PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Bevacizumab (Avastin) for Cervical Cancer

March 23, 2015

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review was to evaluate the effect of bevacizumab added to combination chemotherapy on patient outcomes compared to combination chemotherapy in the treatment of women with metastatic, persistent, or recurrent cervical cancer.

Bevacizumab is a monoclonal antibody which targets vascular endothelial growth factor (VEGF) receptors and inhibits angiogenesis. The Submitter has requested the following funding indication: Bevacizumab, at 15 mg/kg of body weight every 3 weeks as an intravenous infusion, in combination with chemotherapy for the treatment of patients with persistent, recurrent, or metastatic carcinoma of the cervix.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The systematic review identified one multicentre, four-arm 2x2 factorial design phase 3 randomized controlled trial (RCT) that enrolled 452 patients with primary stage IVB, recurrent or persistent carcinoma of the cervix, which was not amenable to curative treatment with surgery and/or radiation therapy.[1] Patients were randomized 1:1 to one of four treatment arms: cisplatin plus paclitaxel (n=114); bevacizumab plus cisplatin plus paclitaxel (115); topotecan plus paclitaxel (n=111), or; bevacizumab plus topotecan plus paclitaxel (n=112). The primary outcomes of the study were overall survival and the frequency and severity of adverse events. Secondary outcomes included progression-free survival, objective response rate, and health-related quality of life. The study conducted one-sided tests of significance using alpha=0.025.[1] The results reported in this summary are for the two bevacizumab-containing arms combined compared to the two non-bevacizumab-containing arms combined.

The lack of blinding in the trial had the potential to bias results for patient-reported outcomes, such as quality of life, and investigator-assessed outcomes, such as response or progression-free survival, in favour of whichever arm the assessor felt was likely to provide benefit. Fifty-one of 225 patients who were randomized to receive combination chemotherapy alone crossed over to receive bevacizumab as salvage therapy; however, a statistically significant difference in overall survival was still demonstrated despite the potential for bias.

Efficacy

The final analysis (March 2014) demonstrated a statistically significant improvement in overall survival in favour of bevacizumab plus combination chemotherapy compared to combination chemotherapy without bevacizumab (median 16.8 months vs. 13.3 months, respectively) with a hazard ratio (HR) for death of 0.765 (95% CI 0.62 to 0.95; p=0.0068), after a total of 348 events.[2] The interim analysis of overall survival conducted in December 2012 had previously shown a similar statistically significant improvement in favour of bevacizumab plus combination chemotherapy.[1] Progression-free survival was also statistically significantly improved in favour of bevacizumab plus combination chemotherapy (median 8.2 months vs. 5.9 months; HR for disease progression 0.67, 95% CI 0.54 to 0.82; one-sided p=0.002).[1]

Quality of life was assessed using three validated health-related quality of life instruments, the Trial Outcome Index of the Functional Assessment of Cancer Therapy-Cervix (FACT Cx-TOI), the Brief Pain Inventory (BPI), and the Functional Assessment of Cancer Therapy/Gynecology Oncology Group neurotoxicity (FACT/GOG-NTX). After adjustment for multiple comparisons, no statistically significant differences were reported for the results obtained utilizing any of the instruments.[1]

Harms

Grade 2 or higher hypertension occurred in a statistically significantly greater proportion of patients who received bevacizumab (25% of 220 patients) compared to those who did not (2% of 219 patients; p<0.001).[1] Grade 4 or higher neutropenia also occurred in a statistically significantly higher proportion of patients who received bevacizumab compared to those who did not (35% vs. 26%; p=0.04).[1] Finally, Grade 3 or higher thromboembolism occurred in a higher proportion of patients who received bevacizumab compared to those who did not (8% vs. 1%; p=0.001).[1]

Gastrointestinal-vaginal fistulas occurred in 8.2%, genitourinary-vaginal fistulas in 1.8%, and gastrointestinal fistulas in 0.5% of 220 patients who received bevacizumab with combination chemotherapy.[1] In patients treated with combination chemotherapy without bevacizumab, gastrointestinal-vaginal fistulas occurred in 0.9% and genitourinary-vaginal fistulas in 1.4% of 219 patients.[1] Less than 1% of patients who received bevacizumab with combination chemotherapy died due to a gastrointestinal perforation.[3]

1.2.2 Additional Evidence

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

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

1.2.3 Interpretation and Guidance

Cervical cancer affects 1,450 Canadian women per year. This review focuses on women who are well (ECOG performance status 0 to 1) and who present with Stage 4B disease, persistent (despite radical chemoradiation treatment i.e., Stage 1B2-4A) or metastatic/recurrent disease. In Canada, the annual incidence of these patients is estimated to be 363 women. These women have incurable disease; instead the goal of treatment is to extend their duration of survival. Currently the only treatment option for disease control is combination chemotherapy, which provides a survival benefit of approximately one year [1,4], or participation in a clinical trial. Novel treatment options are urgently needed.

The GOG 240 was a well conducted four arm RCT that demonstrated a clinically meaningful 3.5 month improvement in overall survival in favour of bevacizumab plus combination chemotherapy compared to combination chemotherapy without bevacizumab. The results of this study are applicable only to the population that met the study inclusion criteria (i.e., highly functioning women with GOG performance status 0-1 [fully active or ambulatory but restricted from strenuous activity]). Health-related quality of life was also assessed in the GOG 240 study; however, no clinically significant differences were demonstrated using the FACT Cx-TOI.

Although the rates of hypertension were higher in the group of patients who received bevacizumab compared to those who did not, this was manageable with the addition of antihypertensives. A higher rate of any type of fistula occurred in the group of patients who received bevacizumab plus combination chemotherapy compared to combination chemotherapy

without bevacizumab (8.2% versus 2.3%, respectively).[2] Less than 1% of patients who received bevacizumab with combination chemotherapy died due to a gastrointestinal perforation.[3] A GI fistula or vescicovagina fistula is a disconcerting complication for women and usually requires hospitalization and surgery (colostomy, conduit) or invasive diagnostic imaging (percutaneous nephrostomy tubes) to manage. Grade 3 or higher thromboembolic events were higher in the bevacizumab arm (8% versus 1%)[1] and may necessitate emergency visits, diagnostic imaging and anticoagulation medication for several months which can be costly. Despite these toxicities, there was no significant deterioration in health-related QOL.[1] In addition, the number of patients who stopped treatment was the same in both groups. There was a higher rate of women who stopped due to toxicity in the bevacizumab group (57 of 227 patients vs. 36 of 225 patients in the chemotherapy alone group) and a lower rate that declined further treatment (28 patients vs. 35 patients).

The GOG 240 trial used cisplatin in their combination therapy regimen, whereas in Canada, carboplatin is substituted for cisplatin based on a Japanese study showing equal efficacy and lower toxicity.[5] In the GOG 240 study, the neutropenia and thrombocytopenia rates were higher in the bevacizumab arm. Carboplatin is also associated with higher neutropenia and thrombocytopenia rates, thus, these would need to be evaluated if bevacizumab was added to the carboplatin paclitaxel combination. The Clinical Guidance Panel (CGP) noted that the use of bevacizumab in combination with carboplatin and paclitaxel has been assessed and found to be safe in other gynecological cancers such as ovarian cancer.

Prior to the GOG 240 study, the standard chemotherapy options in this scenario were single agent paclitaxel or topotecan. This study raises the possibility of combination chemotherapy using topotecan with paclitaxel as being equivalent compared to carboplatin paclitaxel. This study also shows bevacizumab can be safely used with both combination chemotherapeutic options with the option of topotecan in patients with hypersensitivity to platinum.

The overall survival benefit of bevacizumab either alone or in combination with chemotherapy, as compared to chemotherapy alone, for disease recurrence after completion of first-line chemotherapy is not known. Although the Provincial Advisory Group (PAG) asked for advice on this clinical situation, it was beyond the scope of this review. To the knowledge of the Clinical Guidance Panel, there are limited data in this domain. The opinion of the Clinical Guidance Panel is that, for a time limited period (transition period), women who had not previously received bevacizumab, but who otherwise met the performance status criteria and none of the exclusion criteria, should be considered for access to bevacizumab in a setting of second line palliative chemotherapy.

The CGP chose not to make a conclusion for the small group of women (15%) who achieve a complete response to first line chemotherapy with bevacizumab who come off drug and later recur, as the CGP were unaware of data to advise on this situation. Again, this clinical situation was also outside of the scope of this review.

1.3 Conclusions

The Clinical Guidance Panel (CGP) concluded that there is a net overall clinical benefit to bevacizumab with combination chemotherapy in the treatment of Stage 4B, metastatic, persistent or recurrent cervical cancer who have an excellent performance status (GOG or ECOG PS 0-1), have measurable disease and who are not candidates for other curative treatments (RT, Surgery). Bevacizumab significantly prolongs median overall survival, progression-free survival and decreases recurrence rate but at the risk of a low (<10%) but meaningful increase in fistula rate within the radiated field, manageable hypertension and thromboembolic complications. This is based on one high-quality randomized controlled trial that compared bevacizumab and combination chemotherapy with combination chemotherapy alone. Adverse event profiles, while slightly worse in the bevacizumab with combination chemotherapy arm compared to the combination chemotherapy, were manageable with medical treatment.

The CGP also considered that from a clinical perspective:

- While the option of bevacizumab in combination with carboplatin and paclitaxel is preferred based on its toxicity profile, convenience, and cost, the use of bevacizumab in combination with topotecan and paclitaxel could be considered in situations where carboplatin is not an option, such as in cases of platinum allergy.
- In Canada, carboplatin is commonly substituted for cisplatin based on a Japanese study showing equal efficacy and lower toxicity.[5] In the GOG-240 study, the neutropenia and thrombocytopenia rates were higher in the bevacizumab arm. Carboplatin is also associated with higher neutropenia and thrombocytopenia rates, thus, these would need to be evaluated if bevacizumab was added to the carboplatin paclitaxel combination. The CGP noted that the use of bevacizumab in combination with carboplatin and paclitaxel has been assessed and found to be safe in other gynecological cancers such as ovarian cancer.
- Based on the expert opinion of the CGP, women who have not previously received bevacizumab, but who otherwise meet the performance status criteria and none of the exclusion criteria, should be considered for access to bevacizumab in a setting of second line palliative chemotherapy. The CGP noted that, although the Provincial Advisory Group (PAG) asked for advice on this clinical situation, it was beyond the scope of this review and to the Panel's knowledge, there are limited data in this domain.
- The CGP chose not to make a conclusion for the small group of women (15%) who achieve a complete response to first line chemotherapy with bevacizumab who come off drug and later recur, as the CGP were unaware of data to advise on this situation.

