



pan-Canadian Oncology Drug Review Initial Clinical Guidance Report

Bevacizumab (Avastin) for Platinum Resistant Ovarian Cancer

March 3, 2016

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1 GUIDANCE IN BRIEF

1.1 Background

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

Bevacizumab is a recombinant humanized monoclonal antibody that inhibits angiogenesis by neutralizing all isoforms of human vascular endothelial growth factor-A (VEGF-A), and blocking their binding to VEGF receptors.¹ Bevacizumab in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin is approved by Health Canada for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior chemotherapy regimens.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One randomized controlled trial (AURELIA) was identified that met the inclusion criteria for this review.² The AURELIA study was an open-label phase III trial that randomized patients with recurrent platinum-resistant (disease progression within <6 months of platinum therapy) epithelial ovarian, fallopian tube, or primary peritoneal cancer to receive bevacizumab plus chemotherapy (paclitaxel, topotecan, or pegylated liposomal doxorubicin; n=179) or to chemotherapy without bevacizumab (n=182). Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent.

Baseline patient characteristics were balanced between arms. Investigator selection of the chemotherapy options were evenly distributed among the three options (pegylated liposomal doxorubicin [n=126]; paclitaxel [n=115], or topotecan [n=120]). The median age was 61 years in the chemotherapy alone arm and 62 years in the bevacizumab plus chemotherapy arm. Approximately 57% of patients in the trial had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 35% had an ECOG performance status of 1 and 6.4% had an ECOG performance status of 2. In addition, approximately 46% of patients had received two prior chemotherapy regimens and 31% had ascites at baseline. The primary outcome of the trial was progression-free survival. Secondary outcomes included overall survival, objective response (by RECIST and/or Gynecologic Cancer Intergroup [GCIG] cancer antigen [CA]-125 criteria), safety, and quality of life; however, secondary outcomes were not considered when determining the required sample size.

Efficacy

AURELIA demonstrated a statistically significant difference in the primary outcome, progression-free survival, in favour of bevacizumab plus chemotherapy (median 6.7 months) compared with chemotherapy alone (median 3.4 months); unstratified hazard ratio (HR) 0.48, 95% confidence interval (CI) 0.38-0.60. Of note, assessments of tumour progression were conducted by the investigators and, as the AURELIA trial was open-label

(i.e. unblinded), this increases the potential for bias in the progression-free survival results.

The rate of objective response was a secondary outcome and among 350 evaluable patients, it was also found to be statistically significantly higher for patients treated with bevacizumab plus chemotherapy (30.9%) compared with chemotherapy alone (12.6%; $p < 0.001$).

Overall survival was also a secondary outcome. The median overall survival was 16.6 months for patients who received bevacizumab plus chemotherapy compared with 13.3 months for patients who received chemotherapy alone. This difference was not statistically significant (HR 0.85, 95% CI 0.66 to 1.08, $p = 0.174$). Of note, at the time of the analysis, 40% of patients in the chemotherapy alone arm went on to receive single-agent bevacizumab after experiencing disease progression on chemotherapy alone.

Patient-reported outcomes were assessed at baseline and every two or three cycles until disease progression, using the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Ovarian Cancer Module (QLQ-OV28) and the Functional Assessment of Cancer Therapy-Ovarian Cancer symptom index (FOSI).³ The primary quality of life endpoint was that more patients in the bevacizumab plus chemotherapy arm would achieve at least a 15% (≥ 15 -point) absolute improvement on the QLQ-OV28 abdominal/GI symptom subscale at week 8/9 from baseline. At week 8/9, a higher proportion of patients in the bevacizumab plus chemotherapy arm had achieved a $\geq 15\%$ improvement in QLQ-OV28 abdominal/GI symptoms compared to the chemotherapy arm (21.9% vs. 9.3%, respectively; difference 12.7%, 95% CI 4.4 to 20.9; $p = 0.002$). In a subgroup analysis of 99 evaluable patients with ascites at baseline who were expected to have considerable pain/GI symptoms, 44% of patients who received bevacizumab plus chemotherapy experienced a $\geq 15\%$ improvement in pain/GI symptoms versus 4.1% in the CT alone arm (difference 39.9%; 95% CI 23.9% to 55.9%; $p < 0.001$). Of note, the AURELIA trial was open-label, which increases the potential for bias in the patient-reported outcomes in favour of whichever treatment the patient felt was providing more benefit.

Harms

A total of nine patients in the bevacizumab plus chemotherapy arm and 6 patients in the chemotherapy alone arm died due to adverse events. Grade 2-5 gastrointestinal perforation events were reported in three (1.7%) patients who received bevacizumab plus chemotherapy and in one (0.6%) patient who received chemotherapy alone. Grade 3-5 proteinuria events occurred in 2.2% of patients in the bevacizumab plus chemotherapy arm and in no patients in the chemotherapy alone arm. Grade 3-5 hypertension events also occurred in more patients in the bevacizumab plus chemotherapy arm (7.8%) than in the chemotherapy alone arm (1.1%).

1.2.2 Additional Evidence

pCODR received input on bevacizumab for the treatment of platinum-resistant ovarian cancer from one patient advocacy group (Ovarian Cancer Canada [OCC]). Provincial Advisory Group (PAG) 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

Burden of Illness and Need

In 2015, 2,800 Canadian women will be diagnosed with ovarian cancer and approximately 1,750 will die of this disease. Ovarian cancer often affects women in their 50's and 60's removing them from the workforce, leading to a substantial number of person-years of experienced life lost. Treatment options for platinum resistant ovarian cancer are quite limited and new treatments that improve survival, control tumour progression, and improve patients' quality of life are required.

Efficacy

The AURELIA trial demonstrated a statistically significant and clinically meaningful improvement in progression-free survival in favour of bevacizumab in combination with chemotherapy (median 6.7 months) compared with chemotherapy without bevacizumab (median 3.4 months; unstratified HR 0.47, 95% CI 0.38 to 0.60). The rate of objective response was also statistically significantly higher for the bevacizumab plus chemotherapy arm (30.9%) compared with the chemotherapy alone arm (12.6%; $p < 0.001$).

While median overall survival was 16.6 months for bevacizumab plus chemotherapy compared with 13.3 months for chemotherapy alone, this difference was not statistically significant (HR 0.85; 95% CI 0.66 to 1.08). However, this may be due to this outcome being under powered to detect a difference or because a high proportion of patients (40%) who progressed on the chemotherapy alone arm went on to receive single-agent bevacizumab after disease progression and therefore confounded the results.

The AURELIA trial demonstrated that bevacizumab plus chemotherapy may improve abdominal and GI symptoms in a higher proportion of patients than chemotherapy alone. Furthermore, in patients with ascites, the combination of bevacizumab plus chemotherapy may offer an improvement in abdominal and GI symptoms in a much higher proportion of patients than chemotherapy alone. The open-label nature of the trial is a potential source of bias for the patient-reported outcomes.

Harms

The addition of bevacizumab to weekly paclitaxel, pegylated liposomal doxorubicin or two different schedules of topotecan was well tolerated and did not significantly increase the common toxicities normally observed with chemotherapy (i.e., myelosuppression, febrile neutropenia, peripheral sensory neuropathy, etc.). Bevacizumab was associated with potentially serious adverse events such as bowel perforation, fistula/abscess and reversible posterior leukoencephalopathy syndrome; however, the toxicity acceptable. It would be important to consider limiting the use of bevacizumab in the recurrent disease setting based on the number of prior treatment cycles and/or involvement of bowel with tumour. Another concern with the use of bevacizumab, particularly with paclitaxel, is the higher rate of GI perforation. Careful patient selection (i.e., good performance status [ECOG 0-2], no evidence of bowel obstruction, surgery more than 4 weeks prior, prior pelvic or abdominal radiation, platinum refractory and no more than 2 courses or prior chemotherapy) and careful informed consent for treatment are essential.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to bevacizumab given at 10 mg/kg q2weeks or 15 mg/kg q3weeks with monthly liposomal doxorubicin, weekly taxol or 2 different schedules of topotecan until disease progression by RECIST criteria in women with their first treatment for platinum resistant ovarian, primary peritoneal or fallopian tube cancer. This is based on a large multicenter open label randomized trial that demonstrated a statistically significant but clinically modest improvement in progression-free survival in favour of chemotherapy plus bevacizumab compared to chemotherapy without bevacizumab. Serious adverse events such as fistula, GI perforations and thrombosis were more commonly observed with the use of bevacizumab, but were still rare (<4%) and manageable.

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

- Careful patient selection (i.e., good performance status ECOG 0-2, no evidence of bowel obstruction, surgery more than 4 weeks prior, prior pelvic or abdominal radiation, no prior VEGF inhibitor treatment, and not primary platinum refractory) and careful informed consent for treatment is essential.
- Overall survival was a secondary outcome in the AURELIA trial and that, although no statistically significant difference was demonstrated, the trial was not adequately powered to detect such differences. Furthermore, the overall survival results were confounded by the fact that 40% of patients in the chemotherapy alone arm received bevacizumab after disease progression.

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 for platinum-resistant recurrent, epithelial, ovarian, fallopian tube and primary peritoneal cancer. 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 CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding bevacizumab for platinum-resistant recurrent epithelial, ovarian, fallopian tube and primary peritoneal cancer conducted by the Genitourinary 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 and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on bevacizumab for platinum-resistant recurrent epithelial ovarian, fallopian tube and primary peritoneal cancer and a summary of submitted Provincial Advisory Group Input for bevacizumab for platinum-resistant recurrent ovarian cancer 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, with 50% of all cases occurring in women older than 65 years.⁴ In Canada, it is estimated that in 2015, 2,800 women will be diagnosed with ovarian cancer and 1,750 women will die from the disease. This makes it the fifth leading cause of cancer death in women.¹ Epithelial ovarian cancer has few specific symptoms in early stage disease and there is no generally accepted screening strategy. Consequently, when epithelial cancer is finally diagnosed, the carcinoma has metastasized beyond the ovary in more than three fourths of patients.¹

Ovarian cancer is one of the most sensitive of all solid tumors to antineoplastic chemotherapy, and responses are expected in over 80% of women who receive standard platinum- and paclitaxel-based treatment. However, the majority of women with advanced ovarian cancer will ultimately relapse and develop drug-resistant disease.⁵

Women who experience recurrences within 6 months following an initial response to platinum-based therapy or who experience stable disease during platinum-based therapy are characterized as having platinum-resistant ovarian cancer. The prognosis for patients diagnosed with platinum-resistant ovarian cancer is poor, where 80% of patients fail to respond to available therapies. Response rates for current therapies indicate a 20 percent response rate, and this indicates a need for the development of effective treatment strategies for the management of platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.⁶

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.¹ Bevacizumab in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin is a new treatment regimen currently under review for patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who received no more than two prior chemotherapy regimens.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effectiveness and safety/toxicity of bevacizumab in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin, for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens. Only randomized 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 Population²

One randomized controlled trial was identified that met the eligibility criteria of this systematic review and was selected for inclusion.² AURELIA was an open-label, randomized two-arm, phase III trial that examined bevacizumab plus chemotherapy (BEV-CT) versus chemotherapy (CT) alone in patients with recurrent platinum-resistant (disease progression within <6 months of platinum therapy) epithelial ovarian, fallopian tube, or primary peritoneal cancer.

AURELIA enrolled 361 patients across 13 countries in Europe. Eligible patients had histologically confirmed epithelial ovarian, fallopian tube or primary peritoneal cancer (measurable by RECIST) that had progressed within 6 months of completing 4 or more cycles of platinum-based therapy. At the decision of the investigator, patients were assigned to receive one of three chemotherapy agents: paclitaxel (80 mg/m² intravenously (IV) on days 1, 8, 15, and 22 every 4 weeks; pegylated liposomal doxorubicin (PLD) 40 mg/ m² IV on day 1 every 4 weeks, or topotecan 4 mg/ m² IV on days 1, 8, and 15 every 4 weeks or 1.25 mg/ m² on days 1 to 5 every 3 weeks. Patients were then randomized 1:1 to receive either single-agent chemotherapy or to chemotherapy plus bevacizumab (10 mg/kg every 2 weeks, or 15 mg/kg every 3 weeks in those receiving topotecan in a 3-weekly schedule). Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent. Patients in the bevacizumab plus chemotherapy (BEV-CT) arm who experienced toxicities requiring discontinuation of one agent could continue treatment with the other agent and chemotherapy doses could be reduced using individual schedules for each chemotherapy drug. If there was clear evidence of disease progression (as per RECIST 1.0), patients in the CT arm were given the opportunity to crossover to bevacizumab monotherapy, and the treatment was continued until disease progression, unacceptable adverse events, or patient request for discontinuation.

Baseline patient characteristics were balanced between arms. Investigator selection of chemotherapy was evenly distributed among the three options (PLD, n=126,

paclitaxel, n=115, topotecan, n=120). This was made possible due to capping of the chemotherapy recruitment cohort that closed once 120 patients were recruited. The median age was 61 years in the chemotherapy alone arm and 62 years in the bevacizumab plus chemotherapy arm. Approximately 58.8% of the patients in the trial had an ECOG performance status of 0, 34.3% had an ECOG performance status of 1, and 6.7% had an ECOG performance status of 2. Approximately 41.6% of patients had received two prior chemotherapy regimens and 31% had ascites at baseline. The primary outcome of the trial was to compare the efficacy and progression-free survival (PFS) of bevacizumab plus chemotherapy versus chemotherapy alone, with 290 events required to detect a hazard ratio (HR) of 0.72 with 80% power (assuming a median PFS of 5.7 months in the bevacizumab plus chemotherapy arm and 4.0 months in the chemotherapy alone arm). Secondary outcomes were objective response rate (ORR) according to RECIST and/or Gynecologic Cancer Intergroup (GCI) cancer antigen (CA) - 125 criteria, overall survival (OS), safety, tolerability, and quality of life (QoL). However, it is important to note that the sample size requirement was based on the primary outcome of PFS and not on objective response or overall survival.

Intervention²

In AURELIA, patients were randomized 1:1 to BEV-CT or CT alone and were stratified according to selected chemotherapy cohort (PLD vs. paclitaxel vs. topotecan), prior antiangiogenic therapy (yes vs. no), and platinum-free interval (<3 months vs. 3 to 6 months from last platinum therapy to subsequent progression). The initial bevacizumab infusion was over 90 minutes, with subsequent infusions over 60 minutes and then 30 minutes, as tolerated. The median duration of therapy was three cycles (range of 1-17) in the CT arm versus six cycles (range of 1-24) in the BEV-CT arm. Chemotherapy exposure was noted to be higher in the BEV-CT arm, and this was reflected in the longer PFS observed in the bevacizumab-treated patients.

