 (21.5)

EPAR[5]

Discontinuation of treatment

Table 8 Discontinuation of treatment

	ICON 7		GOG-218		
	carbo-pac	**carbo-pac-bev**	**carbo-pac**	**carbo-pac-bev**	**carbo-pac-bev-maintenance**
AEs leading to discontinuation of study treatment n (%)	68 (8.9)	164 (22.0)	58 (9.7)	83 (13.7)	100 (16.4)

EPAR [5]

In the GOG-218 study a higher proportion of patients in the bevacizumab-containing treatment arms discontinued study treatment because of an AE, side effect, or complication than in the carbo-pac-bev arm (carbo-pac: 58 patients, 9.7%; carbo-pac-bev: 83 patients, 13.7%; carbo-pac-bev-maintenance: 100 patients, 16.4%).[5]

In the ICON 7 study, more patients in the bevacizumab-containing treatment arm than in the chemotherapy-alone arm discontinued any component of treatment due to adverse events (carbo-pac: 68 patients, 8.9%; carbo-pac-bev: 164 patients, 22.0%). This difference between the two treatment arms reflects patients who discontinued bevacizumab (carbo-pac-bev: 118 patients, 15.8%) and also reflects to some extent the longer treatment duration in the carbo-pac-bev arm compared with the carbo-pac arm (up to 18 cycles versus 6 cycles, respectively). Around half of all patients who discontinued bevacizumab did so during the six cycles when bevacizumab was administered concurrently with chemotherapy, and the remainder discontinued bevacizumab during the 12 additional cycles when bevacizumab was administered alone. The most common AE leading to discontinuation of bevacizumab treatment in the carbo-pac-bev+ arm was hypertension (22 patients, 2.9%). Discontinuation of either carboplatin or paclitaxel due to AEs during the six cycles of chemotherapy was similar between the two treatment arms.[5]

Table 9. AE's of Special Interest

	ICON 7		*GOG-218*		
	carbo-pac	**carbo-pac-bev**	**carbo-pac**	**carbo-pac-bev**	**carbo-pac-bev-maintenance**
Any special interest	362 (47.4)	552 (74.0)	585 (97.3)	592 (97.5)	591 (97.2)
Arterial Thrombo.	12 (1.6)	26 (3.5)	14 (2.3)	19 (3.1)	19 (3.1)
CNS Bleeding	0 (0.0)	3 (0.4)	0 (0.0)	0 (0.0)	3 (0.5)
NON-CNS Bleeding	84 (11.0)	294 (39.4)	96 (16.0)	216 (35.6)	223 (36.7)
Heart $Failure_{congestive}$	3 (0.4)	3 (0.4)	0 (0.0)	0 (0.0)	3 (0.5)
Febrile Neutropenia	15 (2.0)	21 (2.8)	21 (3.5)	31 (5.1)	27 (4.4)
Fistulae & Abscesses	9 (1.2)	13 (1.7)	7 (1.2)	5 (0.8)	12 (2.0)
GI Perforation	3 (0.4)	10 (1.3)	2 (0.3)	11 (1.8)	12 (2.0)
Hypertension	49 (6.4)	191 (25.6)	81 (13.5)	143 (23.6)	196 (32.2)
Decrease Neutrophil	8 (1.0)	13 (1.7)	574 (95.5)	577 (95.1)	577 (94.9)
Neutropenia	211 (27.7)	199 (26.7)	40 (6.7)	52 (8.6)	51 (8.4)
Proteinuria	17 (2.2)	33 (4.4)	39 (6.5)	32 (5.3)	51 (8.4)
Rev. Posterior Leukoencephalopathy Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Venous Thromboembolic events	34 (4.5)	51 (6.8)	24 (4.0)	21 (3.5)	25 (4.1)
wound-healing complications	12 (1.6)	34 (4.6)	27 (4.5)	29 (4.8)	22 (3.6)

EPAR[5]

Grade 3, 4 Adverse Events

Table 10. ≥Grade 3 AE's

	ICON 7		GOG-218		
	carbo-pac	**carbo-pac-bev**	**carbo-pac**	**carbo-pac-bev**	**carbo-pac-bev-maintenance**
≥Grade 3 (n)	419	491	356*	396*	408*
Grade 3-5 AE with lab data n (%)	NA	NA	559 (93.0%)	577 (95.1%)	574 (94.4%)
Grade 3-5 AE w/o lab data n (%)	414 (54.3%)	482 (64.6%)	274 (45.6%)	307 (50.6%)	337 (55.4%)