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 cervical 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 pCODR website, www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding bevacizumab conducted by the Gynecologic 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 and a summary of submitted Provincial Advisory Group Input on bevacizumab are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

According to the Canadian Cancer Society statistics, in 2014, 1,450 women in Canada will develop cervical cancer making it the 13th leading cancer in Canadian women. Approximately 380 women will die in 2014 as a result of this disease, with a mortality rate of 1.6 per 100,000 women.[6] The cervical cytology screening programs across Canada have been responsible for lowering the incidence and mortality; however, cervical cancer still occurs. Approximately 60% of cases identified occur in women who do not participate in screening programs; the other 40% of cases occur in women who are screened but whose disease is not detected, in part due to less common histologies like adenocarcinomas and improper follow up and treatment of abnormal screening tests. Widespread population based implementation of the HPV vaccine may decrease the rates of cervical cancer in the future for those young women who are candidates for school-based vaccination programs.

Women diagnosed with early clinical stage cervical cancer (cancer limited to the cervix only) are often treated with surgery to remove the central disease and to evaluate for metastatic disease. Women diagnosed with metastatic, persistent or recurrent cervical cancer after failure of primary radical chemo-radiotherapy are usually offered radical exenterative surgery if the disease is still confined to the central pelvis. Radical chemo-radiation to the pelvis would be recommended if the disease was treated initially only with surgery that has recurred loco-regionally. Systemic chemotherapy is used if there is evidence of distant (extrapelvic) disease recurrence. Distant disease has a poor expected 5 year survival rate (<15%).[7,8] Standard first-line systemic therapy for recurrent or metastatic disease is a combination of platinum and taxane chemotherapy. This is modestly effective, with a median overall survival for cisplatin and paclitaxel combination chemotherapy of 12.9 months.[4] All chemotherapy doublets used to treat metastatic, persistent or recurrent cervical cancer have similar median survival rates and differ mainly in their side effect profiles and modes of administration.[4]

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effect of the addition of bevacizumab to chemotherapy in the treatment of patients with recurrent, persistent, or metastatic cervical cancer.

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.

One open label, four arm 2x2 design, phase 3 randomized trial (GOG 240) comparing bevacizumab plus chemotherapy to chemotherapy without bevacizumab was identified and included in this Clinical Guidance Report. A total of 452 patients were randomized to one of four arms; bevacizumab plus cisplatin and paclitaxel; cisplatin and paclitaxel; bevacizumab plus topotecan plus paclitaxel; and topotecan plus paclitaxel. For a more detailed description of the trial's designs and patient characteristics, please see Table 4 in the *Systematic Review* (Section 6.3.2.1).

The primary outcome in this study was overall survival and the frequency and severity of adverse events. Secondary outcomes included progression free survival and the frequency of objective tumour response.

Overall Survival

The primary outcome of the GOG 240 trial was overall survival. At a median follow-up of 20.8 months the addition of bevacizumab significantly improved the median overall survival compared with chemotherapy alone (17.0 months vs. 13.3 months; hazard ratio for death, 0.71; 98% CI, 0.54 to 0.95; one sided p=0.004). At this data point 271 deaths had been reported (60% of the total study population).[1] This can be seen in figure 2.[1] The planned final analysis for overall survival from March 2014 continues to shows the significant improvement for patients treated with bevacizumab 16.8 months vs. 13.3 months; HR 0.765 (95%CI; 0.62-0.95; p=0.0068). This analysis showed that 348 deaths had occurred (77% of the total study population).[2]

Progression free survival

Progression free survival, a secondary outcome measure was also significantly improved for bevacizumab plus combination chemotherapy compared to combination chemotherapy without bevacizumab (8.2 vs. 5.9 months; HR for disease progression, 0.67; 95% CI, 0.54 to 0.82; one sided p 0.002).[1] In subgroup analyses, progression free survival results were similar for the comparison of bevacizumab-cisplatin-paclitaxel vs. cisplatin-paclitaxel as well as the comparison of bevacizumab-cisplatin-topotecan vs. cisplatin-topotecan.

Response Rate

The response rate (complete plus partial responses) was significantly higher in patients who were randomized to bevacizumab than those who received chemotherapy alone (48% vs. 36%) (relative probability of a response, 1.35; 95% CI, 1.08 to 1.68; P=0.008, two-sided test). A complete response was seen in 28 (12.3%)

patients who received bevacizumab, compared to 14 (6.2%) who received chemotherapy alone (P=0.03).[1]

In the bevacizumab plus cisplatin and paclitaxel group the response rate was 50% compared with 45% for the cisplatin and paclitaxel group, (P=0.51, two-sided test). In the bevacizumab plus topotecan and paclitaxel group the response rate was 47% compared to 27% for the topotecan plus paclitaxel group, (P=0.002, two-sided test).[1]

Quality of Life

Quality of life was assessed using 3 validated health related quality of life instruments: The Outcome Index of the Functional Assessment of Cancer Therapy (FACT)-CERVIX (FACT Cx-TOI); the Brief Pain Inventory (BPI) and the FACT/GOG=NTX to measure neurotoxicity.

The addition of bevacizumab adversely affected the scores of the (FACT)-CERVIX (FACT Cx-TOI), with bevacizumab treated patients reporting, on average, 1.2 points lower on quality of life scores. However, this was not statistically significant (98.75%CI -4.1- 1.7; p=0.30).[1] A clinically meaningful change for group comparisons is approximately 4-5 points. The BPI indicated that bevacizumab did not adversely affect quality of life and patients had similar pain scores (p=0.16).[9] The FACT/GOG=NTX scores demonstrated a non-statistically significant pattern for patients in the bevacizumab groups to report fewer neurotoxic symptoms (overall odds ratio, 0.58; 99% CI, 0.29 to 1.17; P=0.05), and the severity of neurotoxic symptoms reported was similar in the two groups (P=0.70).[1] The level of significance was adjusted from 5% using the Bonferroni method and set at 0.0125 to control for overall type 1 errors.[1]

Harms Outcomes

Adverse effects can be seen in table 1. Grade 2 or higher hypertension was significantly more frequent in patients who received bevacizumab plus combination chemotherapy compared to those who received combination chemotherapy without bevacizumab (25% vs. 2%, P<0.001). However, no patients discontinued treatment because of hypertension.[1] Gastrointestinal-vaginal fistulas occurred in 18 (8.2%) patients, genitourinary-vaginal fistulas occurred in 4 (1.8%) patients and gastrointestinal fistulas in 1 (0.5%) patient treated with bevacizumab plus chemotherapy. In the patients treated with chemotherapy alone 2 (0.9%) developed gastrointestinal-vaginal fistulas and 3 (1.4%) developed genitourinary-vaginal fistulas. The fistulas were not associated with peritonitis, sepsis or death. All patients who had gastrointestinal-vaginal fistulas had received prior pelvic radiation.[10] Less than 1% of patients who received bevacizumab with combination chemotherapy died due to a gastrointestinal perforation.[3] In addition thromboembolic events of grade 3 or higher were also significantly associated with bevacizumab treatment (8% vs. 1%, P=0.001). Neutropenia of grade 4 or higher, febrile neutropenia of grade 3 or higher, and pain of grade 2 or higher were not significant between the chemotherapy alone and bevacizumab plus chemotherapy groups. Proteinuria of grade 3 or higher, gastrointestinal and genitourinary bleeding was uncommon.[1] The rates of grade 3-5 peripheral sensory neuropathy, nausea, constipation and vomiting were similar between chemotherapy alone and chemotherapy plus bevacizumab.

Table 1: Adverse events

Event	Chemotherapy alone N=219 (%)	Chemotherapy plus Bevacizumab N=220 (%)	Odds Ratio (95%CI)	P value
Gastrointestinal events (excluding fistulas) grade ≥2	96 (44)	114(52)	1.38(0.93-2.04)	0.10
Fistula (grade ≥3)				
Gastrointestinal-vaginal[10]	2 (0.9%)	18 (8.2%)		
Genitourinary-vaginal[10]	3 (1.4%)	4(1.8%)		
Gastrointestinal[10]	NA	1(0.5%)		
Hypertension (grade ≥2)♀ [1]	4(2)	54(25)	17.50(6.23-67.50)	<0.001
Proteinuria (grade ≥3) [1]	0	4(2)	NA (0.90-∞)	0.12
Pain (grade ≥2) [1]	62(28)	71(32)	1.21(0.79-1.85)	0.41
Neutropenia (grade ≥4) [1]	57(26)	78(35)	1.56(1.02-2.40)	0.04
Febrile neutropenia (grade ≥3) [1]	12(5)	12(5)	1.00 (0.40-2.48)	1.00
Thromboembolism (grade ≥3) [1]	3(1)	18(8)	6.42 (1.83-34.3)	0.001
CNS bleeding (grade ≥ 3) [1]	0	0	NA	
Gastrointestinal bleeding (grade ≥3) ∫∫ [1]	1(<1)	4(2)	4.04 (0.39-200.00)	0.37
Genitourinary bleeding (grade ≥3) ∫∫[1]	1(<1)	6(3)	6.11(0.73-282.00)	0.12
Fatigue (grades 3-5)[3]	(9.9)	(14.2)		
Urinary tract infections (grades 3-5)[3]	(6.3)	(8.3)		
Diarrhea (grades 3-5)[3]	(2.7)	(5.5)		

♀ Hypertension of grade 2 or higher was defined as recurrent or continuous hypertension for a period of more than 24 hours or a symptomatic increase in blood pressure by more than 20mm Hg diastolic or to more than 150/100 mmHg if the blood pressure was previously within the normal range

∫∫ Bleeding was managed primarily with supportive therapy and transfusions of packed red cells, most commonly in the outpatient setting.