Patient Disposition^{2,7}

There were a total of 361 patients in the AURELIA trial who were randomized 1:1 to receive either chemotherapy or BEV-CT. The number of patients randomized to the CT arm was 182 compared to 179 who were randomized to the BEV-CT arm.

A total of 82.4% (n=150) of patients in the CT arm terminated the study vs. 79.3% (n=142) in the BEV-CT arm.

Reasons for termination in the CT arm included: subject withdrew consent (2.2%), death (74.7%), adverse events (0%), protocol violation (1.1%), and other reasons (4.4%). There were 17.6% (n=32) of patients who were under study follow-up as of January 25th 2013.

Reasons for termination in the BEV-CT arm included: withdrawal of consent (3.4%), death (70.4%), adverse events (0.6%), protocol violation (0%), and other reasons (5.0%). There were 20.7% (n=37) of patients who were under study follow-up as of January 25th 2013.

Efficacy^{7,8}

Efficacy analyses were based on an intent-to-treat (ITT) population, which included all randomly assigned patients. Safety analyses were based on the safety population, which included all patients who received greater or equal to one dose of study treatment. The AURELIA study met its primary endpoint and demonstrated a

significant improvement in PFS with the addition of bevacizumab to a chemotherapy regimen (HR = 0.48; 95% CI: 0.38, 0.60; log-rank p-value <0.001). PFS in the two treatment arms was compared using an unstratified two-sided log-rank test. In addition to the improvement in PFS, the AURELIA trial also demonstrated a statistically significant and clinically meaningful improvement in ORR. The ORR increased from 12.6% in the chemotherapy alone arm to 30.9% in the BEV-CT arm (Please see Table 1 below).

Overall survival at the final analysis also indicated a small yet statistically insignificant improvement. However, the OS did not meet statistical significance. At the data cut-off at final analysis, 40% of patients in the CT arm had crossed over to receive single-agent bevacizumab after experiencing disease progression on CT alone. Please refer to section 6.3.2.2 of the systematic review for further details.

Table 1. Key efficacy outcomes of bevacizumab in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer ²			
		Bevacizumab plus Chemotherapy (n=179)	Chemotherapy Alone (n=182)
Progression-Free Survival (PFS)	Median (95% CI) [months]	6.7 (5.7-7.9)	3.4 (2.2-3.7)
	Unstratified HR (95% CI)	0.48 (0.38-0.60; log-rank p<0.001)	
Objective response rate (ORR)	RECIST and/or GCIG CA-125 criteria (350 evaluable patients)	30.9%	12.6%
		Two-sided X ² p<0.001	
	RECIST (287 evaluable patients)	27.3%	11.8%
		Two-sided X ² p=0.001	
GCIG CA-125 (297 evaluable patients)		31.8%	11.6%
		Two-sided X ² p<0.001	
Overall survival (OS)	Median (95% CI) [months]	16.6 (13.7-19.0)	13.3 (11.9-16.4)
	Unstratified HR (95% CI)	0.85 (0.66-1.08; log-rank p<0.174)	
Notes: GCIG-CA-125 = Gynecologic Cancer Intergroup HR= Hazard Ratio			

Harms

As of the data cut-off date of 25th January 2013, a total of 136 (74.7%) patients in the CT arm and 128 patients (71.5%) in the BEV-CT arm had died. The majority of these deaths were attributable to disease progression and ovarian cancer, 130 patients (71.4%) in the CT arm compared to 119 patients (66.5%) in the BEV-CT arm.

A total of 15 patients, 6 in the CT arm and 9 in the BEV-CT arm, died due to adverse events that occurred during the study follow-up period.

Table 6. Summary of Adverse Events of selected grade ≥ 2 & Grade ≥ 3 & AEs of special interest ^{2,7}	Bevacizumab plus Chemotherapy (n=179) [%]	Chemotherapy Alone (n=181) [%]
Hypertension Grade ≥ 2 Grade ≥ 3	20 7	7 1
Proteinuria, Grade ≥ 3	2	0
GI Perforation Grade ≥ 2 Grade ≥ 3	2 2	0 0
Fistula/abscess Grade ≥ 2 Grade ≥ 3	2 1	0 0
Bleeding, Grade ≥ 3	1	1
Thromboembolic event, Grade ≥ 3 Arterial, Grade ≥ 3 Venous, Grade ≥ 3	5 2 3	4 0 4
Wound-healing complication, Grade ≥ 3	0	0
Reversible posterior leukoencephalopathy syndrome, Grade ≥ 3	1	0
CHF, Grade ≥ 3	1	1
Cardiac disorders, Grade ≥ 3 (excluding CHF)	0	0
Notes: AEs= Adverse Events Only grade 2-5 AEs were collected in the AURELIA trial. CHF= congestive heart failure; GI=gastrointestinal.		

During the treatment period, the following adverse events were also experienced.

Grade 2-5 Gastrointestinal (GI) perforations events were reported in 3 patients (1.7%) in the BEV-CT arm and one patient (0.6%) in the CT arm.

Grade 3-5 HTN events were reported in 7.8% of patients in the BEV-CT arm and 1.1% in the CT arm.

Grade 3-5 proteinuria events were reported in 4 patients (2.2%) in the BEV-CT arm and no patients in the CT arm.

One patient (0.6%) in the BEV-CT arm and no patient in the CT arm experienced Posterior Reversible Encephalopathy Syndrome (PRES).

Discontinuation due to adverse events⁷

A higher percentage of patients in the BEV-CT arm than in the CT arm that experienced grade 2-5 AEs that led to withdrawal of study treatment with chemotherapy or bevacizumab (43.6% vs. 8.8%, respectively). Please see section 6.3.2.2 of the systematic review for further details.

Quality of Life

Patient-reported outcomes were reported in a separate publication³ and were assessed at baseline and every two or three cycles until disease progression using the EORTC Quality of Life Questionnaire-Ovarian Cancer Module 28 (QLQ-OV28) and the Functional Assessment

of Cancer Therapy-Ovarian Cancer symptom index (FOSI). There were no substantial differences in baseline characteristics noted between the PRO-evaluable and ITT populations.

The primary HRQoL hypothesis endpoint was that more patients in the BEV-CT group would achieve at least a 15% (≥ 15 -point) absolute improvement on the QLQ-OV28 abdominal/GI symptom subscale at week 8/9 from baseline than in the CT group. A 15% improvement was used by the study authors, rather than the more standard use of a 10% improvement. This was due to wanting a more rigorous definition of a clinically meaningful difference given the open-label nature of the trial.

Baseline questionnaires were completed by 89% of 361 randomized patients (155 in the BEV-CT group and 162 in the CT alone group). Baseline abdominal/GI symptom scores were observed to be similar between groups (bevacizumab plus chemotherapy, mean 32.3, SD 22.13; chemotherapy alone, mean 29.6, SD 22.13).

At week 8/9, 122 patients had completed the questionnaire in the bevacizumab plus chemotherapy group compared to 84 in the chemotherapy alone group. In the BEV-CT group, the 69 patients who did not complete the questionnaire were counted as not having an improvement in patient-reported outcomes. Similarly, in the chemotherapy alone group, the 119 patients who did not complete the questionnaire were counted as not having an improvement in patient-reported outcomes. At week 8/9, a higher proportion of patients in the bevacizumab plus chemotherapy arm had achieved a $\geq 15\%$ improvement in QLQ-OV28 abdominal/GI symptoms compared to the chemotherapy arm (21.9% vs. 9.3%, respectively; difference 12.7%, 95% CI 4.4 to 20.9; $p=0.002$).

It is important to note that symptoms at baseline were not mandatory for enrolment onto the trial. Therefore, the absolute percentages reflect the large proportion (35%) of women in AURELIA who did not have substantial symptoms at baseline, as well as the 15% criteria used to define improvement and the poor prognosis of women with platinum-resistant ovarian cancer.

A subgroup analysis including 99 PRO evaluable patients with ascites at baseline were also included. These made up approximately 27% of the ITT population and were expected to have considerable pain/GI symptoms. This subgroup demonstrated a greater treatment effect with a $\geq 15\%$ improvement in 44% of the BEV-CT arm versus 4.1% in the CT alone arm (difference 39.9%; 95% CI 23.9% to 55.9%; $p<0.001$).

Statistically significant differences were also demonstrated in the QLQ-OV28 abdominal/GI symptom scale in favour of the bevacizumab group from the mixed-model repeated-measures analysis (6.4-point difference over all time points until progression or death; 95% CI 1.3 to 11.6; $p=0.015$), and in the proportion of patients at week 8/9 with a $\geq 15\%$ improvement in FOSI (12.2% vs. 3.1%; difference 9.0%, 95% CI 2.9% to 15.2%; $p=0.003$).

2.1.4 Comparison with Other Literature

No other information identified.

2.1.5 Summary of Supplemental Questions

No supplemental questions were addressed in this review.

2.1.6 Other Considerations

See Section 4 and Section 5 for a complete summary of patient advocacy group input and Provincial Advisory Group (PAG) Input, respectively.

Patient Advocacy Group Input

From a patient's perspective, the impact of ovarian cancer is significant for women diagnosed with this disease and their caregivers. OCC noted areas that were negatively impacted included work life, sleep, cognition, sexual intimacy, and activities of daily living. OCC observed that respondents diagnosed with platinum-resistant ovarian cancer strongly disagreed that their current or past treatments had managed their ovarian cancer. Side effects of their treatment included: fatigue, hair loss, bowel problems and neuropathy. A majority of respondents would be willing to tolerate additional side effects, if the benefits of the treatment were considered to be short term. The majority of respondents, including caregivers indicated that they would expect bevacizumab to prolong their survival, shrink their tumour, and improve their quality of life. Of those who considered taking bevacizumab, their reasons for not using bevacizumab were because it was not offered to them or it was too expensive. OCC noted that women with platinum-resistant ovarian cancer had lower expectations for bevacizumab, wanting only to see a slight improvement in their ovarian cancer. Respondents who have experience with bevacizumab reported side effects, which included high blood pressure, fatigue, bleeding and heart problems. However, respondents also felt that the drug managed their ovarian cancer or managed better their ovarian cancer compared to previous treatment. Some of the key areas of improvement reported by respondents include shrinking their tumour size, prolonging their survival, improving their prognosis, reducing fluid build-up and preventing a recurrence.

PAG Input

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.
- Unknown duration of treatment.

Health System factors:

- Additional resources required to monitor and treat adverse effects.

2.2 Interpretation and Guidance

Burden of Disease

In 2015, 2.9% of all new cancers in Canadian women will be ovarian cancer. This means 2,800 Canadian women will develop ovarian cancer for an Age standardized incidence rate (ASIR) of 10.8 per 100,000 women. In that same year, 4.7% of cancer related deaths in Canadian women will be caused by ovarian cancer. This means, 1,750 women will die of their disease for an age standardized mortality rate of 6.2 per 100,000.⁹ This disease often affects women in their 50s and 60s removing them from the workforce, leading to a substantial number of person-years of experienced life lost.¹⁰

Efficacy

The AURELIA trial, as described in detail in section 2.1.3, is an open-labeled randomized controlled trial of women with recurrent platinum-resistant (defined as (clinical/radiological) disease progression within 6 months of platinum based therapy) epithelial ovarian, fallopian tube or primary peritoneal cancer. The two study arms were chemotherapy agent of physician and patient choice (i.e., pegylated liposomal doxorubicin, paclitaxel, topotecan) with or without the addition of bevacizumab. The objective was to identify the impact of bevacizumab on commonly used chemotherapy in the platinum resistant setting. Randomization between the study arms was 1:1. The bevacizumab dose varied depending on the chemotherapy regimen chosen. For example, bevacizumab was given 10 mg/kg every 2 weeks when delivered with liposomal doxorubicin, weekly paclitaxel or weekly topotecan as a cycle of therapy with these agents is defined by a 4 week interval. Bevacizumab was given 15 mg/kg IV every 3 weeks when topotecan was given daily for 5 days every 3 weeks. Therefore, the dose intensity of bevacizumab was constant, with 5 mg/kg /week given to all patients randomized to receive this agent. The primary end points of the study were progression-free survival and percent of patients with disease progression or death. The study enrolled 361 eligible patients in 13 countries.

At analysis, the median duration of follow-up of was 13 months in the BEV-CT arm versus 13.9 months in the CT arm. Efficacy analyses were based on the intent-to-treat population with a median PFS in the BEV-CT arm of 6.7 (95%CI 5.7-7.9) months compared to that in the CT arm of 3.4 (95% CI 2.2-3.7) months (unstratified HR 0.47 (95%CI 0.38-0.60)). The objective response rate by RECIST and/or GCIG CA-125 criteria was 30.9% in the BEV+CT arm compared to 12.6% in the CT arm (two-side χ^2 $p < 0.001$).

A secondary end point, which was statistically under powered, showed the median overall survival in the BEV-CT arm was 16.6 (95%CI 13.7-19.0) months compared with 13.3 (95%CI 13.3-16.4) months in the CT arm, with an unstratified HR of 0.85 (95%CI 0.66-1.08; log-rank $p < 0.174$).

In an unplanned analysis, the PFS of weekly paclitaxel with or without bevacizumab was 10.4 vs 3.9 months (HR 0.46, 95%CI 0.30-0.71), showing the synergistic interaction of the combination. The PFS of liposomal doxorubicin with or without bevacizumab was 5.4 versus 3.5 months (HR 0.57, 95%CI 0.39-0.83) and for topotecan it was 5.8 versus 2.1 months (HR 0.32, 95%CI 0.21-0.49) showing minimal synergy.¹¹

In terms of HRQOL, a higher proportion of patients in the bevacizumab plus chemotherapy arm achieved a 15% or more improvement on the EORTC QLQ-OV28 abdominal/GI symptom subscale at week 8/9 from baseline than the chemotherapy alone arm (21.9% vs. 9.3%; difference 12.7%; $p = 0.002$). In a subgroup analysis of 99 PRO

evaluable patients with ascites at baseline who were expected to have considerable pain/GI symptoms, 44% of those in the BEV-CT arm compared to only 4.1% in the CT arm had achieved the predefined 15% or higher improvement in abdominal and GI symptoms at 8/9 weeks (difference 39.9%, 95% CI 23.9%-55.9%; $p < 0.001$).

An unplanned analysis showed that in the subgroup of women with ascites at baseline, the median PFS for women with CT was 2.5 months and for BEV-CT it was 5.6 months (HR 0.40, 95%CI: 0.26-0.60, $p < 0.001$). Results in women with ascites are in keeping with that seen in the overall study population.

Two doses of Bevacizumab were used in the trial; 10 mg/kg every 2 weeks and 15 mg/kg every 3 weeks. This appeared to be related to the schedule of the chemotherapy chosen, and the overall dose intensity was the same at 5 mg/kg/week.