EPAR[5], Perren 2011[3], Burger 2011[4] *Sum of Proteinuria, Neutropenia, and Non-CNS bleeding events

Adverse events occurred more frequently in the Bevacizumab arms versus the carbo-pac arm. In ICON 7 the difference in the number in ≥Grade 3 events between groups was 72. In GOG-218 the difference in ≥Grade 3 events was 40 and 52 between Bevacizumab initial and Bevacizumab throughout groups respectively.

Arterial Thromboembolic Events

The incidence of arterial thromboembolic events was higher in the bevacizumab-containing treatment arms than in the carbo-pac arm across both studies. The incidence of events was higher after the chemotherapy treatment than during chemotherapy. Most events were Grade ≥3 in severity. In GOG-218 there were two grade 5 events in the bevacizumab treatment arms, and none in the carbo-pac arm. In ICON 7, one grade 5 event occurred in the carbo-pac arm and two in the carbo-pac -bev arm.[5]

In both studies, adverse events with a MedDRA preferred term of "embolism" without further qualification or characterization by the investigator were categorized as arterial thromboembolic events according to the standard coding practices of the sponsors. Medical review found that 35 of the 52 arterial thromboembolic events in study GOG-218, and 13 of the 38 arterial thromboembolic events in study ICON 7 reported as "embolism" were venous thromboembolic events.[5]

Bleeding (CNS and Non CNS)

The incidence of all bleeding events was higher in the bevacizumab arms within both studies, compared to the respective non-bevacizumab control arms. The majority of bleeding events in both studies were non-CNS bleeding events (in particular, epistaxis), and the majority of those events were Grade 1 or 2 in severity. Three patients were reported to have had CNS bleeding events in each study. Most of the bleeding events occurred during the chemotherapy treatment phase.[5]

Congestive Heart Failure (CHF)

In study GOG-218, CHF events were reported only in the carbo-pac-bev maintenance arm (3 patients, 0.5%), all of whom experienced Grade 3 left ventricular systolic dysfunction during the period from Cycle 2 to the start of Cycle 7. One of these patients also reported Grade 3 cardiomyopathy. In ICON 7, three patients in each arm experienced CHF events. [5]

Febrile Neutropenia

Most febrile neutropenia events were Grade 3 or 4 in severity, and occurred with higher frequency in the treatment arms containing Bevacizumab versus the carbo-pac arms. In study GOG-218, all events of febrile neutropenia were either Grade 3 or 4 in severity. All events were reported prior to Cycle 7. In study ICON 7, the incidence of febrile neutropenia was higher in the carbo-pac-bev than the carbo-pac arm.[5]

Fistula/Abscess

Overall incidence rates of fistulae and abscesses were similar across both studies, with a higher incidence of events recorded in both extended bevacizumab treatment arms. No Grade 5 fistulae or abscesses were reported in either study. [5]

Gastrointestinal Perforation

The incidence rates of gastrointestinal (GI) perforations were higher in all bevacizumab-containing treatment arms compared to the control arms across both studies. Only patients in the bevacizumab-containing treatment arms had GI perforations leading to death.

In the ICON 7 study all GI perforations were Grade ≥3 events and most occurred after the chemotherapy phase. One patient in the carbo-pac-bev arm had an intestinal perforation that resulted in death. An additional patient in the carbo-pac-bev arm experienced a serious adverse event of "abdominal pain" which led to death, but the cause of death was recorded as "gastrointestinal perforation". This patient does not appear under GI perforations in any summary tables of adverse events. There were no Grade 5 GI perforations reported for patients in the control arm. In ICON 7, there were no GI perforation events in patients with early stage (FIGO I and FIGO II) disease. [3]

The majority of GI perforations (any grade) reported in study GOG-218 occurred prior to Cycle 7, with the exception of two patients in the carbo-pac-bev maintenance arm who experienced large-intestine perforations after Cycle 7. The longer course of bevacizumab treatment did not appear to lead to an increased incidence of GI perforations compared to the shorter course of bevacizumab treatment. The majority of GI perforations were Grade ≥ 3 events. Six patients experienced large-intestine perforations leading to death: 4 patients in the carbo-pac-bev arm and 2 patients in the carbo-pac-bev-maintenance arm. No Grade 4 or 5 GI perforations were reported for patients in the control arm. All fatal events occurred prior to Cycle 7. [4]