CNS= Central nervous system; NA = Not applicable

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

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 perspective, it is important to have a greater spectrum of agents with which to treat cervical cancer, as it is estimated that 1,450 Canadian women will be diagnosed with cervical cancer and 380 women will die from it. OCC reported that all respondents were negatively impacted by their diagnosis of cervical cancer in their day-to-day life; specifically, work life, sexual relationships, physical activity and sleep pattern were the areas respondents indicated had been most severely compromised. While 41% of respondents reported that they agreed or strongly agreed that the current (or past) treatments were able to manage their cervical cancer, 34% of respondents strongly or somewhat disagreed and 24% of respondents neither agreed nor disagreed. According to OCC, respondents indicated that the key expectation of using bevacizumab is to prolong survival. Additionally, 79% of the respondents indicated that shrinkage of tumour size was important, and about three quarters of the respondents also wanted to see an improvement in the quality of life. Of the eight respondents who had experience with bevacizumab, 50% indicated that bevacizumab had shrunk the size of their tumour, managed their fatigue, prevented a recurrence and improved their prognosis. 38% of respondents reported that bevacizumab had caused additional side effects, while 63% of respondents indicated that it had not. All eight respondents (100%) experienced high blood pressure. One respondent experienced fatigue and one respondent experienced headaches. Half of the respondents who used bevacizumab agreed or strongly agreed that it had improved their quality of life compared to previous treatments they had used. However, 12.5% (1 respondent) indicated that she strongly disagreed that bevacizumab had improved her life. 37.5% of the respondents neither agreed nor disagreed that it had improved their life.

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 cervical cancer:

Clinical factors:

- The addition of bevacizumab to existing chemotherapies is an important treatment option as there are not many options in this setting with overall survival benefit.
- Time limited need for patients who did not receive bevacizumab in the first-line setting.

Economic factors:

- Small patient population.
- High cost of bevacizumab.

Health System factors:

- Additional resources required to monitor and treat significant adverse effects.

2.2 Interpretation and Guidance

Cervical cancer affects 1,450 Canadian women per year. In high resource settings where population-based cervical screening occurs, there is a stage shift to identifying earlier stage disease which is more likely to be cured. Women from this context present with the following stages of cervical cancer: 55.1% have Stage 1, 16.4% have Stage 2, 15.3% have Stage 3 and 13.1% have Stage 4.[11] The literature suggests that 5 year survival rates by stage are 100% Stage 1A1, 95% Stage 1A2, 90% Stage 1B1, 80-85% Stage 1B2, 75-78% Stage 2, 50% Stage 3, 20-30% Stage 4. In this document, we are focusing on those women who are well (ECOG 0-1) who present with stage 4B disease, persistent (despite radical chemoradiation treatment i.e., Stage 1B2-4A) or metastatic / recurrent disease. In Canada, the annual incidence is estimated to be 363 women. These women are not curable; instead the goal of treatment is to extend their duration of survival. Currently, the only treatment option for disease control is combination chemotherapy which provides a survival benefit of approximately a year [1,12] or participation in a clinical trial. Novel treatment options are urgently needed.

The single identified prospective randomized study, GOG 240, demonstrated a statistically significant increase in median overall survival of bevacizumab in combination with chemotherapy (16.8 months) compared to combination chemotherapy alone (13.3mos) [HR for death 0.77, 98% CI 0.62-0.95]. The treatment arms were stratified based on stage 4b, recurrent or persistent disease, exposure to prior platinum and Gynecology Oncology Group (GOG) performance status. The treatment arms were balanced for age, race, grade, and histologic type.[1] There was minimal crossover to bevacizumab (i.e., only 15 cases). This was a well-conducted four-arm randomized trial. Patients were well matched between the two chemotherapy-alone groups compared to the two chemotherapy plus bevacizumab groups for histology (p=0.862), ethnicity (p0.947) and disease status (i.e., recurrent vs persistent vs advanced (p=0.737)[1]).The Clinical Guidance Panel (CGP) felt strongly that a 3.5 month increase in median overall survival was a clinically meaningful result[13] in this challenging patient population. These results come from an efficacy study. Effectiveness has not yet been evaluated in a phase 4 (post marketing) study. The results of the GOG 240 trial are only applicable to the population who met the study inclusion criteria (i.e. a highly functioning group of women [GOG PS 0-1 i.e., fully active or ambulatory but restricted only from strenuous activity]). There are no additional randomized trials planned to-date that would enrol this patient population, according to ClinicalTrials.gov. The progression-free survival and the response rate data are in keeping with the overall survival data in this study.[1] Other biologic drugs that are on the horizon include pazopanib (intra-cellular small-molecule tyrosine kinase inhibitor that targets VEGF receptor) and sorafenib (multikinase inhibitor); however, these agents have not yet been fully evaluated in the setting of front line therapy.

Other variables that were assessed in the Tewari et al study (GOG 240) include quality of life (QoL) which showed that although scores on the FACT Cx QOL were lower in the bevacizumab arm, this was not clinically meaningful. In addition, effects of the bevacizumab arm on symptom palliation have yet to be determined.[14]

Equal numbers of patients were part of the toxicity analysis. Safety was evaluated and showed a significantly higher rate of hypertension in the patients receiving bevacizumab plus combination chemotherapy compared to combination chemotherapy without bevacizumab (25% vs 2%, respectively), but this was manageable with the addition of antihypertensives and no patient discontinued treatment due to hypertension.

The rate of fistulas was higher in those patients who received bevacizumab. The original paper reported gastrointestinal fistula (3%), gastrointestinal perforation (2%), and genitourinary fistula (2%).[1] An updated recent report from ESMO and IGCS 2014 reported a higher rate of any type of fistula (8.2% versus 2.3%).[2] These fistulas all occurred in women who had received prior pelvic radiation therapy. The data are unclear concerning the impact of fistula on patients. The published paper indicates the fistulas were not associated with peritonitis, sepsis or death[1]; however, the appendix to the Tewari et al publication reports 4 deaths in the chemotherapy alone arm due to infection, and in the bevacizumab arm, 2 deaths due to neutropenic sepsis, 1 from acute respiratory distress syndrome (ARDS) and 1 from GI perforation. Less than 1% of patients who received bevacizumab with combination chemotherapy died due to a gastrointestinal perforation.[3] These fistulas all occurred in a region of disease (except for one patient) and occurred across a spectrum of treatment cycles (i.e., 1-12). A GI fistula or vescicovagina fistula is a disconcerting complication for women and usually requires hospitalization and surgery (colostomy, conduit) or invasive diagnostic imaging (percutaneous nephrostomy tubes) to manage. Grade 3 or higher thromboembolic events were higher in the bevacizumab arm (8% versus 1%).[1] These events necessitate emergency visits, diagnostic imaging and anticoagulation medication for several months, which can be costly. Proteinuria of grade 3 or higher occurred in 2% of bevacizumab patients. Implications include a need to regularly test for significant proteinuria and to stop bevacizumab if it occurs. Grade 4 or higher neutropenia occurred in 35% of the women who received bevacizumab plus combination chemotherapy compared to 26% of the women who received combination chemotherapy alone (p=0.04); but the rate of febrile neutropenia was not different between the groups. Thrombocytopenia of Grade 3 or higher occurred in a greater proportion of patients in the bevacizumab arm (8% vs 1%, p=0.0001); however, bleeding events were seen but there were no differences between the groups. This study did not report any cases of hypertensive encephalopathy or posterior reversible encephalopathy syndrome. There were no data on arterial thrombotic events like myocardial infarction (MI) or cerebrovascular accident (CVA). Despite these toxicities, there was no significant deterioration in health-related QOL.[1] In addition, the number of patients who stopped treatment was the same in both groups. There was a higher rate of women who stopped due to toxicity in the bevacizumab group (57 of 227 patients vs. 36 of 225 patients in the chemotherapy alone group) and a lower rate that declined further treatment (28 patients vs. 35 patients). All patients were included in the efficacy analysis.

Some other considerations relevant to the Canadian context are the number of treatment doses and amount of drug required to achieve these results. Bevacizumab was given at a dose of 15 mg per kg every 3 weeks during chemotherapy and after chemotherapy until complete response, toxicity or disease progression.[1] Twenty-eight (15.2%) women in the bevacizumab group and 14 (7.7%) women in the chemotherapy alone group would have stopped treatment due to a complete response. The median number of doses was 7 but the range was 0 to 36. There were no dose modifications. In the event of low grade toxicity, the dose was held until the toxicity resolved.

Another consideration relevant to the Canadian context involves the chemotherapy standard for this population. In the trial, the standard treatment arm was cisplatin and taxol.[1] In Canada, carboplatin is substituted for cisplatin based on a Japanese study

showing equal efficacy and lower toxicity.[5] In the Tewari study, the neutropenia and thrombocytopenia rates were higher in the bevacizumab arm. Carboplatin is also associated with higher neutropenia and thrombocytopenia rates, thus, these would need to be evaluated if bevacizumab was added to the carboplatin paclitaxel combination.

A final consideration in the Canadian context involves the chemotherapy standard if platinum is not feasible (i.e., renal failure or platinum allergy). Prior to this study, the standard chemotherapy options in this scenario were single agent paclitaxel or topotecan. This study raises the possibility of combination chemotherapy using topotecan with paclitaxel as being equivalent compared to carboplatinum paclitaxel. This study also shows bevacizumab can be safely used with both combination chemotherapeutic options with the option of topotecan in patients with hypersensitivity to platinum. The disadvantages of this newer option include patients' inconvenience (topotecan given 0.75mg/m^2 daily for 3 days), potential increased chair time, drug cost, and total cost.