Limitations of the Evidence

Although this trial is randomized, it is open label and not a placebo controlled trial, thus biases could affect both the efficacy and toxicity results. Bias may affect generalizability for example patients with better performance status would be offered the trial. Bias may affect the treatment as the investigator chose the chemotherapy regimen; however, this would not affect the randomization into Bevacizumab. The finding of a superior progression-free interval (PFI) is limited to PFI and not supported by any improvement in OS which is an objective end point. Unfortunately the authors of the study do not report whether blinded assessors verified either the PFI or ORR endpoint. Thus, an investigator could simply state "clinical progression" even though following RECIST and prematurely record progression in one of the treatment arms. This is the only randomized trial in this population. Thus there is no corroboration of these results. In addition, there was no Bevacizumab only arm in this study so it is not clear if the combination of chemotherapy with Bevacizumab is important.

OS was not different between the groups. We acknowledge that this trial was not powered for an OS end point. A significant confounding factor is that 40% of patients in the control arm (CT) received single agent bevacizumab after progressing thus potentially obscuring any difference in OS between the groups. An unplanned analysis showed no OS benefit from the addition of Bevacizumab to liposomal doxorubicin or topotecan; however, there was an OS difference seen with paclitaxel and bevacizumab versus paclitaxel alone. This observation should be considered as hypothesis generating only.¹²

There are 5 main types of ovarian cancer (high grade serous carcinoma, endometrioid carcinoma, clear cell carcinoma, mucinous carcinoma and low grade serous carcinoma).¹³ These disease histotypes may potentially respond differently to anti-angiogenic therapy. Although the numbers are small, there were 12 (7%) patients with clear cell cancer in the CT arm compared to 4 (2%) in the bevacizumab arm. In terms of serous histology the CT arm had 154 (84%) compared to the bevacizumab arm 156 (87%).² It is possible that the poorer outcome in the chemotherapy arm could be related to a high rate of poor prognosis histologies in the chemotherapy arm.¹⁴ No subgroup analysis was provided.

BRCA mutation status of patients was not reported. BRCA mutation carriers are reported to have better 5-yr survival,¹⁵ and better responses to subsequent treatments.¹⁶ Ensuring balanced randomization of such patients between the treatment arms is important.

Harms Interpretation

Bevacizumab added to weekly paclitaxel, monthly liposomal doxorubicin, or two different schedules of topotecan was well tolerated. It did not significantly increase common toxicities observed with chemotherapy (i.e., myelosuppression, febrile neutropenia, peripheral sensory neuropathy, etc.). Bevacizumab was associated with potentially serious adverse events like bowel perforation, fistula/abscess and reversible posterior leukoencephalopathy syndrome. Rates of grade 3 or higher thromboembolic events and bleeding events were the same between the arms. Bevacizumab was associated with higher rates of hypertension (i.e., 7% vs 1% grade 3 or higher) but these rates were in keeping with its use in other studies.

Compared to Bevacizumab in addition to CT in first-line treatment of ovarian cancer (GOG 218 GI events 2.6%,¹⁷ ICON 7 GI events 3%,¹⁸ Bevacizumab in the recurrent setting had a 4.4% rate of GI events. It would be important to consider limiting the use of Bevacizumab based on number of prior treatment cycles and/or involvement of bowel with tumor.¹⁹ The other concern that has been raised in other disease sites where Bevacizumab was used with taxol is the higher GI perforation rate specifically combined with paclitaxel.²⁰ Of note, in the AURELIA trial the rate of GI perforation was 2% in the bevacizumab plus chemotherapy arm and none in the chemotherapy alone arm.

Treatment related deaths due to adverse events that occurred during the study follow-up period included 6 (3%) in the chemotherapy arm and 9 (5%) in the bevacizumab arm. Risks of bevacizumab added to chemotherapy in women with platinum resistant ovarian like cancer is low but higher than in CT alone. Careful patient selection (i.e., good performance status ECOG 0-2, no evidence of bowel obstruction, surgery more than 4 weeks prior, prior pelvic or abdominal radiation, platinum refractory and no more than 2 courses of prior chemotherapy) and careful informed consent for treatment is essential.

Need

The treatment options for platinum resistant ovarian cancer are quite limited. As AURELIA shows, response rates with topotecan were 3.3%, pegylated liposomal doxorubicin were 7.9%, and weekly paclitaxel 28.8%. Response rates were markedly improved (2-7 fold higher) in all agents with the addition of bevacizumab. Progression free survival was improved in the Bevacizumab arm with acceptable toxicity. A post hoc subgroup analysis suggests a more profound effect of bevacizumab with weekly paclitaxel, but this is hypothesis generating. The lack of survival benefit may be related to aspects of study design. The HRQOL analysis was more stringent than usual requiring an improvement of 15% (rather than the usual 10%). Despite this, the Bevacizumab arm was clearly superior in an outcome variable that is very important to patients in this clinical setting.

The magnitude of the difference in PFS is 3.3 months with no observed difference in OS. Toxicity was acceptable. Withdrawals were 2.2%. No other treatment option are currently available or on the horizon for this population.

Table 4. Assessment of generalizability of evidence for bevacizumab in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. ²				
Domain	Factor	Evidence (trials, and PAG Input)	Generalizability Question	CGP Assessment of Generalizability
Population	ECOG PS	In the AURELIA trial, patients with an ECOG	Do trial results apply to patients	Results apply to patients with ECOG

Table 4. Assessment of generalizability of evidence for bevacizumab in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.²

Domain	Factor	Evidence (trials, and PAG Input)	Generalizability Question	CGP Assessment of Generalizability
		status of >2 were excluded	with an ECOG PS greater than 2? If so, why?	PS 2 or less. There may be some ECOG 3 patients who would benefit i.e., patient whose ECOG is 3 due to massive ascites/pleural effusion whose ECOG improves when drained as we know Bevacizumab could potentially reverse this but this would need to be at the discretion of the physician as many of these women would not be candidates for chemotherapy.
	Number of chemotherapy regimens	In the AURELIA trial, patients who had previous treatment with >2 chemotherapy regimens were excluded	Do trial results apply to patients who had greater than 2 chemotherapy regimens? If so, why?	Bevacizumab in addition to chemotherapy for first line platinum-resistant treatment: There are no data on these patients; however, there may be some benefit to patients who are in their first platinum resistant line of treatment. The trial includes a group of patients with a poorer prognosis compared with patients who have failed 3 lines of platinum-based therapy that would be seen in clinical practice.
	Line of Therapy	The AURELIA trial was specifically undertaken in a patient population who had measurable/assessable ovarian cancer that had progressed <6	Do trial results apply to patients who progressed during a cycle of platinum-based therapy?	Bevacizumab should not be used in primary platinum refractory patients as this population was excluded from the trial

Table 4. Assessment of generalizability of evidence for bevacizumab in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.²

Domain	Factor	Evidence (trials, and PAG Input)	Generalizability Question	CGP Assessment of Generalizability
		<p>months after completing \geq four cycles of platinum-based therapy.</p> <p>Patients with refractory disease were ineligible. In this trial, refractory disease was defined as “progression during previous platinum-containing therapy”</p>		
	Administration of intervention	In the BEV-CT arm of the AURELIA trial, the chosen chemotherapy was combined with bevacizumab 10 mg/kg IV q2w (or bevacizumab 15 mg/kg q3w if used in combination with topotecan 1.25 mg/ m ² on days 1-5 on a q3w schedule.	Are the results of the trial generalizable to a different dose schedule (i.e. is bevacizumab administered differently in clinical practise than in the trial?)	No evidence that 7.5mg/kg is useful as no RCTs in this group of patients have been completed. Based on the opinion of the CGP, a lower dose of bevacizumab (e.g., 7.5 mg/kg every 3 weeks) may have a similar clinical benefit in this patient population as the higher dose used in the AURELIA trial. The CGP also noted that there is evidence in other disease settings where bevacizumab has demonstrated a clinical benefit that is independent of the dose used.
Comparator	Choice of comparator	Chemotherapy comparators used in the AURELIA trial were: paclitaxel, liposomal doxorubicin & topotecan.	Is the comparator used in the AURELIA trial reflective of Canadian practice and standard of care? If so, how?	Suggest use with first line chemotherapy agents used in platinum resistant treatment. This could include, in addition gemcitabine, based on GOG-218 which showed safety of

Table 4. Assessment of generalizability of evidence for bevacizumab in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.²

Domain	Factor	Evidence (trials, and PAG Input)	Generalizability Question	CGP Assessment of Generalizability
				this combination. Study population was platinum sensitive and not resistant. Use of this combination is based on expert opinion.
Outcomes	Progression-free survival (PFS)	The primary outcome in the AURELIA trial was PFS. Secondary outcomes were ORR, OS, QoL & AEs.	Were the primary and secondary outcomes appropriate for the trial design?	Yes. OS and PFS are both important outcomes in this disease. PFS is important because it may be linked to HRQoL (i.e., as tumour burden decreases, patient's HRQoL improves).
Setting	Study Centres	AURELIA enrolled patients 361 patients across 13 countries and 121 study locations across Europe (Belgium, Bosnia and Herzegovina, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Portugal, Spain, Sweden and Turkey).	Do the trial results apply to patients from Canadian centres?	Yes, the trial results apply to a Canadian practice setting as the trial population would be ethnically similar to a Canadian population and the delivery of care in most of the European countries that participated in the study would be similar to that in Canadian jurisdictions.

Notes: CGP = clinical guidance panel; ECOG PS = Eastern Cooperative Oncology Group performance status; ORR= objective response rate; OS= overall survival; QoL= quality of life; AEs = adverse events.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net clinical benefit to bevacizumab given at 10 mg/kg q2weeks or 15 mg/kg q3weeks with monthly liposomal doxorubicin, weekly taxol or 2 different schedules of topotecan until disease progression by RECIST criteria in women with their first treatment for platinum resistant ovarian, primary peritoneal or fallopian tube cancer. This is based on a large multicenter open label randomized trial that demonstrated a statistically significant but clinically modest improvement in progression-free survival in favour of chemotherapy plus bevacizumab compared to chemotherapy without bevacizumab. Serious adverse events such as fistula, GI perforations and thrombosis were more commonly observed with the use of bevacizumab, but were still rare (<4%) and manageable.

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

- Careful patient selection (i.e., good performance status ECOG 0-2, no evidence of bowel obstruction, surgery more than 4 weeks prior, prior pelvic or abdominal radiation, no prior VEGF inhibitor treatment, and not primary platinum refractory) and careful informed consent for treatment is essential.
- Overall survival was a secondary outcome in the AURELIA trial and that, although no statistically significant difference was demonstrated, the trial was not adequately powered to detect such differences. Furthermore, the overall survival results were confounded by the fact that 40% of patients in the chemotherapy alone arm received bevacizumab after disease progression.

3 BACKGROUND CLINICAL INFORMATION

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

3.1 Description of the Condition

Ovarian cancer is one of the deadliest forms of gynecologic cancers with a high case fatality ratio. According to the 2015 Canadian Cancer Statistics,⁹ Canadian women have an estimated lifetime risk of 1.4% to develop the disease. There will be 2800 new ovarian cancer cases diagnosed in Canada with 1750 deaths directly attributable to the disease in 2015. As ovarian cancer is frequently asymptomatic in its early stage, the majority of patients presents with advanced, widely metastatic disease. Standard recommended initial treatment for metastatic disease includes a combination of aggressive tumour reductive surgery to minimize amount of residual disease²¹⁻²³ and platinum/taxane combination chemotherapy.²⁴⁻²⁶ Expected response to this combination therapy is in the range of 75% to 85%. Unfortunately, most patients (80-85%) with advance stage disease (stage III or IV) will subsequently recur after finishing primary treatment requiring additional therapy for further tumour control.

3.2 Accepted Clinical Practice

Disease recurrence is incurable and the goals of any treatment going forward are to maximally control symptoms, delay time to subsequent progression, improve quality of life and extend survival as much as possible. Options for palliative therapies can include any combination of systemic therapies, surgery, and radiation. Treatment plans need to be individualized taking into account each patients' current performance status, prior treatment related residual toxicities, overall disease burden and distribution at time of recurrence diagnosis, and progression free interval (PFI). Most patients with recurrent ovarian cancer can expect to receive multiple lines of different chemotherapies during the course of their illness. It is expected that the PFI after each new line of chemotherapy will be shorter than observed after the previous chemotherapy regimen. At time of clinical or radiological progression after finishing initial (first line) treatment, patients are classified as having either platinum refractory/resistant (PFI of less than 6 months) or platinum sensitive disease (PFI more than 6 months). Platinum sensitive patients are best retreated with platinum based combination therapy^{27,28} with an expected response rate of around 50% - 60%. Eventually, all patients with recurrent disease will develop resistance to platinum drugs with increasingly shortened PFI with each subsequent line of therapy.²⁹ Non-platinum based chemotherapy regimens are then considered when the PFI becomes less than 6 months and the patient is considered to be platinum resistant.

There are currently a number of standard chemotherapy regimens that had shown activity in platinum resistant disease. Most commonly used regimens in this setting are weekly Paclitaxel,³⁰ Pegylated liposomal doxorubicin,³¹ Topotecan,⁸ Oral Etoposide,³² and Gemcitabine.³³ There is no clear-cut superiority of one regimen over the others with an anticipated modest response rate between 15% and 20%. Prolonged responses are uncommon. In a platinum resistant setting, the median PFI can be between 2 to 5 months, and the median overall survival (OS) rarely exceeds 12 months. Selection of regimen is dependent on each oncologist's personal experience and preference, current patient's performance status, convenience of administration, and anticipated toxicities. There is an

urgent need for new therapy to prolong survivals in patients with platinum-resistant ovarian cancer.