Overall the incidence rates of GI perforation were within the known safety profile of the drug: up to 2% across all labelled indication within the current product information. [5]

Hypertension

Hypertension was reported more frequently in the bevacizumab-containing treatment arms compared with the control arm, in GOG-218. From Cycle 2 to the start of Cycle 7 the proportions of patients reporting hypertension events was comparable in the two bevacizumab treatment arms and higher than the control arm. During the period from Cycle 7 onwards, patients in the carbo-pac-bev-maintenance arm had a higher incidence of hypertension. Most events were not severe with most being Grade 1 or 2 events.

In study ICON 7, more patients in carbo-pac-bev arm experienced hypertension events compared with the carbo-pac-bev arm. The numbers of patients reporting hypertension events was similar during and after the chemotherapy phase. The majority of hypertension events were Grade 1 or 2.

There were no Grade 5 hypertension events in either study.[5]

Neutropenia

The rate of neutropenia was higher in the GOG-218 study compared to the ICON 7 study due to the methods of data. Forty (6.7%), 52 (8.6%), and 51 (8.4%) events occurred in the carbo-pac, carbo-pac-bev, and carbo-pac-bev-maintenance arms respectively. In the ICON 7 7 study overall incidence of adverse events reported as neutropenia was essentially the same in both arms (carbo-pac (27.7%) vs. carbo-pac-bev (26.7%). Most events occurred during the chemotherapy phase and there were no Grade 5 neutropenia events in either study arm.

In study GOG-218, the majority of patients experienced an adverse event of decreased neutrophil count, the incidence rate of which was similar across all three treatment groups. More patients reported neutropenia during the chemotherapy phase than in the period from Cycle 7 onwards. The majority of events were Grade ≥3 events. One patient in the CPB15 arm and three patients in the carbo-pac-bev-maintenance arm had adverse events of neutropenia leading to death which occurred during the period from Cycle 2 to the start of Cycle 7. No death related to Neutropenia was reported in the carbo-pac arm. [5]

Proteinuria

In study GOG-218, the highest incidence of proteinuria was observed in the Bev Throughout treatment arm while the lowest incidence was observed in the carbo-pac-bev arm (CP (6.5%), Bev Initial (5.3%), and carbo-pac-bev-maintenance (8.4%)). Most events were either Grade 1 or 2 and no Grade 5 proteinuria events were reported.

In study ICON 7, the incidence of proteinuria was higher in the carbo-pac-bev arm versus the CP arm (Bev: 4.4%; vs. CP: 2.2%). Similar to GOG-218 proteinuria events in the two treatment arms were Grade 1 or 2 in severity.[5]

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

In study GOG-218, there was one case of RPLS reported. No reported events of RPLS occurred in the ICON 7 study.[5]

Venous Thromboembolic Events

In study GOG-218, the incidence of venous thromboembolic events was similar across the three treatment arms. Twenty four (4.0%), 21 (3.5%), and 25 (4.1%) events occurred in the carbo-pac, carbo-pac-bev, and carbo-pac-bev-maintenance arms respectively. Most events occurred during the chemotherapy period and were Grade 3 events.

In study ICON 7, 6.8% of patients in the carbo-pac-bev arm experienced a venous thromboembolic event compared with 4.5% in the carbo-pac arm. Most events occurred during the chemotherapy phase. Grade ≥3 venous thromboembolic events were reported in 12 patients (1.6%) in the carbo-pac arm and 30 patients (4.0%) in the carbo-pac-bev arm. Eleven patients (1.5%) in the carbo-pac-bev arm had a Grade 4 event compared with two patients (0.3%) in the carbo-pac arm.

A medical review revealed that 35/52 arterial thromboembolic events across treatment groups in study GOG-218 and 13/38 arterial thromboembolic events across treatment groups in study ICON 7 that were reported as "embolism unqualified" were actually venous thromboembolic events.