One of the problems with chemotherapy alone is a reduced benefit for tumours that recur within the radiated field. In the Tewari study, half of the women had disease in the previously radiated field. The subgroup analysis showed a statistically significant benefit in the bevacizumab arm for this patient population. This analysis also showed a benefit of bevacizumab in patients with prior platinum exposure, recurrent or persistent disease and squamous histology.[1]

The subgroup analysis did not show a benefit for bevacizumab arm in the following groups; disease outside the pelvis and adenocarcinoma histologies. Only 20% of women on the trial had disease located outside of the pelvis. Also, only 86 participants in the Tewari study had adenocarcinoma or adenosquamous. In general these histologies make up 20-25% of cervical cancers in Canada. The lack of benefit seen with bevacizumab in these two situations may reflect a small sample size with wide confidence intervals. Larger studies to address these contexts would be needed to evaluate such hypotheses.

The overall survival benefit of bevacizumab either alone or in combination with chemotherapy, as compared to chemotherapy alone, for disease recurrence after completion of first-line chemotherapy is not known. Although the Provincial Advisory Group (PAG) asked for advice on this clinical situation, it was beyond the scope of this review. To the knowledge of the Clinical Guidance Panel, there are limited data in this domain. There is one Phase 2 study by Monk et al using bevacizumab alone in recurrent cervical cancer in women, many of whom had had chemotherapy.[15] In 38 patients with recurrent squamous cell cervical cancer, of whom 73.9% had 1 prior chemotherapy regimen and 26.1% had 2 prior chemotherapy regimens for recurrence, the median response duration was 6.21 months (95%CI 2.83 -8.28), median PFS was 3.40 months (95% CI 2.53-4.53 months) and median OS was 7.29 months (95% CI 6.11-10.2 months). The median OS was in keeping with that of single agent topotecan. Thus, for a time limited period (transition period), the Clinical Guidance Panel felt that if women who had not previously received bevacizumab but who otherwise met the performance status criteria and none of the exclusion criteria, should be considered for access to bevacizumab in a setting of second line palliative chemotherapy.

The Clinical Guidance Panel chose not to make a conclusion for the small group of women (15%) who achieve a complete response to first line chemotherapy with bevacizumab who come off drug and later recur, as the CGP were unaware of data to advise on this situation. Again, this clinical situation was also outside of the scope of this review.

The CGP noted that the GOG 240 trial used the GOG performance status system when determining patient eligibility. Table 2 includes a comparison of the GOG performance status to ECOG performance status.

Table 2. Comparison of GOG Performance Status to ECOG Performance Status

	GOG[16]	ECOG[17]
0	Fully active, unrestricted activities of daily living	Fully active, able to carry on all pre-disease performance without restriction
1	Ambulatory, but restricted in strenuous activity	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory, and capable of self care. Unable to work. Out of bed for greater than 50% of waking hours	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Limited self care, or confined to bed or chair 50% of waking hours. Needs special assistance	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled, and no self care	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead	Dead

2.3 Conclusions

Bevacizumab given during combination chemotherapy and continued as maintenance treatment every 21 days until complete response, significant toxicities or disease progression significantly prolongs median overall survival, progression free survival and decreases recurrence rate but at the risk of a low (<10%) but meaningful increase in fistula rate within the radiated field, manageable hypertension and thromboembolic complications.

The CGP concluded that there is a net overall clinical benefit to bevacizumab with combination chemotherapy in the treatment of Stage 4B, metastatic, persistent or recurrent cervical cancer who have an excellent performance status (GOG or ECOG PS 0-1), have measurable disease and who are not candidates for other curative treatments (RT, Surgery). This is based on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in overall survival for bevacizumab with combination chemotherapy compared with combination chemotherapy alone and adverse event profiles, while slightly worse in the bevacizumab with combination chemotherapy arm compared to the combination chemotherapy, that were manageable with medical treatment.

The CGP also considered that from a clinical perspective:

- While the option of bevacizumab in combination with carboplatin and paclitaxel is preferred based on its toxicity profile, convenience, and cost, the use of bevacizumab in combination with topotecan and paclitaxel could be considered in situations where carboplatin is not an option, such as in cases of platinum allergy.
- In Canada, carboplatin is substituted for cisplatin based on a Japanese study showing equal efficacy and lower toxicity.[5] In the GOG-240 study, the neutropenia and thrombocytopenia rates were higher in the bevacizumab arm. Carboplatin is also associated with higher neutropenia and thrombocytopenia rates, thus, these would need to be evaluated if bevacizumab was added to the carboplatin paclitaxel combination. The CGP noted that the use of bevacizumab in combination with carboplatin and paclitaxel has been assessed and found to be safe in other gynecological cancers such as ovarian cancer.
- Based on the expert opinion of the CGP, women who have not previously received bevacizumab, but who otherwise meet the performance status criteria and none of the exclusion criteria, should be considered for access to bevacizumab in a setting of second line palliative chemotherapy. The CGP noted that, although the Provincial Advisory Group (PAG) asked for advice on this clinical situation, it was beyond the scope of this review and to the Panel's knowledge, there are limited data in this domain.
- The CGP chose not to make a conclusion for the small group of women (15%) who achieve a complete response to first line chemotherapy with bevacizumab who come off drug and later recur, as the CGP were unaware of data to advise on this situation.

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

Cervical cancer is the fourth leading cancer in women globally.[18] According to the Canadian Cancer Society statistics, in 2014, 1,450 women in Canada will develop cervical cancer making it the 13th leading cancer in Canadian women. Approximately 380 women will die in 2014 as a result of this disease for a mortality rate of 1.6 per 100,000 women.[6] In part, cervical cytology screening programs across Canada have been responsible for lowering the incidence and mortality; however, cervical cancer still occurs. Approximately 60% of cases identified occur in women who do not participate in screening programs; the other 40% of cases occur in women who are screened but failed detection in part due to less common histologies like adenocarcinomas and improper follow up and treatment of abnormal screening tests. Widespread population based implementation of the HPV vaccine may decrease the rates of cervical cancer in the future for those young women who are candidates for school-based vaccination programs.

3.2 Accepted Clinical Practice

Women diagnosed with early stage cervical cancer (cancer clinically limited to the cervix only) are often treated with surgery to remove the central disease (hysterectomy or radical hysterectomy) and to assess regional lymph nodes (sentinel lymph nodes or lymphadenectomy). If the central disease is larger than 4 cm or the disease involves significant tissue adjacent to the cervix, but sill confined in the pelvis, or there is evidence of nodal spread, often chemo-radiation is the treatment of choice.

Women diagnosed with metastatic, persistent or recurrent cervical cancer after failure of primary radical chemo-radiotherapy are usually offered radical exenterative surgery if the disease is still confined to the central pelvis. Chemo-radiation to the pelvis would be recommended if disease was treated initially only with surgery that has recurred loco-regionally. Systemic chemotherapy is used if there is evidence of distant (extrapelvic) disease recurrence. Distant disease has a poor expected 5 year survival rate (<15%).[7,8] Standard first-line systemic therapy for recurrent or metastatic disease is a combination of platinum and taxane chemotherapy. This is initially effective but median overall survival is only 12.9 months.[4]

Treatment options

Treatment options aside from the combination of platinum and taxane include: cisplatin vinorelbine, cisplatin gemcitabine and cisplatin topotecan. All these chemotherapy doublets have similar median survival rates but differ mainly in their side effect profiles and modes of administration.[4] In routine clinical practice in Canada, cisplatin is often replaced with carboplatin due to the better toxicity profile.[19] More recently the benefits of anti-angiogenic agents (i.e., bevacizumab) have been evaluated.

Bevacizumab

Bevacizumab is a monoclonal antibody which targets VEGF receptors. Bevacizumab showed favourable results in a GOG Phase 2 multicentre trial of bevacizumab at 15 mg/kg every 3 weeks in 46 women with persistent or recurrent squamous cell carcinoma or the cervix. This population were heavily pre-treated with palliative chemotherapy regimens with an observed response rate of 10.9% (95%CI 4.4-21.5%). Of note, 24% of participants survived for 6 months or longer. The grade 3-4 toxicities included hypertension (15.2%), DVT/PE (11%), and gastrointestinal fistula (2%).[11,15]

More recently the GOG conducted a 4 arm prospective randomized multicentre trial (GOG 240) studying the impact of a platinum combination (cisplatin and paclitaxel) compared to a non-platinum combination (paclitaxel and topotecan) and also concurrently addressed the effect of adding bevacizumab (15 mg/kg) to both chemotherapy regimens in advanced metastatic stage and recurrent cervical cancer. There was no significant difference in survival outcome between the two chemotherapy regimens. However, when bevacizumab was added, the median OS was 17.0 months compared to 13.3 months with chemotherapy alone (HR death 0.71, 97.6% CI 0.54-0.94, p=0.0035). This 3.7 month improvement in OS with bevacizumab was statistically significant and considered to be clinically meaningful. Toxicity was higher in the bevacizumab arms but the serious adverse event rate was below 10%.[20] Health related quality of life was not significantly lower in the bevacizumab arm.

Summary

Cervical cancer tends to affect women in their reproductive years (at an age 10 years younger than the age that other cancers affect the population). Patients with advanced stage / persistent, recurrent disease and those with extra pelvic recurrences have an expected poor overall survival with the current standard single agent platinum or combination platinum based chemotherapy treatments. There is now an opportunity to significantly prolong survival by adding antiangiogenic agents like bevacizumab to combination chemotherapy in these high risk patients.

3.3 Evidence-Based Considerations for a Funding Population

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

The study population of GOG 240 included: women with metastatic, stage IVB, persistent or recurrent cervical cancer not amenable to curative treatment with surgery and/or radiation therapy, which have a performance status of 0-1, adequate renal, hepatic, bone marrow function. Women may not have bevacizumab if they have a non-healing wound, an active bleeding condition, thromboembolic condition, uncontrolled hypertension, bowel obstruction, or surgery within 28 days.