Bevacizumab is a recombinant humanized monoclonal antibody that inhibits angiogenesis by neutralizing human vascular endothelial growth factor-A (VEGF-A) receptors. Bevacizumab in combination with Carboplatin and Paclitaxel had been shown to significantly improve PFI in the front line setting in two large phase 3 prospective randomized clinical trials.^{17,34} Bevacizumab had also been studied as a potentially active single agent in a platinum resistant recurrent setting. The Gynecologic Oncology Group (GOG) 170D phase 2 trial treated 36 women with platinum-resistant disease with bevacizumab at a dose of 15 mg/kg every three weeks.³⁵ A partial response rate of 5.5% was reported with stable disease seen in 47% of patients. Another study reported the use of Bevacizumab in a platinum resistant setting in 44 patients demonstrated a partial response rate of 16 percent with an additional 27 patients (61%) achieving stable disease.³⁶ Bevacizumab had also been reported to be effective in a palliative setting to control progressive ascites in end stage ovarian cancer to limit the frequency of paracentesis for symptomatic reliefs.^{37,38}

Due to the observed activity of Bevacizumab as a single agent in platinum resistance, it had been studied prospectively in combination with standard cytotoxic regimens. The result of the AURELIA phase 3 prospective randomized trial has been published recently.² The primary objective of this study was to compare PFI with chemotherapy alone vs. Avastin plus chemotherapy in the treatment of platinum resistant ovarian cancers. Secondary objectives included assessments of overall response rate, overall survival, safety and quality of life. A total of 361 patients with platinum-resistant ovarian cancer (defined as progression ≤ 6 months after ≥ 4 platinum-based cycles) were randomly assigned treatment with chemotherapy with or without the inclusion of Bevacizumab. The inclusion criteria included: platinum resistant ovarian, fallopian tube, or peritoneal cancer, no more than two prior lines of chemotherapy, no prior history of bowel obstruction, and no prior treatment with Bevacizumab. The specific chemotherapy regimen was left to each investigator's preference to include either: Paclitaxel 80 mg/m² on days 1, 8, 15, and 22 every four weeks (n = 115), Topotecan 4 mg/m² on days 1, 8, and 15 every four weeks (or 1.25 mg/m² on days 1 through 5 every three weeks) (n = 120), or Pegylated liposomal doxorubicin (PLD) 40 mg/m² on day 1 every four weeks (n = 126). Patients were treated to progression or intolerable toxicities. Patients who received chemotherapy alone were allowed to cross over to single-agent Bevacizumab at the time of disease progression. With a median follow-up of 13.0 months, compared with chemotherapy alone, patients received chemotherapy plus Bevacizumab have a significantly improvement in the overall response rate (ORR 31 versus 13 percent). There was a significant reduction in the risk of disease progression (hazard ratio [HR] 0.48, 95% CI 0.38-0.60; median duration 6.7 versus 3.4 months) favoring the Bevacizumab group. There was no statistically significant improvement in overall survival (OS, HR 0.85, 95% CI 0.66-1.08; median 16.6 versus 13.3 months) between the two study groups. The primary measure of quality of life within the AURELIA study was abdominal/GI subscale of the EORTC QLQ-OV28. AURELIA showed that the addition of bevacizumab to chemotherapy resulted in a higher proportion of patients experiencing abdominal/GI symptom improvement across all time points, except week 30. The patient subgroup with ascites at baseline also showed an increased proportion reporting improvement in abdominal/GI symptoms at all time points when bevacizumab was added to chemotherapy.

In a planned subset analysis of the AURELIA study¹¹ to evaluate the outcomes stratified per individual chemotherapy regimens, it was shown again that the addition of Bevacizumab to

chemotherapy consistently resulted in better outcomes compared with treatment with chemotherapy alone:

- In patients treated with weekly Paclitaxel, the overall response rate was 52 versus 29 percent with or without bevacizumab, respectively with a median progression-free survival (PFS) of 10 versus 4 months (HR 0.46, 95% CI 0.30-0.71).
- In patients treated with Topotecan, the overall response rate was 23 versus 3 percent; median PFS was 6 versus 2 months (HR 0.32, 95% CI 0.21-0.49).
- In patients treated with Pegylated liposomal doxorubicin, the overall response rate was 18 versus 8 percent; median PFS was 5 versus 4 months (HR 0.57, 95% CI 0.39-0.83).

Adverse events were observed at a higher percentage in Bevacizumab-treated patients for the following in decreasing order of frequency: hypertension, peripheral sensory neuropathy, fistula and abscess, proteinuria, GI perforation, ATE, wound healing complication, and reversible posterior leukoencephalopathy syndrome/ posterior reversible encephalic syndrome. These results are in line with previous experience with Avastin. Of note, four patients (2.2 percent) treated with Bevacizumab experienced a gastrointestinal perforation \geq grade 2.

These results suggest some potential palliative benefit of combining chemotherapy and Bevacizumab in the treatment of women with platinum-resistant ovarian cancer.

3.3 Evidence-Based Considerations for a Funding Population

As discussed above, the expected patient population will be for all patients with ovarian, fallopian tubes, and primary peritoneal cancers who had developed platinum resistant disease who are being considered for further palliative chemotherapy with weekly Paclitaxel, Topotecan, or Pegylated liposomal doxorubicin. It is estimated that about 70% to 80% of all ovarian, fallopian tubes, and primary peritoneal cancers would be considered for this therapy during the course of their illness. The clinician using standard criteria will easily define platinum resistance. Utilization of bevacizumab should conform to the AURELIA defined inclusion criteria: platinum resistant ovarian, fallopian tube, or peritoneal cancer, no more than two prior lines of chemotherapy, no prior history of bowel obstruction, and no prior treatment with Bevacizumab. Bevacizumab has also been incorporated into the NCCN guideline for use in combination with chemotherapy regimens similar to that used in the AURELIA trial.³⁹

3.4 Other Patient Populations in Whom the Drug May Be Used

Potential use of Bevacizumab as a single agent to control ascites accumulation can also be considered.^{37,38} It is also possible that in patients who had been previously treated with Bevacizumab in the front line setting can also benefit to re-exposure in a recurrent setting.^{40,41}

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Ovarian Cancer Canada (OCC), provided input for bevacizumab (Avastin) for the treatment of platinum-resistant ovarian cancer.

OCC conducted an online survey in English and French, which was promoted to women and caregivers of women: 1) diagnosed with epithelial ovarian, fallopian tube or primary peritoneal cancer and who have been treated with chemotherapy; 2) or who have had a recurrence of ovarian cancer and have been treated with additional chemotherapy; 3) or who have taken bevacizumab as a treatment for their recurrent ovarian cancer. The survey was promoted through OCC's database, website, social media sites and partners.

OCC received input from a total of 89 respondents of which 77 were patients and 12 were caregivers. Respondents included women diagnosed with epithelial ovarian cancer (n=66), fallopian tube cancer (n=8), primary peritoneal cancer (n=7) and other (n=8). Of the 89 respondents, the majority of women (65%) had been diagnosed between 2012 and 2015. In total, 57 respondents had a recurrence, with more than half (n=31) experiencing more than two recurrences. There were four (4) women who had their first recurrence at 8 or 9 months after diagnosis. Of the 89 respondents, 79 respondents were from Canada; none were from New Brunswick, Prince Edward Island, the Northwest Territories, Nunavut or the Yukon. Ten (10) respondents were from the United States. Respondents ranged in age from 21-71 years. OCC reported that of the 89 respondents, the majority (75%) were younger than the average age of diagnosis (63 years) and were between 40-59 years of age.

OCC followed up with respondents to determine if they had been diagnosed with platinum-resistant ovarian cancer. A total of six (6) women were diagnosed with platinum-resistant ovarian cancer and three (3) caregivers had provided care to someone with platinum-resistant ovarian cancer. OCC indicated that those (9) women that had platinum-resistant ovarian cancer were between the ages of 46-71 years when diagnosed. OCC reported that fourteen (14) respondents had direct experience with bevacizumab as a treatment for ovarian cancer: 12 of which were women diagnosed with ovarian cancer (1 of whom had platinum-resistant ovarian cancer) and 2 of which were caregivers of women diagnosed with ovarian cancer (1 of whom had platinum-resistant ovarian cancer). OCC acknowledged an error in the reporting of the respondents who indicated experience with bevacizumab; more than fourteen (total of 16) respondents answered questions about their experience with bevacizumab.

From a patient's perspective, the impact of ovarian cancer is significant for women diagnosed with this disease and their caregivers. OCC noted areas that were negatively impacted included work life, sleep, cognition, sexual intimacy, and activities of daily living. OCC observed that respondents diagnosed with platinum-resistant ovarian cancer strongly disagreed that their current or past treatments had managed their ovarian cancer. Side effects of their treatment included: fatigue, hair loss, bowel problems and neuropathy. A majority of respondents would be willing to tolerate additional side effects, if the benefits of the treatment were considered to be short term. The majority of respondents, including caregivers indicated that they would expect bevacizumab to prolong their survival, shrink their tumour, and improve their quality of life. Of those who considered taking bevacizumab, their reasons for not using bevacizumab were because it was not offered to them or it was too expensive. OCC noted that women with platinum-resistant ovarian cancer had lower expectations for bevacizumab, wanting only to see a slight improvement in their ovarian cancer. Respondents who have experience with bevacizumab reported side effects, which included high blood pressure, fatigue, bleeding and heart problems. However, respondents also felt that the drug managed their ovarian cancer or managed better their ovarian cancer compared to previous treatment. Some of the key areas of improvement reported by respondents include shrinking their tumour size, prolonging their survival, improving their prognosis, reducing fluid build-up and preventing a recurrence.

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, without modification.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Platinum-Resistant Ovarian Cancer

OCC reported that the impact of ovarian cancer is significant for women diagnosed with this disease and their caregivers. When OCC asked respondents to describe overall how their life has been affected by their diagnosis of ovarian cancer, respondents described significant psycho-social impacts, including fear, depression, worry and anxiety. OCC noted other areas that were negatively impacted: work life, sleep, cognition, sexual intimacy, and activities of daily living.

Respondents were asked to rate the impact of ovarian cancer on their lives on a scale from 1 (no effect) to 5 (extremely negative effect). OCC reported that 71 respondents answered this question and the top five areas rated 4 (very negative) or 5 (extremely negative) were as follows:

Work life - (n=45)
Sexual relationship - (n=43)
Physical activity - (n=41)
Sleep pattern - (n=40)
Level of well-being - (n=36)

According to OCC, for respondents with platinum-resistant ovarian cancer, the ratings were often higher (scores of 5) than compared to other respondents.

To help better illustrate some of the key issues, the majority of respondents with platinum-resistant ovarian cancer reported the following:

- *"I am chronically tired which leaves me unable to do many things for my kids. I had to give up my very good job. I am paying \$4138/21 days for Avastin so we will run out of money and lose our home."*
- *"It has stolen my life away from me. I have zero control of anything about my life, and treatment side effects are life changing, uncontrollable, debilitating, upsetting and extremely challenging."*
- *"Since diagnosis I have been unable to work, energy is very low so difficult to be physically active or do ordinary activities like shopping or housework. Not able to plan far ahead because of chemo treatment and then recovery time. Always thinking about cancer so yes my life has changed drastically."*
- *"It is a huge challenge to escape from the constant fear of recurrence and all that can mean I have now recurred within 6 months of treatment. I fill my days with caring for myself...but all is overshadowed with my ever present fear... Forced into early retirement."*
- *"The most difficult thing is knowing there is almost no effective treatment, that the cancer recurs for almost everyone and life expectancy is short."*
- *"I have slowed down - seems like I suddenly grew 10 years older...The cancer has affected my quality of living in every way."*
- *"You would think the worst moment of my life would have been when I was told I had Ovarian Cancer at age 21, however, that moment came soon afterwards when I was told how few effective treatment options were actually available." (not a platinum-resistant diagnosis)*

4.1.2 Patients' Experiences with Current Therapy for Platinum-Resistant Ovarian Cancer

Respondents reported that their current treatments included chemotherapy and surgery. OCC indicated that overall, the respondents neither agreed nor disagreed that their current or past treatments had managed their ovarian cancer. OCC, however, noted that those diagnosed with platinum-resistant ovarian cancer strongly disagreed that their current treatment is managing their cancer. Specifically, those diagnosed with platinum-resistant ovarian cancer stated that they are *"incurable"*, or *"tumours were never gone and continued to grow"*, *"I have recurred within 6 months of 5 months of wretched chemotherapy"*, *"no matter what chemo drugs mom was given the progress of her disease was relentless and aggressive."*

Respondents indicated that the ovarian cancer treatments negatively affected them. OCC noted that the respondents who had platinum-resistant ovarian cancer responded similarly. OCC reported that respondents were deeply affected by the fatigue, hair loss, bowel problems and neuropathy from their treatment.

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. According to OCC, there are a number of areas that were rated as having a negative influence on the women's lives. OCC reported that 79 respondents answered this question and the key areas that rated as 4 (very negative) or 5 (extremely negative) were also follows:

Fatigue - (n=52)
Bowel problems - (n=43)
Hair loss - (n=40)
Neuropathy - (n=35)
Aching joints - (n=30)
Nausea/vomiting - (n=28)
Blood problems - (n=26)
Ascites - (n=16)
Skin irritations - (n=13)
Loss of fertility - (n=8)

According to OCC, many respondents reported that particular side effects were worse the second time they had treatment. OCC stated that this was particularly the case for joint pain. Recorded responses from those with platinum-resistant ovarian cancer included:

- *"Foggy brain difficult to concentrate and comprehend things...very low energy tired all of the time, emotional."*
- *"I was nauseous though (sic) almost the entire treatment...my sleep has been altered...my neutrophils were low...had a blood transfusion....very constipated...lots of neuropathy....peripheral nerves were damaged...joints all achemouth sores."*

A majority of respondents noted the impact of fatigue. Specifically, 66% of respondents rated their fatigue as having a large effect or extremely large effect on their quality of life.

- *"So fatigued...sleep about two hours every afternoon...could do little socially..."*
- *"Energy is very low so difficult to be physically active or do ordinary activities (sic) like shopping or housework."*
- *"Very low energy tired all of the time."*

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

- *"I was very constipated most of the time through treatment...had severe diarrhea from trying to correct it. Currently my bowel movements are very loose and constant through the day."*
- *"I am constantly constipated."*

Many respondents also commented on the impact of the neuropathy.

- *"Neuropathy makes walking difficult."*
- *"Neuropathy in hands and feet, both arms fall asleep during the night and I wake in pain and numbness."*

In addition to the above symptoms, aching joints was also mentioned.

- *"My joints all ache which limits my activities."*
- *"The joint pain has been so severe I have had many days where it was difficult just to walk in the house for bare necessities."*

OCC also asked respondents if they would have been willing to tolerate additional side effects, if the benefits of the treatment were considered to be short term (e.g. months versus years of improvement). Out of 79 respondents, 47 respondents answered "yes", six (6) respondents answered "no" and 26 respondents were "uncertain". Of the nine (9) respondents with platinum-resistant ovarian cancer, 5 respondents answered "yes", 1 respondent answered "no" and 3 respondents were "not sure".

In particular, respondents diagnosed with platinum-resistant ovarian cancer reported the following:

- *"I would tolerate side effects to any extent. I have children."*
- *"I would tolerate almost any side effect if it increased the chances of controlling the spread of the cancer and if the probability was that any severe effects would lessen over time, eg (sic) noticeably and manageable within about three to six months."*

Respondents were also asked about the barriers (e.g.: financial, travel and treatment not available) that they encountered in accessing their treatment. OCC reported the following barriers rated between significant and extremely significant (total out of 69 respondents):

Financial difficulties - (n=21)

- *"Money. I am paying for Avastin by using all of my family's savings, including money that was for my kids (sic) education." (platinum-resistant respondent)*
- *"I was forced into early retirement can not live on long term disability and cpp income savings diminishing not sure what to do..."(platinum-resistant respondent)*

Travel issues - (n=20)

- *"Waiting seven weeks for surgery and travelling nine hrs for surgery. Traveling twelve times four hr trips each way for chemo."*

Treatment not available - (n=20)

- *"Treatment availability has had a huge impact."*

4.1.3 Impact of Platinum-Resistant Ovarian Cancer and Current Therapy on Caregivers

OCC reported that 12 caregivers responded to this survey: five (5) respondents were a spouse/partner; three (3) respondents were a mother; three (3) respondents were a sister; and

one (1) respondent was a friend. Three (3) of the caregivers provided care to women diagnosed with platinum-resistant ovarian cancer.