There were no Grade 5 venous thromboembolic events in either study. [5]

Wound Healing Complications

In study GOG-218, the incidence of wound-healing complications/dehiscence events was similar across the treatment arms. Twenty seven (4.5%), 29(4.8%), and 22(3.6%) events occurred in the carbo-pac, carbo-pac-bev, and carbo-pac-bev-maintenance arms respectively. One patient in the carbo-pac-bev arm and one patient in the carbo-pac-bev-maintenance arm experienced Grade 4 wound complications. There were no wound-healing complications that led to death. [5]

In study ICON 7, wound-healing complications were reported in 4.6% of patients in the Bevacizumab arm compared with 1.6% in the CP arm. The majority of wound-healing complications in the two treatment arms were Grade 1 or 2 events. Grade 3 wound-healing complications were recorded for one patient (0.1%) in the carbo-pac arm and nine patients (1.2%) in the CPB7.5+ arm. No Grade 4 or 5 wound-healing complications were reported in either treatment arm.[5]

Infusion reactions

No information was publically available on infusion reactions. At the Checkpoint Meeting, the Submitter disclosed that no patient in the ICON7 study or the GOG-218 study experienced a Grade 3-5 infusion reaction.[27]

Fatigue

No information was publically available on fatigue. At the Checkpoint Meeting, the Submitter disclosed that 3.2% of patients who received bevacizumab plus carboplatin and paclitaxel experienced Grade 3-5 fatigue compared with 1.7% of patients who received carboplatin and paclitaxel. [27]

Thrombophlebitis

No information was publically available on thrombophlebitis. At the Checkpoint Meeting, the Submitter disclosed that no patient in the ICON7 study experienced thrombophlebitis. [27]

Ovarian failure

No information on ovarian failure was publically available. At the Checkpoint Meeting, the Submitter disclosed that no patient in the ICON7 study or the GOG-218 study experienced ovarian failure.[27]

Quality of life (QOL)

In the ICON 7 study Health related quality of life (HRQOL) was reported by patients using the EORTC QLQc-30 and OV28 questionnaires before each chemotherapy cycle, 6 weekly for the remainder of year 1, then at 15, 18, 21 and 24 months or until progression, and at 36 months from randomization. Results showed improvement in global QOL over time but there was no difference between the arms until the end of chemotherapy when there was a marginal improvement in global quality of life in the control arm.[5]

In the GOG-218 study a mixed effect model for the TOI scores was built using all scores post-baseline as dependent variables, and treatment group, time and interaction between treatment group and time as fixed effects and baseline score and age as covariates. Three pre-specified interaction contrasts were tested and showed that:

The contrast examining change in HRQOL in the second half of the chemotherapy phase (between Cycles 4 and 7) indicated a slightly stronger improvement in TOI scores over this period for patients in the Bev Initial and Bev Throughout arms compared to those for patients in the CPP arm, but this was not statistically significant (p=0.0864).

The contrast examining change in HRQOL between the second half of the chemotherapy phase (Cycles 4 and 7) and the latter portion of the extended treatment phase (Cycles 13 and 21) indicated a statistically significant improvement in TOI scores over time for patients in the carbo-pac-bev-maintenance arm compared to those for patients in the carbo-pac arm (p=0.0008). This change (2.6 points) did not exceed the minimally important difference of 5 points.

The contrast examining change in TOI scores during the latter portion of the extended treatment phase (Cycles 13 and 21) found no statistically significant difference between the carbo-pac-bev and carbo-pac-bev-maintenance arms (p=0.8236).[4]

6.4 Ongoing Trials

102 studies were returned from Clinicaltrials.gov, and only one trial was eligible based upon the inclusion criteria.