3.4 Other Patient Populations in Whom the Drug May Be Used

Currently, women with metastatic, recurrent, or persistent cervical cancer who are not candidates for other curative treatments (radiation therapy, surgery) and who have excellent performance status, receive combination chemotherapy without bevacizumab. If the addition of bevacizumab to combination chemotherapy were funded in this group of patients, there may

be a limited time period during which patients who would have otherwise met the inclusion criteria of the GOG-240 study, would not have received bevacizumab with combination chemotherapy in the first-line setting.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Ovarian Cancer Canada (OCC), provided input on bevacizumab (Avastin) in combination with chemotherapy for the treatment of patients with persistent, recurrent, or metastatic carcinoma of the cervix, and their input is summarized below.

OCC conducted an anonymous online survey which was promoted to women living with cervical cancer through the organization's website, social media sites and partners. OCC reported receiving a total of 31 respondents, all women with cervical cancer. There was no outreach to caregivers. Responses were received from Canadian respondents, but there were no respondents from Newfoundland, Prince Edward Island, Northwest Territories, Nunavut or the Yukon. There were also 10 respondents from the United States. A total of eight (8) respondents indicated that they had used bevacizumab.

From a patient perspective, it is important to have a greater spectrum of agents with which to treat cervical cancer, as it is estimated that 1,450 Canadian women will be diagnosed with cervical cancer and 380 women will die from it. OCC reported that all respondents were negatively impacted by their diagnosis of cervical cancer in their day-to-day life; specifically, work life, sexual relationships, physical activity and sleep pattern were the areas respondents indicated had been most severely compromised. While 41% of respondents reported that they agreed or strongly agreed that the current (or past) treatments were able to manage their cervical cancer, 34% of respondents strongly or somewhat disagreed and 24% of respondents neither agreed nor disagreed. According to OCC, respondents indicated that the key expectation of using bevacizumab is to prolong survival. Additionally, 79% of the respondents indicated that shrinkage of tumour size was important, and about three quarters of the respondents also wanted to see an improvement in the quality of life. Of the eight respondents who had experience with bevacizumab, 50% indicated that bevacizumab had shrunk the size of their tumour, managed their fatigue, prevented a recurrence and improved their prognosis. 38% of respondents reported that bevacizumab had caused additional side effects, while 63% of respondents indicated that it had not. All eight respondents (100%) experienced high blood pressure. One respondent experienced fatigue and one respondent experienced headaches. Half of the respondents who used bevacizumab agreed or strongly agreed that it had improved their quality of life compared to previous treatments they had used. However, 12.5% (1 respondent) indicated that she strongly disagreed that bevacizumab had improved her life. 37.5% of the respondents neither agreed nor disagreed that it had improved their life.

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

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients Have with Cervical Cancer

OCC reported that the age of diagnosis of the respondents ranged from 22 to 60 years. The majority of respondents were in the 30 – 39 year range (35%); the next largest group was aged 40 – 49 (29%).

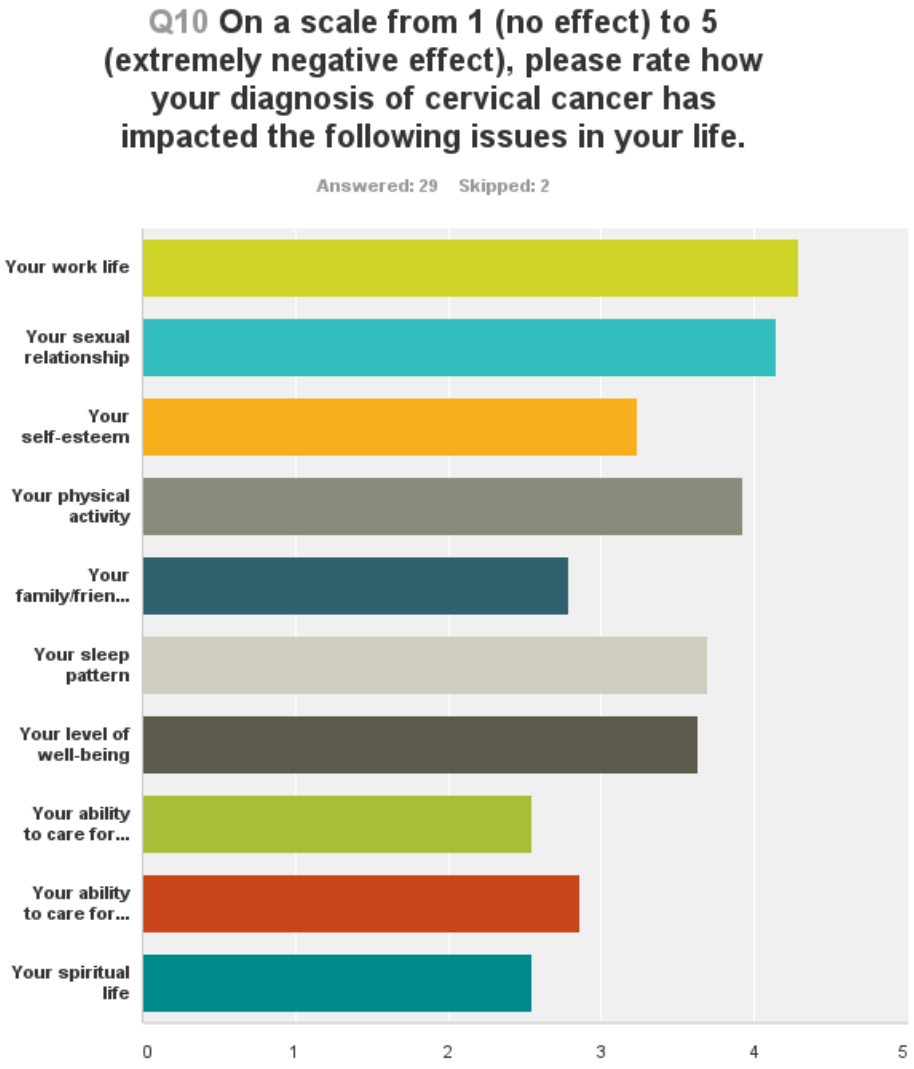
Approximately 58% of the respondents surveyed had a recurrence of cervical cancer and, of that group all 18 respondents had one recurrence.

OCC found that all respondents were negatively impacted by their diagnosis of cervical cancer in their day-to-day life. Respondents were asked to rate the effect of cervical cancer, on a scale from 1 (no effect) to 5 (extremely negative effect), on aspects of their life which included:

- Work life
- Sexual relationship
- Self esteem
- Physical activity
- Family/friend relationships
- Sleep pattern
- Level of well being
- Ability to care for oneself
- Ability to care for family
- Spiritual life

According to OCC, there was nothing rated less than 2.55 which translated to a rating of "some impact." Work life, sexual relationship, physical activity and sleep pattern were the areas respondents indicated had been most severely compromised. Of those, 52% of respondents indicated their diagnosis had a large or extremely large impact on their level of well-being (26% - large; 26% extremely large).

The table reproduced below shows the average (or MEAN) rating on the impact of cervical cancer on each component of the respondents' life.



4.1.2 Patients' Experiences with Current Therapy for Cervical Cancer

OCC reported that twelve respondents had used chemotherapeutic agents, six had surgery and two were administered radiation. Eight had been treated with bevacizumab; of these in two instances it was used as a single agent. Two respondents mentioned they could not be treated with bevacizumab because of high blood pressure.

Respondents were asked about the effectiveness of the treatment used for their cervical cancer. When asked to rate the extent to which a respondent agree or disagree with the following statement: "*My current (or past) treatments are (were) able to manage my cervical cancer*", 34% of respondents strongly or somewhat disagreed, 24% of respondents neither agreed nor disagreed and 41% of respondents agreed or strongly agreed.

According to OCC, cervical cancer treatments, specifically chemotherapy, negatively impacts this group of women. Respondents were asked to rate the side effect of treatments they received on a scale from 1 (no effect) to 5 (extremely negative effect) on aspects of their life which included:

hair loss, nausea/vomiting, fatigue, blood problems (e.g. anemia), bowel problems, neuropathy (numbness, tingling pain in hands and/or feet), aching joints, skin irritations, loss of fertility and bladder problems.

It was reported that none of the aspects noted were graded lower than 2, which according to OCC indicates that all side effects impacted their lives negatively. Those side effects which had an average rating of 2.5 or more were as follows in descending order:

1. Fatigue
2. Bowel problems
3. Aching joints
4. Neuropathy
5. Nausea/vomiting
6. Bladder problems
7. Loss of fertility
8. Blood problems

A majority of respondents indicated the impact of treatment, including fatigue. 68% of respondents rated their fatigue as having a large effect or extremely large effect on their quality of life. The average rating for fatigue was 4.0, on a scale of 1 to 5 with 5 being extremely large effect.

16 respondents took the time to also comment on the impact of this fatigue. The following comments are reproduced below:

> *Fatigue affects my ability to exercise or even to walk around all day some days.*
>
> *Fatique (sic) who wants to be tired all of the time.*
>
> *Fatigue is ongoing and the worst problem as it effects all parts of my life.*

Bowel problems were also noted as having had had a large or extremely large impact on the women. The average rating to this question was 3.6, on a scale of 1 to 5 with 5 being extremely large effect. 10 respondents provided comments on their severe bowel problems as follows:

> *Have had to have sigmoidoscopy twice due to issues with my bowels and acute pain in stomach and bleeding.*
>
> *The … bowel issues are humiliating...*

Six respondents also commented on their severe peripheral neuropathy. The following comments were reported:

> *The … neuropathy means that I can't exercise as much as I'd like (prior to cancer, I was a runner).*
>
> *Neuropathy causes significant pain and discomfort in my feet at all times.*

In addition to the above, OCC also reported side effects of treatment having a profound effect on women being treated for cervical cancer. Below are examples of some of the negative experiences that respondents' have encountered:

> *Wearing a head scarf is not something that I would have done. Before this I was a very busy person. Dealing with my 4 kids, working a full time job as an (sic) Registered Nurse*

in an Intensive Care Unit as well as holding down a part time teaching job. Now, I'm temporarily not working and need help from my parents and husband to manage house and kid stuff. This is not at all who I am!!!