OCC indicated that the majority of caregivers have been providing care for 1-2 years for approximately 1-6 hours most days. OCC also noted that the majority of women for whom caregivers provided care had experienced a recurrence. Depression, anxiety, panic and physical strain were noted as negative impacts of caregiving.

Caregivers also noted that the following key areas of their life were negatively impacted (total of 11 respondents):

- Work life - (n=9)
- Sleep pattern - (n=9)
- Well-being - (n=9)
- Physical activity - (n=8)
- Family/friend relationships - (n=8)

Caregivers were asked to describe how their life has been affected by ovarian cancer (for instance, describe how their daily routines, physical functioning, mental state, overall life etc. have been affected) and to include anything relevant to their experience. OCC reported the following responses from those caring for someone with platinum-resistant ovarian cancer:

- *"We all share a sense of panic about the decisions that need to be made. Overwhelmed."*
- *"My ability to function at work was impaired. I ended up seeing a psychiatrist...I took stress leave from my job...I participated in her care 24/7 at that point, although physically I had to hand off some...I'm still receiving mental health care; my mom died eight months ago."*

According to OCC, the majority of caregivers (70%) disagreed or strongly disagreed that the current treatments managed their loved one's ovarian cancer. Caregivers reported that fatigue and bowel problems were the most troublesome side effects affecting the women's quality of life. Notwithstanding, OCC stated that 80% of respondents thought the person for whom they were 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).

OCC asked caregivers if your family member or friend was to take bevacizumab, how important would it be that bevacizumab was able to address certain issues. OCC reported that all of the caregivers who responded rated the following issues as very to extremely important: the drug should also prolong survival, shrink the tumour size, improve quality of life and decrease the fluid build-up.

OCC also asked caregivers if they thought bevacizumab should be available as a treatment option for women in Canada who have platinum-resistant ovarian cancer. Out of seven (7) respondents, six (6) respondents thought it "should be available" and one (1) respondent said "maybe". One respondent noted the following: *"Women with platinum resistant ovarian cancer have very few effective treatment options. The studies I've seen show that Avastin can be effective for a good subset of these women, and is generally much better tolerated than standard cytotoxic treatments. The issue is the cost of the treatment."*

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Bevacizumab

OCC indicated that of the 62 women who have not been treated with bevacizumab, 24 considered taking bevacizumab. For those who considered taking bevacizumab (n=24), their reasons for not using bevacizumab were because it was not offered to them or it was too expensive.

OCC asked respondents if they were able to take bevacizumab, what are the outcomes that respondents would expect the drug to address. According to OCC, the majority of respondents, including caregivers indicated that they would expect the drug to prolong their survival, shrink their tumour, and improve their quality of life. OCC reported a total of 58 respondents rated the following items 4 (very important) or 5 (extremely important): prolong survival (n=55), shrink tumour size (n=53), improve quality of life (n=45), and decrease fluid buildup (n=33). OCC noted that respondents with platinum-resistant ovarian cancer scored this question higher than other respondents, rating the items as 5 (extremely important).

According to OCC, the majority of respondents would want to see some improvement in their ovarian cancer when considering to take bevacizumab. OCC reported that on a scale of 1 (no improvement) to 5 (no sign of ovarian cancer), women and caregivers rated the improvement they would want to see as a 3. OCC noted that women with platinum-resistant ovarian cancer had lower expectations for bevacizumab, wanting only to see a slight improvement in their ovarian cancer.

OCC indicated that the majority of women were willing to deal with many of the side effects. The specific side effects respondents (total out of 58) were willing to accept are indicated below:

Fatigue - (n=50)
Nausea/poor appetite - (n=46)
Constipation/diarrhea - (n=44)
High blood pressure - (n=41)
Numbness - (n=40)
Blood problems - (n=28)
Increased risk of bleeding - (n=27)
Heart problems - (n=21)

OCC stated that 42% of respondents indicated that they would tolerate the side effects because they wanted to improve their chance of survival. Almost half of respondents noted that the side effects seemed manageable as they were no different than their chemotherapy side effects. Some of the responses reported from those with platinum-resistant ovarian cancer and their caregivers are cited below:

- *"Similar to chemo."*
- *"To stay off chemo."*
- *"I can live with these and manage them I already live with fatigue, numbness and diarrhea."*
- *"The other option is death...no hope of symptom free survival for even a short period of time."*
- *"For effective treatment - she wants to live as long as possible."*
- *"Maintenance or stable disease is something that many people can live with."*

According to OCC, the majority of women and caregivers surveyed believe "yes" that the benefits of bevacizumab would outweigh the risks. OCC noted that although this was not the case for women with platinum-resistant ovarian cancer, who answered that they were "not sure"; their comments below, indicated that they are very interested in having access to bevacizumab as a treatment option.

The majority of respondents believe bevacizumab should be available as a treatment option for women in Canada who have platinum-resistant ovarian cancer. Below were some of the responses that were noted:

- *“Anything that may grant us longer life would be fantastic.” (platinum-resistant respondent)*
- *“I think Canada takes far too long to approve use of drugs/treatment for conditions/diseases that reduce life expectancy dramatically such as ovarian cancer...Trust the conclusions of others who have also participated in these trials that are usually conducted across border (sic) and oceans.” (platinum-resistant respondent)*
- *“It is helping others in other countries, we deserve the same opportunity.”*
- *“Clinical trials have shown Avastin to be superior choice for platinum-resistant, recurrent ovarian cancer. Not making the drug available to women in Canada is unethical and indefensible.”*

OCC reported that fourteen (14) respondents had direct experience with bevacizumab as a treatment for ovarian cancer: 12 of which were women diagnosed with ovarian cancer (1 of whom had platinum-resistant ovarian cancer) and 2 of which were caregivers of women diagnosed with ovarian cancer (1 of whom had platinum-resistant ovarian cancer). However, it is important to note that there were in fact 16 respondents who answered questions about their experience with bevacizumab generally; therefore, the number of respondents varied.

Out of 16 respondents, six (6) respondents indicated that bevacizumab caused additional side effects, five (5) respondents indicated that there were no additional side effects and (5) respondents did not know (caregiver responses). Respondents (total out of 10) noted the following treatment side effects: high blood pressure (n=2), fatigue (n=2), bleeding (n=2), heart problems (n=1) and the remainder didn't know (caregiver respondents) (n=3).

Respondents (total out of 15) were asked to rate the extent to which they agree or disagree with the following statement: *“AVASTIN has improved my quality of life compared to previous treatments I have used.”* The responses were:

- Strongly or somewhat disagree - (n=0)
- Neither disagree nor agree - (n=2)
- Agree - (n=3)
- Strongly agree - (n=5)
- Don't know - (n=4) (caregiver respondents)

The 16 respondents were asked to rate the top three issues that bevacizumab has managed their ovarian cancer or managed better their ovarian cancer compared to previous treatment. OCC stated that most respondents reported that the top issues (rated as #1) bevacizumab managed or managed better than previous treatment for ovarian cancer was shrinking their tumour size (n=11) and prolonging their survival (n=11). The issues rated as #2 were their fatigue (n=5) and improving their prognosis (n=5). The issues rated #3 were fluid build-up (n=8) and preventing a recurrence (n=7).

OCC reported that respondents did not note any side effects that were not acceptable. OCC found that a few respondents specifically noted that they considered hypertension and arthralgia as acceptable side effects.

OCC stated that out of 8 who responded to the question, the majority of respondents strongly agreed that bevacizumab has improved their quality of life compared to their previous treatments.

One respondent with platinum-resistant ovarian cancer stated: *“Avastin has allowed me to stave off recurrence for longer, giving me a chance to raise my kids, and enjoy life, maybe even taking a job again and being productive.”*

Other comments about the effects of bevacizumab on their quality of life included:

- *“I feel I am able to breathe better which of course takes away the anxiety I faced before.”*
- *“Treatments are every 3 weeks as opposed to weekly with chemo, they take only 1 hour and do not require pre-medication. I will not lose my hair...Avastin will not destroy my immune system.”*
- *“I’ve had only very minor side effects from Avastin but had a complete response to the treatment...allowing me to live a normal live while fighting cancer.”*
- *“I can live independently.”*

4.3 Additional Information

OCC would like to highlight that the low number of respondents who were diagnosed with platinum-resistant ovarian cancer and/or who took bevacizumab as treatment 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 for ovarian cancer. Additionally, most women with platinum-resistant ovarian cancer are living with a 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 following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for bevacizumab in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. 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 CADTH website (www.cadth.ca/pcodr).

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.
- Unknown duration of treatment.

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 platinum-resistant ovarian cancer is pegylated liposomal doxorubicin, paclitaxel and/or topotecan. These were the comparators used in the pivotal clinical trial.

5.2 Factors Related to Patient Population

PAG indicated that women with platinum-resistant ovarian cancer is a relatively small patient population. However, the prevalent population eligible for treatment may be large, if heavily pre-treated patients are considered eligible.

PAG noted that eligible patients in the pivotal trial were strictly defined. PAG is seeking information on the generalizability of trial results to patients who

- have received more than two prior treatments
- have progressed more than six months after completion of platinum-based therapy

- began treatment with pegylated liposomal doxorubicin, paclitaxel and/or topotecan prior to funding of bevacizumab for platinum-resistant ovarian cancer but not yet progressed
- have received bevacizumab, in combination with paclitaxel and carboplatin, in the first-line setting.

PAG is seeking clarity on the exclusion criteria, continuation of bevacizumab as monotherapy when chemotherapy is withheld, retreatment with bevacizumab in combination with another chemotherapy in later lines of therapy, and the definition of platinum-resistant disease versus platinum-refractory disease. PAG is also seeking information on the optimal sequencing of treatments, recognizing that there may not be evidence available.

5.3 Factors Related to Dosing

PAG noted that the dosing schedule of bevacizumab coincides with the dosing schedules for topotecan and paclitaxel. However, PAG indicated that for patients receiving pegylated liposomal doxorubicin, there is an additional infusion day to accommodate the bevacizumab. This has implications for both patient access and chemotherapy chair time.

PAG is seeking clarity on the optimal dosing schedule of bevacizumab. It was noted that bevacizumab is 10mg/m² every 2 weeks if administered with pegylated liposomal doxorubicin or paclitaxel. However, the dose of bevacizumab is 15mg/m² every 3 weeks if administered with topotecan.

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.

Patients on pegylated liposomal doxorubicin receive the treatment on day 1 of a 28-day cycle. If bevacizumab is added-on, there is an additional day to schedule as bevacizumab is administered every 2 weeks.

In addition, the unknown duration of therapy makes budget impact analysis uncertain.

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. However, there is additional monitoring for adverse events that is new to this patient population and the higher dosage of bevacizumab (compared to use in colorectal cancer) 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 and the potentially large budget impact, as bevacizumab is add-on therapy, would be barriers to implementation.

6 SYSTEMATIC REVIEW

6.1 Objectives

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

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
Published and unpublished RCTs or non RCTs In the absence of RCT data, fully published clinical trials investigating the safety and efficacy of bevacizumab should be included.	Adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.	Bevacizumab dose of 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion, in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan in patients who cannot receive platinum therapy.	All appropriate multi-agent chemotherapy regimens including but not limited to: ➤ Paclitaxel ➤ Pegylated liposomal doxorubicin (PLD) ➤ Topotecan ➤ Gemcitabine	<ul style="list-style-type: none"> • OS • PFS • ORR • HRQoL • AEs • SAEs • WDAE
<p>[Abbreviations] OS= overall survival; PFS= progression-free survival; ORR= overall response rate; HRQoL= health-related quality of life; RCT=randomized controlled trial; SAE=serious adverse events; AE=adverse events; WDAE=withdrawals due to adverse events</p>				

* All treatments in combination with supportive care.

† 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-present) with in-process records & daily updates via Ovid; Embase (1974-present) via Ovid; The Cochrane Central Register of Controlled Trials (October 2015) via Ovid; 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 Avastin/bevacizumab, ovarian, fallopian, and peritoneal cancers, paclitaxel, topotecan, and doxorubicin.

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year. The search is considered up to date as of February 4 2016.

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 - clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (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 additional 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. One member of the pCODR Methods Team independently made the final selection of studies to be included in the review.

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.

A data audit was conducted by another member of the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

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

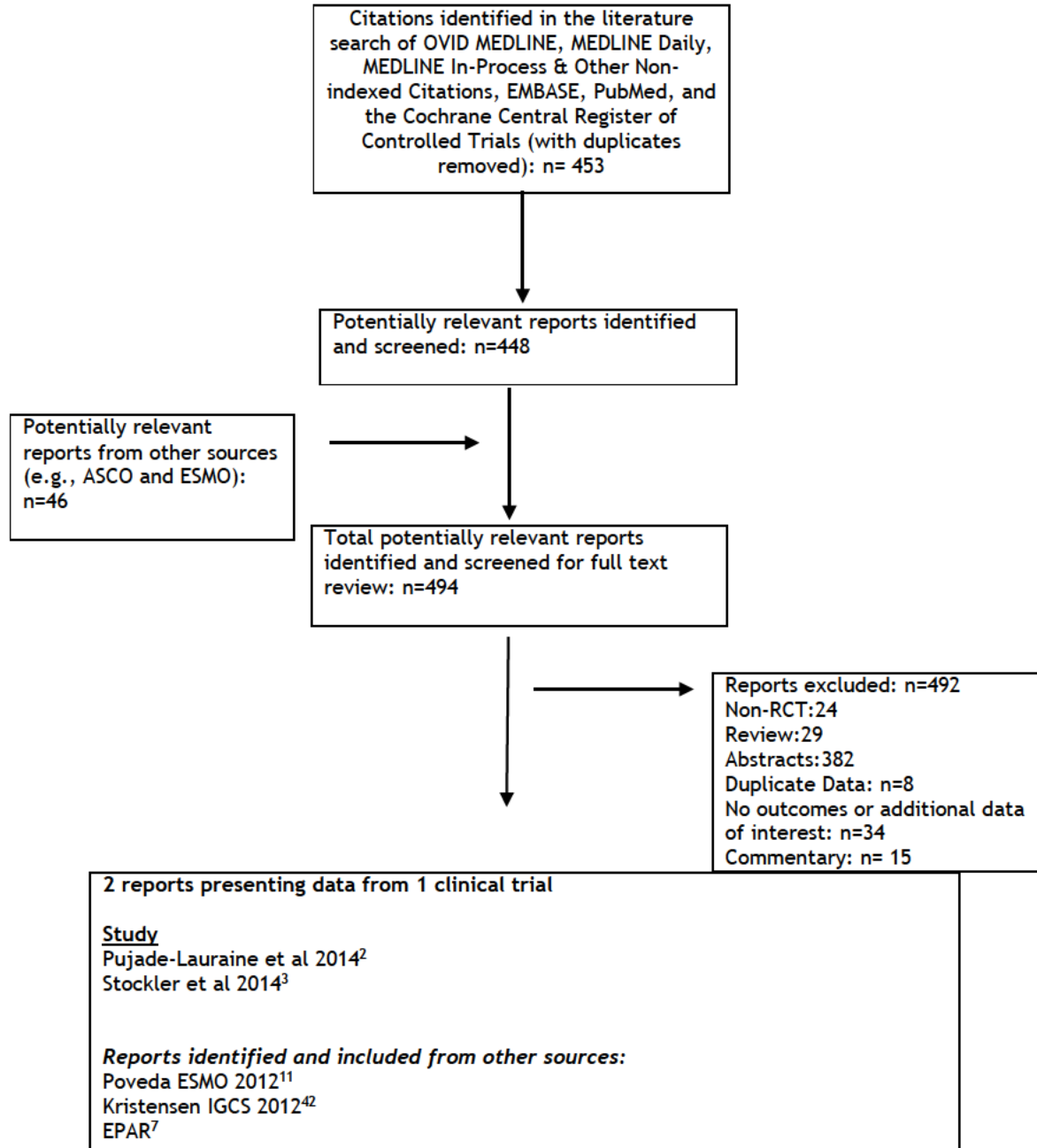
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental issues.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information, the interpretation of the systematic review and wrote guidance and conclusions for the report.