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
A Prospective Randomised Phase III Trial to Evaluate Optimal Treatment Duration of First-line Bevacizumab in Combination With Carboplatin and Paclitaxel in Patients With Primary Epithelial Ovarian, Fallopian Tube or Peritoneal Cancer Study ID#: NCT01462890 Estimated Enrollment:800 Study Start Date: 11/2011 Estimated Study Completion Date: 11/2021	**Inclusion Criteria** • Signed written informed consent obtained prior to initiation Primary diagnosis is confirmed by specialized pathology review (Germany only) • Females aged ≥ 18 years • Histologically confirmed, newly diagnosed o Epithelial ovarian carcinoma o Fallopian tube carcinoma o Primary peritoneal carcinoma AND FIGO stage IIb - IV (all grades and all histological types) • Patients should have already undergone surgical debulking, by a surgeon experienced in the management of ovarian cancer, with the aim of maximal surgical cytoreduction according to the GCIG Conference Consensus Statement. • Patients must be able to commence cytotoxic chemotherapy within 8 weeks of cytoreductive surgery. The first dose of bevacizumab can be omitted in both arms if the investigator decides to start chemotherapy within 4 weeks of surgery. • ECOG 0-2 • Life expectancy > 3 months	Drug: Bevacizumab 15 mg/kg, iv on day 1 every 3 weeks up to and including cycle 22 Drug: Paclitaxel 175 mg/m^2, iv on day 1 every 3 weeks for 6 cycles Drug: Carboplatin AUC 5, iv on day 1 every 3 weeks for 6 cycles **Vs.** Drug: Bevacizumab 15 mg/kg, iv on day 1 every 3 weeks up to and including cycle 44 Drug: Paclitaxel 175 mg/m^2, iv on day 1 every 3 weeks for 6 cycles Drug: Carboplatin AUC 5, iv on day 1 every 3 weeks for 6 cycles	**Primary Outcome Measures:** Progression-free survival **Secondary Outcome Measures:** Overall survival, objective response, HRQOL, safety & tolerability

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
	• Adequate bone marrow function (within 14 days prior to randomization) o ANC ≥ 1.5 x 10^9/L o PLT ≥ 100 x 10^9/L o Hb ≥ 9 g/dL (can be post-transfusion) • Adequate coagulation parameters (within 14 days prior to randomization) • Patients not receiving anticoagulant medication who have an INR ≤ 1.5 and an aPTT ≤ 1.5 x ULN • The use of full-dose oral or par-enteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to institution medical standard) and the patient has been on a stable dose of anticoagulants for at least two weeks at the time of randomization. • Adequate liver function (within 14 days prior to randomization) Serum bilirubin ≤ 1.5 x ULN, Serum transaminases ≤ 2.5 x ULN Urine dipstick for proteinuria < 2+. If urine dipstick is ≥ 2+, 24 hour urine must demonstrate ≤ 1 g of protein in 24 hours • Adequate postoperative GFR > 40 ml/min (estimates based on the Cockroft-Gault or Jelliffe formula are sufficient)		

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Gynecologic Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on bevacizumab (Avastin) for ovarian cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Gynecologic Clinical Guidance Panel is comprised of three clinical oncologists .The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

Literature search via OVID platform

1. (ovarian or fallopian or primary peritoneal, cancer).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]
2. (bevacizumab or avastin).ti,ab,rn,nm,sh,hw,ot. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]
3. *bevacizumab/
4. or/2-3
5. 1 and 4
6. exp animals/
7. exp animal experimentation/
8. exp models animal/
9. exp animal experiment/
10. nonhuman/
11. exp vertebrate/
12. or/6-11
13. exp humans/
14. exp human experiment/
15. or/13-14
16. 12 not 15
17. 5 not 16
18. (randomized controlled trial or controlled clinical trial).pt.
19. randomized controlled trial/
20. randomized controlled trials as topic/
21. controlled clinical trial/
22. controlled clinical trials as topic/
23. randomization/
24. random allocation/
25. double-blind method/
26. double-blind procedure/
27. double-blind studies/
28. single-blind method/
29. single-blind procedure/
30. single-blind studies/
31. placebos/
32. placebo/
33. control groups/
34. control group/
35. (random: or sham or placebo:).ti,ab,hw.
36. ((singl: or doubl:) adj (blind: or dumm: or mask:)).ti,ab,hw.
37. ((tripl: or doubl:) adj (blind: or dumm: or mask:)).ti,ab,hw.
38. (control: adj3 (study or studies or trial:)).ti,ab.
39. (nonrandom: or non random: or non-random: or quasi-random: or quasirandom:).ti,ab,hw.
40. allocated.ti,ab,hw.
41. ((open label or open-label) adj5 (study or studies or trial:)).ti,ab,hw.
42. or/18-41
43. 17 and 42
44. remove duplicates from 43
45. limit 44 to english language

Literature search via PubMed/Cochrane Library/Grey Literature search

i. ovarian or fallopian or primary peritoneal cancer
ii. bevacizumab or avastin
iii. i and ii

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