Losing my hair was devastating. When I looked in the mirror and saw the woman with no hair, eyebrows or lashes, I could barely believe it was me. On top of fighting for my life and being ill, the hair loss was (sic) reminded me constantly of my struggle. I rated (sic) inside as often as possible and even wore a scarf around my children because it was hard for them to see me bald. I was usable (sic) to lift my head at times from nausea and illness. I was an active mother who could not even climb a flight of stairs. I have three children and it was a struggle to care for them. I went without pain medication in order to drive them to their sports etc. I still have difficulty getting comfortable at night and sleeping well due to peripheral neuropathy in my feet. If my fingers get even remotely cold, I feel like I have frost bite. My joint pain was excruciating. I had to lay on my back stiff as a board and still hurt. I took heave (sic) pain medication during that time. It affects every aspect.

All respondents noted the negative impact of cervical cancer and its treatment on daily life. This impact included anxiety, mood changes, uncertainty about the future, and debilitation. Work life had the most mentions as being an area of life negatively affected (52%), followed by family (21%) and finances (17%). The following four comments reflect the enormous toll cervical cancer and its treatment take on the daily lives of the respondents:

I now have a colostomy and Indiana pouch. Embarrassing times, of noises and smells, leaking No intimacy, scaring, depression*, I was once a successful independent professional now a bumbling freak.*

The cervical cancer diagnosis has had a massive impact on my life. I am a mother of twins 10, an 8 year old, and a 4 year old. I am tearful all the time, scared to die and leave my family. I have had to take time off work to have surgery, receive chemotherapy. My entire family has been impacted by my diagnosis. Im (sic) tired and have other side effects from the medications. I have had to start on an antidepressant. My life has been turned upside down. I have had to worry about money due to time of work.

My whole life has canged (sic). The tumor blocked my bladder resulting in bilateral nephrostomy tubes. All my activities and hobbies were very physical and can no longer do them. No more swimming, long tub soaks, clearing snow from my walks, restoration of cars and furniture right down to not being able to work. I am still in treatment with hopes I will still be able to return to work one day.

My diagnosis has made me aware that life is too short. Every ache and pain makes me wonder if it's coming back. I worry about being too stressed that maybe it will come back. Now that it has metastisized I just don't know where it would come back. There's always that uncertainty.

In addition to the above, almost half of the respondents indicated that they experienced some financial hardship in accessing their treatment for cervical cancer.

4.1.3 Impact of Cervical Cancer and Current Therapy on Caregivers

N/A

4.2 Information about the Drug Being Reviewed

Respondents were asked "*If you were to take AVASTIN, how important it is to you that AVASTIN would be able to address the following issues*?" OCC reported that all respondents indicated it would be important to prolong survival. Additionally, 79% of the respondents indicated that shrinkage of tumour size was important. About three quarters of the respondents also wanted to see an improvement in the quality of life.

For the respondents to consider taking bevacizumab, respondents reported that they would expect it to provide a moderate to excellent improvement in their cervical cancer.

The respondents reported that they would be willing to tolerate side effects from bevacizumab. Below are those side effects in which respondents would be most willing to tolerate.

- Decreased appetite 95%
- Fatigue 89%
- Decreased weight 89%
- Decreased magnesium in the blood 53%
- Urinary tract infection 53%
- Increased blood glucose 47%
- Headaches 47%
- Perforations of the GI tract 16%

The respondents expect to see significant benefits with bevacizumab. In particular they noted: a better chance at treatment, a stop to the disease, remission, prolongation of life and a shrinking of their metastases. Some of the comments reported include:

> *They say there is no cure for cervical cancer but it can be stopped to increase survival. I have lots to live for and am not ready to check out just yet.*
>
> *I suppose they (the side effects) can be control (sic) by other medications. I would do anything to survive.*
>
> *Have most of them (side effects) already anyway.*

Two respondents indicated they did not know what might be the benefits of bevacizumab.

Respondents were also asked what risks they might face if they used bevacizumab as a treatment. Eight out of the nineteen respondents (42%) could not identify potential risks associated with bevacizumab. Six respondents (32%) saw side effects as a potential risk, including heart attack or stroke.

Fifteen out of nineteen respondents (79%) reported that they were not sure that the benefits with using bevacizumab would outweigh the risks; while four (21%) respondents indicated benefits would outweigh risks.

4.2.1 Patient Expectations for and Experiences to Date with Bevacizumab

OCC reported that eight respondents had experience with bevacizumab. Of those respondents, 50% indicated that bevacizumab had shrunk the size of their tumour, managed their fatigue, prevented a recurrence and improved their prognosis.

Three of the eight (38%) respondents reported that bevacizumab had caused additional side effects and five respondents (63%) indicated that it had not. All eight respondents (100%) experienced high blood pressure. One respondent experienced fatigue and one respondent experienced headaches.

The two respondents that indicated high blood pressure and the one respondent that indicated fatigue noted that these side effects were an acceptable side effect. In contrast, two respondents indicated that fatigue, increased pain and renal impairment were not acceptable side effects. When asked about the impact of the side effects, many respondents described the importance they placed on survival which outweighed any discomfort or concerns resulting from the side effects.

Half of the respondents who used bevacizumab agreed or strongly agreed that it had improved their quality of life compared to previous treatments they had used. However, 12.5% (1 respondent) indicated that she strongly disagreed that bevacizumab had improved her life. 37.5% of the respondents neither agreed nor disagreed that it had improved their life.

Respondents described the effect on the quality of life (positive and negative) in the following way:

> *I don't believe that I have had any negative impacts from receiving Avastin. I believe that by receiving chemotherapy plus the Avastin it increases my chances of survival and hopefully no further reoccurances (sic).*
>
> *Compared to my previous chemos, I am more tired on this blend, but less nauseous. I have been more constipated also. I haven't noticed any other differences.*
>
> *It's not near as bad alone as when I had the chemo with it. However, it does cause me to have chronic sinusitis, joint pain, and an overall flu like feeling.*
>
> *Avastin shrunk my tumor, which no previous treatment had done. Then taken singly, it kept my disease stable for another year with minimal side effects.*
>
> *It has giving me more time to my life due to the fact is is (sic) maintaining the size of my tumor. Plus it does not make me sick or feel sick. Only thing is it prevents the healing process.*
>
> *Feel more confident that I won't have another recurrence right away.*

4.3 Additional Information

Ovarian Cancer Canada does not include cervical cancer in its mandate. Given that there is no patient advocacy group for cervical cancer patients in Canada and the requirements of pCODR around patient submissions, Ovarian Cancer Canada decided to take a leadership role on this submission.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

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

Overall Summary

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

Clinical factors:

- The addition of bevacizumab to existing chemotherapies is an important treatment option as there are not many options in this setting with overall survival benefit.
- Time limited need for patients who did not receive bevacizumab in the first-line setting.

Economic factors:

- Small patient population.
- High cost of bevacizumab.

Health System factors:

- Additional resources required to monitor and treat significant adverse effects.

Please see below for more details.

5.1 Factors Related to Comparators

The current standard of care for metastatic cervical cancer in most of the provinces is a platinum-based product (i.e. carboplatin or cisplatin) plus paclitaxel. In one province, the standard of care is platinum-based product plus topotecan. PAG noted that the GOC 240 trial included both standards of care.

5.2 Factors Related to Patient Population

PAG indicated that this would be a relatively small patient population. The addition of bevacizumab to existing chemotherapy has additional clinical benefits for these patients. These are enablers to implementation.

PAG would like pERC to consider the time limited need for previously treated patients who have recurrence of disease and who did not receive bevacizumab in the first-line setting. PAG would like the use in adjuvant setting and continuing bevacizumab beyond disease progression to be addressed by pERC. In addition, PAG would like clarity on whether all or specific histologic types of cervical cancer benefit from the addition of bevacizumab.

5.3 Factors Related to Dosing

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

5.4 Factors Related to Implementation Costs

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

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

5.5 Factors Related to Health System

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

5.6 Factors Related to Manufacturer

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

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of the addition of bevacizumab to chemotherapy in the treatment of patients with recurrent, persistent, or metastatic cervical cancer

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 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCT	Women with persistent, recurrent or metastatic cervical cancer	bevacizumab 15 mg/kg plus chemotherapy	cisplatin carboplatin cisplatin + paclitaxel/docetaxel, carboplatin + paclitaxel/docetaxel cisplatin + topotecan topotecan + paclitaxel /docetaxel cisplatin + gemcitabine cisplatin + vinorelbine carboplatin + topotecan	-Response rate **-Overall survival** -Progression free survival **-Quality of life** -Grade 3 or 4 adverse events (including bleeding, fatigue hypertension, proteinuria, thromboembolic events, sepsis, **fistulas and GI perforations**) -withdrawals and dose reductions / increases
[Abbreviations] GI = Gastrointestinal; RCT = Randomized controlled Trial				

** 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- November 12, 2014) with in-process records & daily updates via Ovid; EMBASE (1980- November 12, 2014) via Ovid; The Cochrane Central Register of Controlled Trials (2014, November 2014) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were [bevacizumab - avastin] and cervical cancer.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human

population. Retrieval was not limited by publication year. Retrieval was limited to the English language.

The search is considered up to date as of February 4, 2015.