- 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

Sample QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

One randomized controlled trial was identified that met the eligibility criteria of this systematic review and was selected for inclusion (Please see Table 2). AURELIA is an open-label, randomized two-arm, phase III trial that examined bevacizumab plus chemotherapy (BEV-CT) versus chemotherapy (CT) alone in patients with recurrent platinum-resistant (disease progression within <6 months of platinum therapy) epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Further information was also available from EPAR reports, information that comes from the trial noted above but that is not found in the primary publication. Even further information was also 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 studies of bevacizumab in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer ^{2,43}			
Trial Design	Key Inclusion Criteria	Intervention and Comparators	Outcomes
<p>NCT00976911</p> <p>Other study ID numbers: MO22224, 2009-011400-33</p> <p>AURELIA</p> <p>Open-label, randomized, multi-center, two-arm interventional Phase III trial</p> <p>Enrollment: 361</p> <p>Start date: October 2009</p> <p>Completion date: July 2014</p> <p>Study Sponsor: Hoffman-La Roche</p>	<ul style="list-style-type: none"> Female patients ≥ 18 years of age epithelial ovarian, fallopian tube or primary peritoneal cancer platinum-resistant disease (disease progression within <6 months of platinum therapy) ECOG performance status of 0-2 <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> non-epithelial tumours ovarian tumours with low malignant potential previous treatment with >2 chemotherapy regimens prior radiotherapy to the pelvis or abdomen 	<p>Intervention:</p> <ul style="list-style-type: none"> bevacizumab: <ul style="list-style-type: none"> 10m/kg iv every 2 weeks or 15mg/kg iv every 3 weeks Pegylated liposomal doxorubicin: <ul style="list-style-type: none"> 40mg/m² iv every 4 weeks paclitaxel: <ul style="list-style-type: none"> 80mg/m² iv on days 1, 8, 15 and 22 of each 4-week cycle topotecan: <ul style="list-style-type: none"> 4mg/m² iv on days 1, 8 and 15 of each 4-week cycle, or 1.25 mg/m² on days 1-5 of each 3-week cycle <p>Comparator:</p>	<p>Primary:</p> <ul style="list-style-type: none"> PFS Percentage of patients with disease progression or death <p>Secondary:</p> <ul style="list-style-type: none"> ORR Duration of objective response Percentage of participants who died OS QoL: EORTC-QLQ-OV28, HADS, FOSI Safety and Tolerability AEs

		<ul style="list-style-type: none"> • Pegylated liposomal doxorubicin • paclitaxel • topotecan 	
Notes: ECOG = Eastern Cooperative Oncology Group; PS = performance status; QoL = quality of life; AEs = adverse events; PFS= progression-free survival; ORR= objective response rate; OS=overall survival; EORTC-QLQ-OV28= European Organization for Research and Treatment of Cancer's Quality of life questionnaire-Ovarian Cancer Module 28; HADS= Hospital Anxiety and Depression Scale; FOSI= Functional Assessment of Cancer Therapy- Ovarian Cancer Symptom Index; AEs = adverse events.			

a) *Trials*^{2,7}

AURELIA was an open-label phase III randomized controlled trial. Eligible patients had histologically confirmed epithelial ovarian, fallopian tube or primary peritoneal cancer (measurable by RECIST) that had progressed within 6 months of completing 4 or more cycles of platinum-based therapy. At the decision of the investigator, patients were assigned to receive one of three chemotherapy agents: paclitaxel (80 mg/m² intravenously (IV) on days 1, 8, 15, and 22 every 4 weeks; pegylated liposomal doxorubicin (PLD) 40 mg/ m² IV on day 1 every 4 weeks, or topotecan 4 mg/ m² IV on days 1, 8, and 15 every 4 weeks or 1.25 mg/ m² on days 1 to 5 every 3 weeks. Patients were then randomized 1:1 to receive either single-agent chemotherapy or to chemotherapy plus bevacizumab (10 mg/kg every 2 weeks, or 15 mg/kg every 3 weeks in those receiving topotecan in a 3-weekly schedule). Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent. Patients in the bevacizumab plus chemotherapy (BEV-CT) arm who experienced toxicities requiring discontinuation of one agent could continue treatment with the other agent and chemotherapy doses could be reduced using individual schedules for each chemotherapy drug. The initial bevacizumab infusion was over 90 minutes, with subsequent infusions over 60 minutes and then 30 minutes as tolerated. Dose reductions for bevacizumab were not permitted. If there was clear evidence of disease progression (as per RECIST 1.0), patients in the CT arm were given the opportunity to crossover to bevacizumab monotherapy, and the treatment was continued until disease progression, unacceptable adverse events, or patient request for discontinuation.

b) *Populations*^{2,7,43}

AURELIA enrolled patients 361 patients across 13 countries and 121 study locations in Belgium, Bosnia and Herzegovina, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Portugal, Spain, Sweden and Turkey. Baseline patient characteristics were balanced between arms. Investigator selection of chemotherapy was evenly distributed among the three options (PLD, n=126, paclitaxel, n=115, topotecan, n=120). This was made possible due to capping of the chemotherapy recruitment cohort that closed once 120 patients were recruited. The median age was 61 years in the chemotherapy alone arm and 62 years in the bevacizumab plus chemotherapy arm. Approximately 58.8% of the patients in the trial had an ECOG performance status of 0, 34.3% had an ECOG performance status of 1, and 6.7% of had an ECOG performance status of 2. Approximately 41.6% of patients had received two prior chemotherapy regimens and 31% had ascites at baseline. The primary outcome of the trial was to compare the efficacy and progression-free survival (PFS) of bevacizumab plus chemotherapy versus chemotherapy alone, with 290 events required to detect a hazard ratio (HR) of 0.72 with 80% power (assuming a median PFS of 5.7 months in the bevacizumab plus chemotherapy arm and 4.0 months in the chemotherapy alone arm). Secondary outcomes were objective response rate (ORR) according to RECIST and/or Gynecologic Cancer Intergroup (GCIg) cancer antigen (CA) - 125 criteria, overall survival (OS), safety, tolerability, and quality of life (QoL). However, it is important to note that

the sample size requirement was based on the primary outcome of PFS and not on objective response or overall survival.

Table 3. Baseline Patient Characteristics in the included studies of bevacizumab in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer²		
	Bevacizumab plus Chemotherapy (BEV-CT) (n=179)	Chemotherapy Alone (CT) (n=182)
Patient Characteristics		
Origin of cancer, ovary	93%	86%
Median age (years, range)	62 (25-80)	61 (25-84)
ECOG PS		
0	60%	54%
1	32%	38%
2	7%	6%
Histologic grade at diagnosis		
1	6%	5%
2	30%	26%
3	53%	58%
Missing	12%	11%
Two prior chemotherapy regimens	40%	43%
Platinum-free interval <3 months*	28%	25%
Ascites	33%	30%
Notes: *From last platinum to subsequent disease progression ECOG PS= Eastern Cooperative Oncology Group Performance Status		

c) Interventions^{2,7}

In AURELIA, patients were randomized 1:1 to BEV-CT or CT alone and were stratified according to selected chemotherapy cohort (PLD vs. paclitaxel vs. topotecan), prior antiangiogenic therapy (yes vs. no), and platinum-free interval (<3 months vs. 3 to 6 months from last platinum therapy to subsequent progression). In both arms, chemotherapy consisted of one of the following regimens: paclitaxel (80 mg/m² intravenously (IV) on days 1, 8, 15, and 22 every 4 weeks; PLD 40 mg/m² IV on day 1 every 4 weeks, or topotecan 4 mg/ m² IV on days 1, 8, and 15 every 4 weeks or 1.25 mg/m² on days 1 to 5 every 3 weeks. In the BEV-CT arm, the chosen chemotherapy was combined with bevacizumab 10 mg/kg IV q2w (or bevacizumab 15 mg/kg q3w if used in combination with topotecan 1.25 mg/ m² on days 1-5 on a q3w schedule). The initial bevacizumab infusion was over 90 minutes, with subsequent infusions over 60 minutes and then 30 minutes, as tolerated. The median duration of therapy was three cycles (range of 1-17) in the CT arm versus six cycles (range of 1-24) in the BEV-CT arm. Chemotherapy exposure was noted to be higher in the BEV-CT arm, and this was reflected in the longer PFS observed in the bevacizumab-treated patients.

d) Patient Disposition⁷

There were a total of 361 patients in the AURELIA trial who were randomized 1:1 to receive either chemotherapy or BEV-CT. The number of patients randomized to the CT arm was 182 compared to 179 who were randomized to the BEV-CT arm. A total of 82.4% (n=150) of patients in the CT arm terminated the study vs. 79.3% (n=142) in the BEV-CT arm.

Reasons for termination in the CT arm included: subject withdrew consent (2.2%), death (74.7%), adverse events (0%), protocol violation (1.1%), and other reasons (4.4%). There were 17.6% (n=32) of patients who were under study follow-up as of January 25th 2013.

Reasons for termination in the BEV-CT arm included: subject withdrew consent (3.4%), death (70.4%), adverse events (0.6%), protocol violation (0%), and other reasons (5.0%). There were 20.7% (n=37) of patients who were under study follow-up as of January 25th 2013.

e) Limitations/Sources of Bias

- The trial was open-label, and thus is at risk for a number of different biases that can affect the internal validity of a trial. Examples of such biases are patient selection as part of inclusion criteria for eligibility and performance bias due to knowledge of the study treatment. In addition, assessments of tumour progression for the primary outcome of PFS, were conducted by the investigator, which increases the potential for bias.
- Approximately 40% of patients randomized to receive chemotherapy alone crossed over to receive single-agent bevacizumab at 15 mg/kg once every 3 weeks on clear evidence of disease progression. This introduces a potential for bias as the control arm received the experimental drug which could have reduced the difference in effect size between the two treatment arms.
- Subgroup Analysis of patients by chemotherapy cohort was unplanned and thus is at risk of increasing the type I error rate. Unplanned subgroup analyses may also lead to treatment groups being incomparable because of randomization issues causing confounding and bias within the results. Consequently, the corresponding p-values cannot be interpreted with rigour and validity.
- Patient-reported outcomes have a high risk of bias given the open-label nature of the trial.
- Patient-reported outcomes for this trial also had missing data/questionnaires which have the potential of introducing bias regarding handling of missing data in the resulting analysis.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes²

a) Efficacy Outcomes

The data cut-off for the primary analysis was November 14, 2011. The median duration of follow-up was 13.0 months in the BEV-CT arm versus 13.9 months in the CT arm. Efficacy analyses were based on an intent-to-treat (ITT) population, which included all randomly assigned patients. Safety analyses were based on the safety population, which included all patients who received greater or equal to one dose of study treatment. Tumour assessment was performed by blinded assessors in the AURELIA study, and was only performed post-study treatment in the absence of confirmation of disease progression, at 8-week intervals. Patients were followed up with tumour assessments for a minimum of 6 months unless disease progression occurred earlier. Follow-up for survival continued until the last patient had completed a minimum of 12 months after the end of treatment.⁷

The AURELIA study met its primary endpoint (investigator-assessed) and demonstrated a significant improvement in PFS with the addition of bevacizumab to a chemotherapy regimen (HR = 0.48; 95% CI: 0.38, 0.60; log-rank p-value <0.001). PFS in the two treatment arms was compared using an unstratified two-sided log-rank test. PFS was also determined by an independent review

committee (IRC) by baseline risk factor and demonstrated similar results (HR= 0.48; 95% CI: 0.37-0.63).

In addition to the improvement in PFS, the AURELIA trial also demonstrated a statistically significant and clinically meaningful improvement in ORR. The ORR increased from 12.6% in the chemotherapy alone arm to 30.9% in the BEV-CT arm (Please see Table 5 below). The analysis of duration of objective response rate (ORR) included only randomized patients with an objective response. Patients who had an objective response and did not experience disease progression or death at the time of analysis were censored at the time of the last tumour assessment.²

Overall survival at the final analysis also indicated a small improvement. However, the OS did not meet statistical significance. At the data cut-off at final analysis, 40% of patients in the CT arm had crossed over to receive single-agent bevacizumab after experiencing disease progression on CT alone.

Patients were assessed for disease response or progression every 8 or 9 weeks, throughout the study until PD, using the same imaging method used during screening (CT scan, MRI or plain X-ray).⁷

Table 4 Key efficacy outcomes of bevacizumab in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. ²			
		Bevacizumab plus Chemotherapy (n=179)	Chemotherapy Alone (n=182)
Progression-Free Survival (PFS)	Median (95% CI) [months]	6.7 (5.7-7.9)	3.4 (2.2-3.7)
	Unstratified HR (95% CI)	0.48 (0.38-0.60; log-rank p<0.001)	
Objective response rate (ORR)	RECIST and/or GCIG CA-125 criteria (350 evaluable patients)	30.9%	12.6%
		Two-sided X ² p<0.001	
	RECIST (287 evaluable patients)	27.3%	11.8%
		Two-sided X ² p=.001	
	GCIG CA-125 (297 evaluable patients)	31.8%	11.6%
		Two-sided X ² p<0.001	
Overall survival (OS)	Median (95% CI) [months]	16.6 (13.7-19.0)	13.3 (11.9-16.4)
	Unstratified HR (95% CI)	0.85 (0.66-1.08; log-rank p<0.174)	
Notes:			

Figure 1. Kaplan-Meier plot of Progression Free Survival in Randomized patients⁷

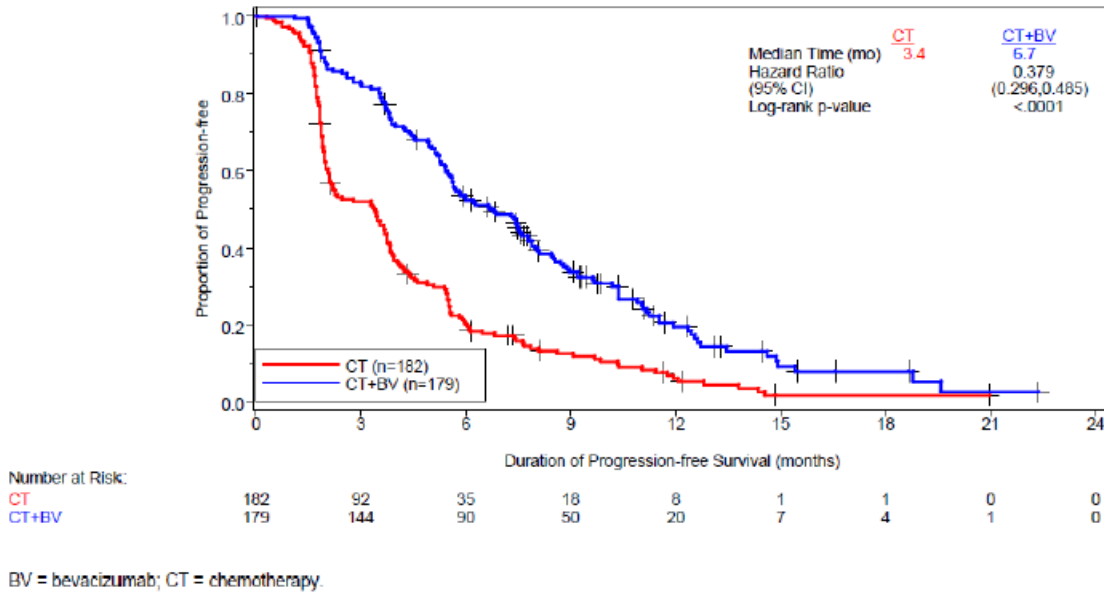
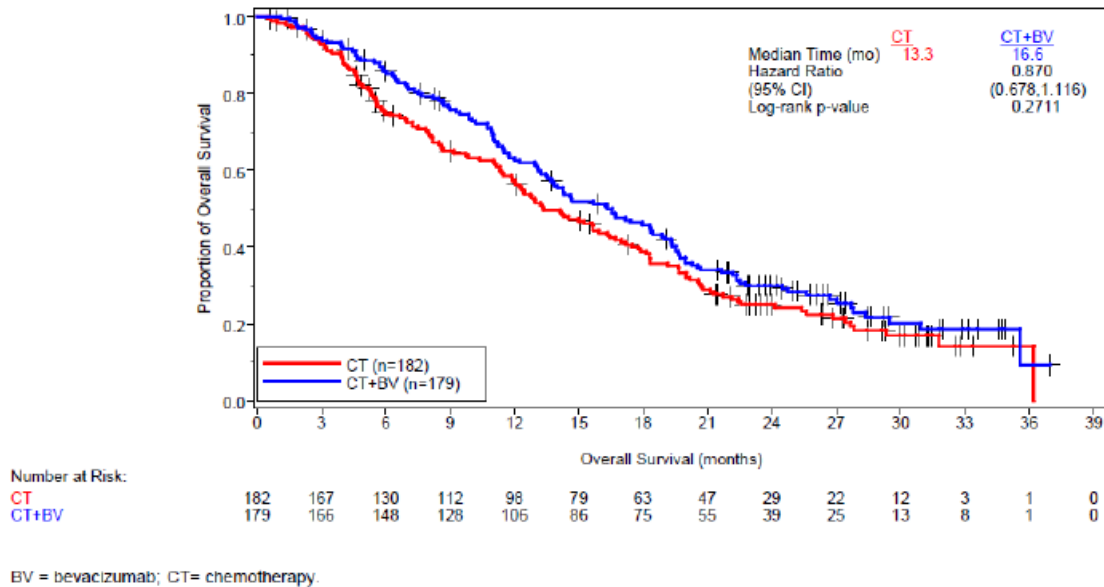


Figure 2. Kaplan-Meier plot of Overall Survival: Final Analysis⁷



Subgroup Analysis of patients by chemotherapy cohort in the AURELIA trial¹¹

AURELIA trial design included the following chemotherapy options by investigator's choice:

1. Paclitaxel 80 mg/m² on days 1, 8, 15, and 22 every 4 weeks
2. Topotecan 4 mg/m² on days 1, 8, and 15 every 4 weeks (or 1.25 mg/m² on days 1-5 every 3 weeks)
3. PLD 40 mg/m² on day 1 every 4 weeks

The weekly paclitaxel cohort consisted of 115 patients in total, of which 30.2% were allocated to the CT arm and 33.5% to the BEV-CT arm from October 2009 to April 2011. The PLD cohort consisted of 126 patients in total, of which 35.2% were allocated to the CT arm, and 34.6% to the BEV-CT arm from October 2009 to October 2010. The topotecan cohort consisted of 120 patients in total, of which 34.6% were allocated to the CT arm, and 31.8% to the BEV-CT arm from October 2009 to April 2011.

Baseline characteristics between the 3 cohorts were generally well balanced. However, there were more patients in the weekly paclitaxel cohort who had 2 prior chemotherapy regimens and a platinum-free interval of less than 3 months, measured from last platinum therapy to subsequent progressive disease, than compared to the other 2 cohorts of PLD and topotecan.

Progression-Free Survival by chemotherapy cohort

In the paclitaxel cohort, there was a greater observed difference for median PFS in the BEV-CT arm of 10.4 months (95% CI: 7.9-11.9) compared to 3.9 months (95% CI: 3.5-5.6) in the CT arm. The unstratified hazard ratio was 0.46 (95% CI: 0.30-0.71).

In the PLD cohort, there was a slight observed difference for median PFS in the BEV-CT arm of 5.4 months (95% CI: 3.9-6.6) compared to 3.5 months (95% CI: 1.9-3.9) in the CT arm. The unstratified hazard ratio was 0.57 (95% CI: 0.39-0.83).

In the topotecan cohort, there was a slight observed difference for median PFS in the BEV-CT arm of 5.8 months (95% CI: 5.3-7.5) compared to 2.1 months (95% CI: 1.9-3.3). The unstratified hazard ratio was 0.32 (95% CI: 0.21-0.49).

Overall Response Rate by chemotherapy cohort

In the weekly paclitaxel cohort, the ORR in the BEV-CT arm was 51.7% compared to 22.8% in the CT arm. The difference in the ORR was 22.9% (95% CI: 3.9-41.8).

In the PLD cohort, the ORR in the BEV-CT arm was 18.3% compared to 7.9% in the CT arm. The difference in the ORR was 10.4% (95% CI: -2.4-23.2).

In the topotecan cohort, the ORR in the BEV-CT arm was 22.8% compared to 3.3% in the CT arm. The difference in the ORR was 19.5% (95% CI: 6.7-32.3).

Subgroup analysis of patients with ascites at baseline⁴²

In the AURELIA trial, of the 361 patients included in the ITT population, there were 113 (31%) who had ascites at baseline. Of these, 54 (30%) of these patients were in the CT arm and 59 (33%) in the BEV-CT arm.

In this subgroup of patients with ascites at baseline, the median PFS was 5.6 months in the BEV-CT arm compared to 2.5 months in the CT alone arm. The PFS HR was 0.40 (95% CI: 0.26-0.60; p<0.001).

b) Harms Outcomes⁷

As of the data cut-off date of January 25 2013, a total of 136 (74.7%) patients in the CT arm and 128 patients (71.5%) in the BEV-CT arm had died. The majority of these deaths were attributable to disease progression and ovarian cancer, 130 patients (71.4%) in the CT arm compared to 119 patients (66.5%) in the BEV-CT arm.

A total of 15 patients, 6 in the CT arm and 9 in the BEV-CT arm, died due to adverse events that occurred during the study follow-up period.

Table 5. Summary of Adverse Events of selected grade ≥ 2 & Grade ≥ 3 & AEs of special interest ^{2,7}	Bevacizumab plus Chemotherapy (n=179) [%]	Chemotherapy Alone (n=181) [%]
Hypertension Grade ≥ 2	20	7
Grade ≥ 3	7	1
Proteinuria, Grade ≥ 3	2	0
GI Perforation Grade ≥ 2	2	0
Grade ≥ 3	2	0
Fistula/abscess Grade ≥ 2	2	0
Grade ≥ 3	1	0
Bleeding, Grade ≥ 3	1	1
Thromboembolic event, Grade ≥ 3	5	4
Arterial, Grade ≥ 3	2	0
Venous, Grade ≥ 3	3	4
Wound-healing complication, Grade ≥ 3	0	0
Reversible posterior leukoencephalopathy syndrome, Grade ≥ 3	1	0
CHF, Grade ≥ 3	1	1
Cardiac disorders, Grade ≥ 3 (excluding CHF)	0	0
Notes: AEs= Adverse Events Only grade 2-5 AEs were collected in the AURELIA trial. CHF= congestive heart failure; GI=gastrointestinal.		

Adverse Events of Special Interest to the Clinical Guidance Panel included gastrointestinal perforation, hypertension, proteinuria, and neurologic symptoms.

Gastrointestinal (GI) Perforation⁷

During the treatment period, 4 patients (2.2%) experienced grade 2-5 GI perforation events.

The following GI related adverse events occurred in the BEV-CT arm:

- One patient experienced a grade 4 intestinal perforation that occurred 89 days after the start of treatment and was assessed as probably related to bevacizumab and unrelated to topotecan. This event was resolved.

- One patient had a grade 3 ileal perforation event that occurred 94 days after start of treatment and was assessed as possibly related to bevacizumab and possibly related to topotecan. The event was ongoing at the time of the clinical cut-off. This patient also experienced a grade 3 arterial embolism event.
- One patient had a non-serious grade 2 anal fistula event that was assessed as possibly related to bevacizumab and unlikely related to paclitaxel. This event occurred 57 days after the start of treatment and was resolved at the time of clinical cut-off.
- One patient developed a grade 4 GI perforation that occurred >30 days after the last doses of paclitaxel and bevacizumab. The event occurred 349 days after start of treatment and after documentation of disease progression and >30 days after starting treatment with doxorubicin. The investigator assessed the event as related to bevacizumab and unrelated to paclitaxel. Additional data related to this event indicated that ovarian cancer was the other possible causal factor for the event.

Hypertension (HTN)

Grade 3-5 HTN events were reported in 7.8% of patients in the BEV-CT arm and 1.1% in the CT arm.

The following HTN related adverse events occurred during treatment period:

- 2 patients in the CT arm experienced grade 3 HTN events
- One patient in the BEV-CT arm experienced a grade 3 event of increased blood pressure and 12 patients experienced grade 3 HTN events.
- One patient experienced a grade 4 hypertensive crisis that occurred 71 days after treatment start and was assessed as probably related to bevacizumab and unrelated to PLD treatment. The event was resolved.

Proteinuria

Grade 3-5 proteinuria events were reported in 4 patients (2.2%) in the BEV-CT arm and no patients in the CT arm. Of the 4 patients in the BEV-CT arm, one patient (0.6%) developed grade 4 nephrotic syndrome that occurred 71 days after start of treatment. This event was assessed by the investigator as possibly related to bevacizumab and unlikely related to PLD, and was resolved. The remaining 3 patients experienced grade 3 proteinuria events and no patient experienced grade 5 proteinuria.

Neurologic Symptoms

One patient (0.6%) in the BEV-CT arm and no patient in the CT arm experienced Posterior Reversible Encephalopathy Syndrome (PRES). One patient experienced grade 3 PRES on study day 58 that resolved without sequelae and was considered possibly related to bevacizumab treatment.

Discontinuation due to adverse events

There were a higher percentage of patients in the BEV-CT arm than in the CT arm that experienced grade 2-5 AEs that led to withdrawal of study treatment with chemotherapy or bevacizumab (43.6% vs. 8.8%, respectively).

The most common (i.e. >2%) grade 2-5 AEs which led to study drug discontinuation in the BEV-CT arm were as follows:

- Peripheral sensory neuropathy (BEV-CT: 4.5% vs CT: 1.7%)
- Palmar plantar erythrodysesthesia syndrome (BEV-CT: 3.4% vs. CT: 0.6%)
- Fatigue (BEV-CT: 3.4% vs. CT: 0)
- HTN (BEV-CT: 2.8% vs. CT: 0)
- Neutropenia (BEV-CT: 2.2% vs. CT: 0)
- Proteinuria (BEV-CT: 2.2% vs. CT: 0)

Health-Related Quality of Life (HRQoL) - Patient-Reported Outcomes³

Patient-reported outcomes were reported in a separate publication by Stockler et al 2014 and were assessed at baseline and every two or three cycles until disease progression using the EORTC Quality of Life Questionnaire-Ovarian Cancer Module 28 (QLQ-OV28) and the Functional Assessment of Cancer Therapy-Ovarian Cancer symptom index (FOSI). There were no substantial differences in baseline characteristics noted between the PRO-evaluable and ITT populations.

The primary HRQoL hypothesis endpoint was that more patients in the BEV-CT group would achieve at least a 15% (≥ 15 -point) absolute improvement on the QLQ-OV28 abdominal/GI symptom subscale at week 8/9 from baseline. A 15% improvement was used by the study authors, rather than the more standard use of a 10% improvement. This was due to wanting a more precise definition of a clinically meaningful difference given the open-label nature of the trial.

Baseline questionnaires were completed by 89% of 361 randomized patients (155 in the BEV-CT group and 162 in the CT alone group). Baseline abdominal/GI symptom scores were observed to be similar between groups (bevacizumab plus chemotherapy, mean 32.3, SD 22.13; chemotherapy alone, mean 29.6, SD 22.13).

At week 8/9, 122 patients had completed the questionnaire in the bevacizumab plus chemotherapy group compared to 84 in the chemotherapy alone group. In the BEV-CT group, the 69 patients who did not complete the questionnaire were counted as not having an improvement in patient-reported outcomes. Similarly, in the chemotherapy alone group, the 119 patients who did not complete the questionnaire were counted as not having an improvement in patient-reported outcomes. At week 8/9, a higher proportion of patients in the bevacizumab plus chemotherapy arm had achieved a $\geq 15\%$ improvement in QLQ-OV28 abdominal/GI symptoms compared to the chemotherapy arm (21.9% vs. 9.3%, respectively; difference 12.7%, 95% CI 4.4 to 20.9; $p=0.002$).