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

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

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

6.2.4 Quality Assessment

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

6.2.5 Data Analysis

No additional data analyses were conducted as part of this 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:

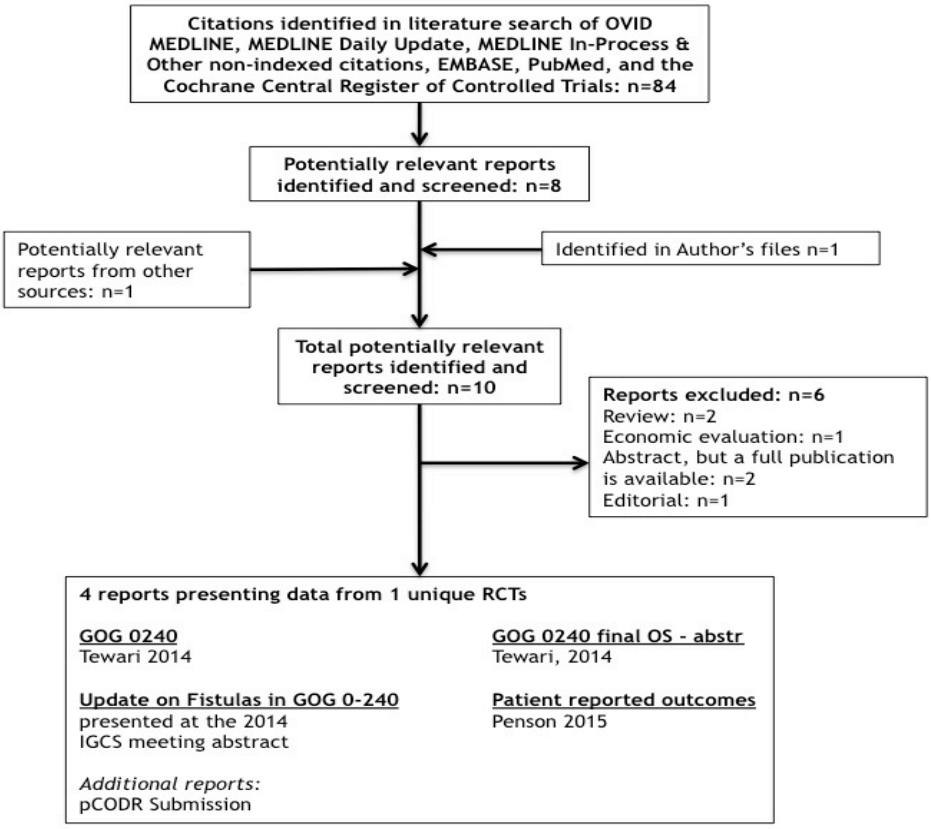
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions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

6.3 Results

6.3.1 Literature Search Results

Of the 9 potentially relevant reports identified, 4 reports representing one study were included in the pCODR systematic review [1,2,10 21] and 6 studies were excluded. Studies were excluded because they were [reviews,[22,23]], [an economic evaluation,[24]], [found an abstract, but the full publication is available,[20,25]], [editorial,[26]].

Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of studies



Note: Additional data related to studies [GOG 240] were *also obtained through requests to the Submitter by pCODR*

6.3.2 Summary of Included Studies

One randomized controlled trial was identified that met the eligibility criteria of this systematic review (see Table 4).

6.3.2.1 Detailed Trial Characteristics

5.6.1.1 **Table 4. Summary of Trial characteristics of the included Study[2,27]**

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
GOG 240 NCT00803062 Phase 3 open label multicentre study N=452 cisplatin + paclitaxel n=114 cisplatin + paclitaxel + bevacizumab n=115 topotecan + paclitaxel n=111 topotecan + paclitaxel + bevacizumab n=112 162 centres in 2 countries: Spain and the United States of America	• Primary stage IVB, recurrent or persistent squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which is not amenable to curative treatment with surgery and/or radiation therapy • Must have measurable disease • GOG performance status of 0 or 1 • Recovered from the effects of surgery, radiation therapy, or chemoradiotherapy; 6 weeks from the last administration of chemoradiotherapy, and 3 from the last administration of radiation therapy • Free of active infection requiring antibiotics **Exclusion criteria:** • Bilateral hydronephrosis which cannot be alleviated by ureteral stents or percutaneous drainage o Previously treated with chemotherapy except when used concurrently with radiation therapy; patients who have received concurrent paclitaxel and/or concurrent topotecan with radiation therapy • Non-healing wounds, active bleeding conditions or inadequately anticoagulated thromboembolism • History or evidence of central nervous system (CNS) disease • Patients with clinically significant cardiovascular disease • Patients with or with anticipation of invasive procedures.	Arm I: cisplatin (50 mg/m^2 plus paclitaxel (135 or 175 mg/m^2 on day 1 Arm II: cisplatin (50 mg/m^2 plus paclitaxel (135 or 175 mg/m^2 on day 1 plus bevacizumab (15 mg/kg on day 1) Arm III: topotecan (0.75 mg/m^2 on days 1 to 3) plus paclitaxel (175 mg/m^2 on day 1) Arm IV: topotecan (0.75 mg/m^2 on days 1 to 3) plus paclitaxel (175 mg/m^2 on day 1) plus bevacizumab (15 mg/kg on day 1)	Primary Outcome Measures: • Overall survival • Frequency and severity of adverse events Secondary Outcome Measures: • Progression-free survival • Frequency of objective tumor response Other Outcome Measures: • Health-related quality of life

5.6.1.1 Table 4. Summary of Trial characteristics of the included Study[2,27]			
Trial Design	**Key Inclusion Criteria**	**Intervention and Comparator**	**Outcomes**
Patients enrolled from April 2009 to January 2012 Funded by: National Cancer Institute (NCI)	• Patients who are pregnant or nursing; patients of childbearing potential must agree to use contraceptive measures • Patients who have received prior therapy with any anti-vascular endothelial growth factor (VEGF) drug, including bevacizumab		
GOG = Gynecologic Oncology Group			

a) Trials

One open label phase 3 randomized trial (GOG 240) was found that met the inclusion criteria for this review. Characteristics of the study's design can be found in Table 4. The study included patients with metastatic, persistent or recurrent cervical cancer. The study had four arms and used a 2x2 factorial design. The intravenous treatments were repeated at 21-day intervals until disease progression or unacceptable side effects. Arm 1 consisted of cisplatin plus paclitaxel, arm 2 consisted of cisplatin plus paclitaxel plus bevacizumab, arm 3 consisted of topotecan plus paclitaxel and arm 4 consisted of topotecan plus paclitaxel plus bevacizumab. Details of the doses for each arm can be found in Table 4. The study was open labelled and, therefore, not blinded. There was also no independent tumour response assessment. The patients were centrally randomized to one of each of the treatment arms.[1] The patients were stratified by GOG performance status, prior use or non-use of radiosensitizing platinum, and disease status (recurrence or resistant disease vs. advanced primary disease). The study was multicentred with 162 sites in 2 countries (Spain the United States of America). The National Cancer Institute sponsored the study.[1,27] The study commenced on April 6, 2009. On January 3, 2012 the target accrual was reached (n=452). An interim analysis was planned when the study reported 174 deaths. This took place on February 6, 2012. This data showed that topotecan was not a superior (or inferior) substitute for cisplatin, therefore the data and safety monitoring committee voted for an early release of this data. This data was released to all investigators and patients on March 13, 2012. A second planned efficacy analysis took place on December 12, 2012 after 271 deaths. The data and safety monitoring committee recommended partially releasing the data from this data freeze. The results in this review are primarily from the December 2012 release.[1] Final overall survival data from March 2014 were presented at the European Society for Medical Oncology (ESMO) in September of 2014 and is also included in this report.

The primary outcomes in this study were overall survival and the frequency and severity of adverse events. This study needed to enrol 450 patients with 346 deaths to provide the study with 90% power to detect a reduction in the risk of death of at least 30% with either experimental treatment, with the one-sided type 1 error rate

limited to 2.5% for each arm (overall all rate 5%).[1] An interim analysis was scheduled after 173 deaths had taken place in the study. The interim analyses allowed for the elimination of one of the experimental arm or discontinuation of the study for futility or for reporting treatment activity early in the event of dramatic improvement in survival.[1]

The secondary outcomes were progression-free survival and response rate. The differences in overall and progression-free survival were assessed largely by means of the log-rank test. The analyses were stratified according to clinical prognostic markers and the level of the other intervention. The hazard ratios were estimated using a Cox proportional-hazards model.[1] Quality of Life was also assessed, using three different tools: the Trial Outcome Index of the Functional Assessment of Cancer Therapy (FACT)-Cervix (FACT-Cx-TOI) was used to assess physical and functional well-being. Pain was measured with the use of the Brief Pain Inventory (BPI) and neurotoxicity was measured with the neurotoxicity subscale short form (FACT/GOG-NTX).[1]

b) Populations

A total of 452 patients were randomized to one of four arms: cisplatin + paclitaxel n=114; cisplatin + paclitaxel + bevacizumab n=115; topotecan + paclitaxel n=111; topotecan + paclitaxel + bevacizumab n=112.[1] The study baseline patient demographics can be seen in Table 5. Patients were balanced between the chemotherapy and the chemotherapy plus bevacizumab arms. Most of the patients had recurrent disease (72%) vs. persistent disease (11%) and 70% of the patients had received prior platinum-based chemoradiotherapy.

Table 5: Baseline patient demographic and disease characteristics for the GOG 240 trial[1]

Characteristic	Category	Total	Chemotherapy alone N (%)	Chemotherapy + Bevacizumab alone N (%)	P value
Median age yrs	-	-	46	48	0.960
Range yrs	-	-	20-83	22-85	
Age group	20-29	18	7(3)	11(5)	0.376
	30-39	94	55(24)	39(17)	
	40-49	144	69(31)	75(33)	
	50-59	116	51(23)	65(29)	
	60-69	56	31(14)	25(11)	
	70-79	19	10(4)	9(4)	
	≥80	5	2(1)	3(1)	
Ethnicity	Hispanic	54	28(12)	26(11)	0.947