It is important to note that symptoms at baseline were not mandatory for enrolment onto the trial. Therefore, the absolute percentages reflect the large proportion (35%) of women in AURELIA who did not have substantial symptoms at baseline, as well as the 15% criteria used to define improvement and the poor prognosis of women with platinum-resistant ovarian cancer.

A subgroup analysis including 99 PRO evaluable patients with ascites at baseline were also included. These made up approximately 27% of the ITT population and were expected to have considerable pain/GI symptoms. This subgroup demonstrated a greater treatment effect with a $\geq 15\%$ improvement in 44% of the BEV-CT arm versus 4.1% in the CT alone arm (difference 39.9%; 95% CI 23.9% to 55.9%; $p<0.001$).

Statistically significant differences were also demonstrated in the QLQ-OV28 abdominal/GI symptom scale in favour of the bevacizumab group from the mixed-model repeated-measures

analysis (6.4-point difference over all time points until progression or death; 95% CI 1.3 to 11.6; $p=0.015$), and in the proportion of patients at week 8/9 with a $\geq 15\%$ improvement in FOSI (12.2% vs. 3.1%; difference 9.0%, 95% CI 2.9% to 15.2%; $p=0.003$).

6.4 Ongoing Trials

No ongoing trials for bevacizumab in the platinum-resistant recurrent ovarian cancer setting have been identified.

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 platinum-resistant 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 CADTH 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 Initial Clinical Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Clinical Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Clinical Guidance Report will supersede this Initial Clinical Guidance Report.

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 CADTH 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

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): EBM Reviews - Cochrane Central Register of Controlled Trials October 2015, Embase 1974 to 2015 November 9, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

#	Searches	Results
1	(Bevacizumab* or avastin* or altuzan* or NSC 704865 or NSC704865 or rhuMAb-VEGF or rhumabvegf or 216974-75-3 or 250ZZM9Q9V).ti,ab,rn,nm,hw,ot,kf.	52100
2	exp Ovarian neoplasms/ or exp peritoneal neoplasms/ or fallopian tube neoplasms/	206736
3	(ovarian or ovary or ovaries or fallopian or uterine tube* or oviduct* or salphinx or salphinges or salpinx or salpinges or peritoneal or peritoneum or adnexa or adnexal).ti,ab.	675365
4	(Cancer* or neoplasia or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcinoma* or cystadenocarcinoma* or choriocarcinoma* or dysgerminoma* or gonadoblastoma* or metastas* or cyst or cysts or polyp or polyps or malignancy or malignancies).ti,ab.	5799086
5	3 and 4	267435
6	2 or 5	326798
7	(paclitaxel* or taxol or abraxane or aclipak or aclixel or alzene or anzatax or asotax or biotax or bristaxol or britaxol or capxol or celtax or clitaxel or coroflex or cryoxet or cyclopax or cynviloq or cypher select or dalys or ebetaxel or empac or endotag or genaxol or genetaxyl or genexol or infinnium or intaxel or lipopac or meditaxel or mitotax or nanoxel or oncogel or onxol or pacliex or paclimedac or paclitaxin or paclitaxel or pacxel or padexol or panataxel or parexel or paxceed or paxel or paxene or paxus or plaxicel or praxel or santotaxel or sindaxel or taxalbin or taxocris or taxus or vexel or yewtaxan or zisu or ABI007 or "ABI 007" or BMS 181339-01 or BMS 18133901 or BMS18133901 or CCRIS 8143 or CCRIS8143 or DHP 107 or DHP107 or "DRG 0190" or DRG0190 or HSDB 6839 or HSDB6839 or "IG 001" or IG001 or LEP ETU or LEPETU or "MBT 0206" or MBT0206 or NK 105 or NK105 or NSC 125973 or NSC125973 or QW 8184 or QW8184 or P88XT4IS4D or 33069 62 4).ti,ab,rn,nm,hw,ot,kf.	117861

8	(topotecan* or hycamptamine or hycamtin or CCRIS 8163 or CCRIS8163 or firotex or nogitecan or NSC 609699 or NSC609699 or oncotecan or potactasol or potekam or topoced or topodria or topokebir or topophore or topotel or 104864A or 104864 A or SKF104864A or SKF104864 A or SKF 104864A or SKF 104864 A or 7M7YKX2N15 or 123948 87 8 or DRG0288 or "DRG 0288" or 956S425ZCY or 119413-54-6).ti,ab,rn,nm,hw,ot,kf.	12932
9	(doxorubicin* or doxil or adriablastin or Adriamycin or adriblastin* or caelyx or CCRIS 739 or CCRIS739 or doxopeg or EINECS 245 495 6 or EINECS2454956 or FI 106 or FI106 or HSDB 3070 or HSDB3070 or lipo dox or lipodox or myocet or NCI C01514 or NCIC01514 or NDC 38242 874 or NDC38242874 or NDC38242 874 or NSC 123127 or NSC123127 or 80168379AG or 23214 92 8).ti,ab,rn,nm,hw,ot,kf.	217948
10	7 or 8 or 9	318292
11	1 and 6 and 10	2119
12	11 use pmez	188
13	11 use cctr	40
14	*Bevacizumab/	10740
15	(Bevacizumab* or avastin* or altuzan* or nsc-704865 or nsc704865 or rhuMAb-VEGF or rhumabvegf).ti,ab.	30024
16	14 or 15	30984
17	exp ovary tumor/ or exp peritoneum cancer/ or uterine tube tumor/ or uterine tube carcinoma/	119136
18	(ovarian or ovary or ovaries or fallopian or uterine tube* or oviduct* or salpinx or salpinges or salpinx or salpinges or peritoneal or peritoneum or adnexa or adnexal).ti,ab.	675365
19	(Cancer* or neoplasia or neoplasm* or tumor* or tumour* or carcinoma* or adenocarcinoma* or cystadenocarcinoma* or choriocarcinoma* or dysgerminoma* or gonadoblastoma* or metastas* or cyst or cysts or polyp or polyps or malignancy or malignancies).ti,ab.	5799086
20	18 and 19	267435

21	17 or 20	300994
22	*Paclitaxel/	31578
23	(paclitaxel* or taxol or abraxane or aclipak or aclixel or alzene or anzatax or asotax or biotax or bristaxol or britaxol or capxol or celtax or clitaxel or coroflex or cryoxet or cyclopax or cynviloq or cypher select or dalys or ebetaxel or empac or endotag or genaxol or genetaxyl or genexol or infinnium or intaxel or lipopac or meditaxel or mitotax or nanoxel or oncogel or onxol or paclieux or paclimedac or paclitaxin or pacxel or padexol or panataxel or parexel or paxceed or paxel or paxene or paxus or plaxicel or praxel or santotaxel or sindaxel or taxalbin or taxocris or taxus or vexel or yewtaxan or zisu or ABI007 or "ABI 007" or BMS 181339-01 or BMS 18133901 or BMS18133901 or CCRIS 8143 or CCRIS8143 or DHP 107 or DHP107 or "DRG 0190" or DRG0190 or HSDB 6839 or HSDB6839 or "IG 001" or IG001 or LEP ETU or LEPETU or "MBT 0206" or MBT0206 or NK 105 or NK105 or NSC125973 or NSC 125973 or QW 8184 or QW8184).ti,ab.	70340
24	*Topotecan/	2826
25	(topotecan* or hycamptamine or hycamtin or CCRIS 8163 or CCRIS8163 or firotex or nogitecan or NSC 609699 or NSC609699 or oncotecan or potactasol or potekam or topoced or topodria or topokebir or topophore or topotel or 104864A or 104864 A or SKF104864A or SKF104864 A or SKF 104864A or SKF 104864 A or DRG0288 or "DRG 0288").ti,ab.	6277
26	*Doxorubicin/	66253
27	(doxorubicin* or doxil or adriablastin or Adriamycin or adriblastin* or caelyx or CCRIS 739 or CCRIS739 or doxopeg or EINECS 245 495 6 or EINECS2454956 or FI 106 or FI106 or HSDB 3070 or HSDB3070 or lipo dox or lipodox or myocet or NCI C01514 or NCIC01514 or NDC 38242 874 or NDC38242874 or NDC38242 874 or NSC 123127 or NSC123127).ti,ab.	106581
28	22 or 23 or 24 or 25 or 26 or 27	200574
29	16 and 21 and 28	606
30	29 use oemezd	413
31	12 or 13 or 30	641

32	limit 31 to english language	607
33	remove duplicates from 32	436

2. Literature search via PubMed

A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#5	Search #1 AND #2 AND #3 AND #4 AND publisher[sb] Filters: English	5
#4	Search (paclitaxel*[tiab] OR taxol[tiab] OR abraxane[tiab] OR aclipak[tiab] OR aclixel[tiab] OR alzene[tiab] OR anzatax[tiab] OR asotax[tiab] OR biotax[tiab] OR bristaxol[tiab] OR britaxol[tiab] OR capxol[tiab] OR celtax[tiab] OR clitaxel[tiab] OR coroflex[tiab] OR cryoxet[tiab] OR cyclopax[tiab] OR cynviloq[tiab] OR cypher select[tiab] OR dalys[tiab] OR ebetaxel[tiab] OR empac[tiab] OR endotag[tiab] OR genaxol[tiab] OR genetaxyl[tiab] OR genexol[tiab] OR infinnium[tiab] OR intaxel[tiab] OR lipopac[tiab] OR meditaxel[tiab] OR mitotax[tiab] OR nanoxel[tiab] OR oncogel[tiab] OR onxol[tiab] OR pacliex[tiab] OR paclimedac[tiab] OR paclitaxin[tiab] OR paclitaxel[tiab] OR pacxel[tiab] OR padexol[tiab] OR panataxel[tiab] OR parexel[tiab] OR paxceed[tiab] OR paxel[tiab] OR paxene[tiab] OR paxus[tiab] OR plaxicel[tiab] OR praxel[tiab] OR santotaxel[tiab] OR sindaxel[tiab] OR taxalbin[tiab] OR taxocris[tiab] OR taxus[tiab] OR vexel[tiab] OR yewtaxan[tiab] OR zisu[tiab] OR ABI007[tiab] OR ABI 007[tiab] OR BMS 181339-01[tiab] OR BMS 18133901[tiab] OR BMS18133901[tiab] OR CCRIS 8143[tiab] OR CCRIS8143[tiab] OR DHP 107[tiab] OR DHP107[tiab] OR DRG 0190[tiab] OR DRG0190[tiab] OR HSDB 6839[tiab] OR HSDB6839[tiab] OR IG 001[tiab] OR IG001[tiab] OR LEP ETU[tiab] OR LEPETU[tiab] OR MBT 0206[tiab] OR MBT0206[tiab] OR NK 105[tiab] OR NK105[tiab] OR NSC125973[tiab] OR NSC 125973[tiab] OR QW 8184[tiab] OR QW8184[tiab] OR P88XT4IS4D[tiab] OR 33069 62 4[tiab] OR topotecan*[tiab] OR hycamptamine[tiab] OR hycamtin[tiab] OR CCRIS 8163[tiab] OR CCRIS8163[tiab] OR firetex[tiab] OR nogitecan[tiab] OR NSC 609699[tiab] OR NSC609699[tiab] OR oncotecan[tiab] OR potactasol[tiab] OR potekam[tiab] OR topoced[tiab] OR topodria[tiab] OR topokebir[tiab] OR topophore[tiab] OR topotel[tiab] OR SKF104864A[tiab] OR SKF104864 A[tiab] OR SKF 104864A[tiab] OR SKF 104864 A[tiab] OR 7M7YKX2N15[tiab] OR 123948 87 8[tiab] OR DRG0288[tiab] OR DRG 0288[tiab] OR 956S425ZCY[tiab] OR 119413-54-6[tiab] OR doxorubicin*[tiab] OR doxil[tiab] OR adriablastin[tiab] OR Adriamycin[tiab] OR adriablastin*[tiab] OR caelyx[tiab] OR CCRIS 739[tiab] OR CCRIS739[tiab] OR doxopeg[tiab] OR EINECS 245 495 6[tiab] OR EINECS2454956[tiab] OR FI 106[tiab] OR FI106[tiab] OR HSDB 3070[tiab] OR HSDB3070[tiab] OR lipo dox[tiab] OR lipodox[tiab] OR myocet[tiab] OR NCI C01514[tiab] OR NCIC01514[tiab] OR NDC 38242 874[tiab] OR NDC38242874[tiab] OR NDC38242 874[tiab] OR NSC 123127[tiab] OR NSC123127[tiab] OR 80168379AG[tiab] OR 23214 92 8[tiab]) Filters: English	75606
#3	Search (Cancer*[tiab] OR neoplasia[tiab] OR neoplasm*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR cystadenocarcinoma*[tiab] OR choriocarcinoma*[tiab] OR dysgerminoma*[tiab] OR gonadoblastoma*[tiab] OR metastas*[tiab] OR cyst[tiab] OR cysts[tiab] OR polyp[tiab] OR polyps[tiab] OR malignancy[tiab] OR malignancies[tiab]) Filters: English	2148374
#2	Search (Ovarian[tiab] OR ovary[tiab] OR ovaries[tiab] OR fallopian[tiab] OR uterine tube*[tiab] OR oviduct*[tiab] OR salpinx[tiab] OR salpinges[tiab] OR salpinx[tiab] OR salpinges[tiab] OR peritoneal[tiab] OR peritoneum[tiab] OR adnexa[tiab] OR adnexal[tiab]) Filters: English	262900
#1	Search (bevacizumab[Supplementary Concept] OR bevacizumab*[tiab] OR avastin*[tiab] OR altuzan*[tiab] OR nsc-704865[tiab] OR nsc704865[tiab] OR rhuMab-VEGF[tiab] OR rhuMabVEGF[tiab] OR 216974-75-3[tiab] OR 2S0ZZM9Q9V[tiab]) Filters: English	10709

3. **Cochrane Central Register of Controlled Trials (Central)**

Searched via Ovid

4. **Grey Literature search via:**

Clinical trial registries:

U.S. NIH ClinicalTrials.gov

<http://www.clinicaltrials.gov/>

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials

<http://www.canadiancancertrials.ca/>

Search terms: Avastin, bevacizumab

Select international agencies including:

Food and Drug Administration (FDA):

<http://www.fda.gov/>

European Medicines Agency (EMA):

<http://www.ema.europa.eu/>

Search terms: Avastin, bevacizumab

Conference abstracts:

American Society of Clinical Oncology (ASCO)

<http://www.asco.org/>

European Society for Medical Oncology

<http://www.esmo.org/>

Search terms: Avastin, bevacizumab/ last 5 years

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