Characteristic	Category	Total	Chemotherapy alone N (%)	Chemotherapy + Bevacizumab alone N (%)	P value
	Non-Hispanic	374	185(82)	189(83)	
	Unknown/Unsp	24	12(5)	12(5)	
Race	Asian	19	7(3)	12(5)	
	Black	60	24(11)	36(16)	
	Amer Indian	5	2(1)	3(1)	
	White	351	180(80)	171(75)	
	Unknown/Unsp	17	12(5)	5(2)	
PS	0	263	131(58)	132(58)	0.988
	1	189	94(42)	95(42)	
Cell Type	Squamous	310	152(68)	158(70)	0.862
	Adeno unsp.	86	44(20)	42(19)	
	Adenosquamous	44	21(9)	23(10)	
	Clear cell adeno	4	3(1)	1(0)	
	Mucinous	4	2(1)	2(1)	
	Serous adeno	2	1(0)	1(0)	
	Endometrioid	1	1(0)	0	
	Undifferentiated	1	1(0)	0	
Tumour Grade	1	24	18(8)	6(3)	0.066
	2	213	97(43)	117(52)	
	3	176	88(39)	88(39)	
	Indeterminate	37	21(9)	16(7)	
Disease Status	Recurrent	325	165(73)	160(70)	0.737
	Persistent	51	23(10)	28(12)	
	Advanced	76	37(16)	39(17)	
Disease Site	Pelvis	242	119(53)	123(54)	0.782
	Not Pelvis	210	106(47)	104(46)	
Prior Platinum	Yes	337	166(74)	171(75)	0.705
	No	115	59(26)	56(25)	
PS= performance status; unsp= unspecified					

c) Interventions

All treatments were administered intravenously. The treatment protocols can be seen in Table 4. Treatments were given on a 21 day cycle and treatment was discontinued upon disease progression or unacceptable side effects or if the patient had a complete response.[1] Dose modification of bevacizumab was only allowed if the patient's weight changed by 10% or more. Patients who had adverse side effects to bevacizumab, such as uncontrolled hypertension, proteinuria, arterial thrombosis, venous thrombosis, coagulopathy or intestinal obstruction or disruption could have their dose delayed or discontinued. Dose delays were allowed for the patient to recover from side effects before starting the next cycle. Dose modifications were permitted for chemotherapy treatment. If a patient's chemotherapy was delayed due to a low absolute neutrophil count or thrombocytopenia then bevacizumab was also delayed.[1] The median number of cycles for the chemotherapy alone group was 6 (range 0-30) and the median number of cycles for the chemotherapy plus bevacizumab group was 7 (range 0-36).[1] The median dose intensities can be seen in Table 6.

Table 6: Median Dose intensity

Drug	Median Dose
Cisplatin	49.850
Paclitaxel	174.673
Cisplatin	50.000
Paclitaxel	174.125
Bevacizumab	14.993
Paclitaxel	173.987
Topotecan day 1	0.748
Topotecan day 2	0.746
Topotecan day 3	0.743
Paclitaxel	174.862
Topotecan day 1	0.748
Topotecan day 2	0.748
Topotecan day 3	0.748
Bevacizumab	15.000
Dosages for cisplatin, paclitaxel and topotecan in mg/m^2 Dosages for bevacizumab in mg/kg	

d) Patient Disposition

There were 114 patients in the cisplatin plus paclitaxel arm and 111 patients in the topotecan plus paclitaxel arm. Of these 225 patients assigned to the chemotherapy alone arms, 219 were included in the safety analysis, as 6 patients did not have adverse event data submitted. All 225 patients were included in the efficacy analysis and all 225 had discontinued treatment; 6 had a complete response to the treatment; 115 had disease progression; 36 had toxic side effects; 35 declined further treatment; 5 died; 2 had other disease; 21 had other reasons; and 5 had unspecified reasons. No patients were lost to follow-up. In this group of chemotherapy alone patients 51 had crossed over to salvage therapy; 12 to bevacizumab, 20 to cisplatin, 16 to topotecan; 1 to both bevacizumab and

topotecan; and 2 to both bevacizumab and cisplatin. In this group of chemotherapy alone patients 184 reached the progression free survival endpoint and 140 died. There were 115 patients in the cisplatin plus paclitaxel plus bevacizumab group and 112 in the topotecan plus paclitaxel plus bevacizumab group. Of these 227 patients assigned to the chemotherapy plus bevacizumab arms, 220 were included in the safety analysis, as 7 patients did not have adverse event data submitted. All 227 patients were included in the efficacy analysis and all 227 had discontinued treatment; 15 had a complete response to the treatment; 86 had disease progression; 57 had toxic side effects; 28 declined further treatment; 6 died; 4 had other disease; 23 had other reasons; and 8 had unspecified reasons. No patients were lost to follow-up. In this group of chemotherapy plus bevacizumab patients 33 had crossed over to salvage therapy; 7 to bevacizumab, 12 to cisplatin, 13 to topotecan; 0 to both bevacizumab and topotecan; and 1 to both bevacizumab and cisplatin. In this group of chemotherapy plus bevacizumab patients 183 reached the progression free survival endpoint and 131 died.[1]

e) Limitations/Sources of Bias

The study personnel, treating physicians, and patients were not blinded to treatment assignment. This could have affected the results, especially for patient-reported outcomes such as quality-of-life, in favour of whichever arm the assessor (either study personnel or the patient in the case of quality-of-life) felt was likely to provide benefit. Additionally there were no independent assessments of the study outcomes and the investigators provided the analyses. This can be a potential bias. Most of the study data is also based on interim analyses. This can lead to biases as the study is not yet completed and results could change during the final analyses. The study used one sided p values. This was done because the study was designed with futility rules. To allow for this the level of significance was conducted at 2.5% instead of 5%.[1] Fifteen patients (6.7%) who received chemotherapy alone crossed over to bevacizumab as salvage therapy. The primary endpoint in this study was overall survival and there was still a significant difference despite the patients who crossed over. There was no further temporal endpoint beyond overall survival that could be diluted.[1]

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Overall survival

The primary outcome of the GOG 240 trial is overall survival. At a median follow-up of 20.8 months the addition of bevacizumab significantly improved the median overall survival compared with chemotherapy alone (17.0 months vs. 13.3 months; hazard ratio for death, 0.71; 98% CI, 0.54 to 0.95; one sided p=0.004). At this data point 271 deaths had been reported (60% of the total study population).[1] The survival curves for this analysis separate and stay separated.[1] The planned final analysis for overall survival from March 2014 continues to shows the significant improvement for patients treated with bevacizumab 16.8 months vs. 13.3 months; HR 0.765 (95%CI; 0.62-0.95; p=0.0068). This analysis showed that 348 deaths had occurred (77% of the total study population).[2]
Data from the December 2012 analysis show that when the results for women receiving bevacizumab plus cisplatin and paclitaxel were compared to the results for women receiving cisplatin and paclitaxel alone the hazard ratio for death was 0.68; 95%CI 0.48-0.97; one sided p=0.04). This can be seen in figure 3A. When bevacizumab plus topotecan and paclitaxel was compared to topotecan and

paclitaxel alone the hazard ratio for death was 0.74; 95%CI 0.53-1.05; one sided p=0.09).[1] However, this analysis was not powered enough to detect a difference in overall survival.[28]

The secondary outcome progression free survival was also significantly improved with the addition of bevacizumab (8.2 vs. 5.9 months; hazard ratio for disease progression, 0.67; 95% CI, 0.54 to 0.82; one sided p 0.002). In this analysis the survival curve separated and then came together at the end.[1] In subgroup analyses, progression free survival results were similar for the comparison of bevacizumab-cisplatin-paclitaxel vs. cisplatin-paclitaxel as well as the comparison of bevacizumab-cisplatin-topotecan vs. cisplatin-topotecan.

Response

The response rate (complete plus partial responses) was also significantly higher in patients who were randomized to bevacizumab plus combination chemotherapy compared to those who received combination chemotherapy without bevacizumab (48% vs. 36%) (relative probability of a response, 1.35; 95% CI, 1.08 to 1.68; P=0.008, two-sided test). A complete response was seen in 28 (12.3%) patients who received bevacizumab, compared to 14 (6.2%) who received chemotherapy alone (P=0.03).[1]

In the cisplatin plus paclitaxel plus bevacizumab group the response rate was 50% compared with 45% for the cisplatin and paclitaxel group, (P=0.51, two-sided test); 17 patients and 9 patients had a complete response, respectively. In the topotecan plus paclitaxel plus bevacizumab group the response rate was 47% compared to 27% for the topotecan plus paclitaxel group, (P=0.002, two-sided test); 11 patients and 5 patients had a complete response, respectively.[1]

Quality of Life

Quality of life was assessed using 3 validated health related quality of life instruments. The Outcome Index of the Functional Assessment of Cancer Therapy (FACT)-CERVIX (FACT Cx-TOI) was used to asses physical and functional well-being. The Brief Pain Inventory (BPI) measured pain and neurotoxicity was measured using a subscale short from of the (FACT/GOG-NTX). The most commonly-used single items from the Brief Pain Inventory (BPI), and the four most responsive items from the 11-item FACT-Neurotoxicity (FACT/GOG-Ntx) subscale were selected instead of the use of whole questionnaires for pain and neurotoxicity to reduce the assessment burden.

The mean FACT Cx-TOI scored above 70 for the bevacizumab plus combination chemotherapy group and the combination chemotherapy alone group at each time point. Each item in the FACT-Cx TOI subscale are scored using a 5-point scale (0=not at all; 1=a little bit; 2=somewhat; 3=quite a bit; 4=very much. A clinically meaningful change for group comparisons is approximately 4-5 points.[1] The addition of bevacizumab adversely affected the scores, with bevacizumab treated patients reporting, on average, 1.2 points lower on quality of life scores. This was not statistically significant (98.75%CI -4.1- 1.7; p=0.3).[1] The BPI also indicated that bevacizumab did not adversely affect quality of life and patients had similar pain scores (p=0.16).[9] The FACT/GOG=NTX scores demonstrated a non-statistically significant pattern for patients in the bevacizumab groups to report fewer neurotoxic symptoms (overall odds ratio, 0.58; 99% CI, 0.29 to 1.17; P=0.05), and the severity of neurotoxic symptoms reported was similar in the two groups (P=0.70).[1] The level of significance

was adjusted from 5% using the Bonferroni method and set at 0.0125 to control for overall type 1 errors.[1]

Harms Outcomes

Adverse effects can be seen in table 7. Grade 2 or higher hypertension was significantly more frequent in patients who received bevacizumab plus combination chemotherapy compared to those who received combination chemotherapy without bevacizumab (25% vs. 2%, P<0.001). However, no patients discontinued treatment because of hypertension.[1] Gastrointestinal-vaginal fistulas occurred in 18 (8.2%) patients, genitourinary-vaginal fistulas occurred in 4(1.8%) patients and gastrointestinal fistulas in 1(0.5%) of patients treated with bevacizumab plus chemotherapy. In the patients treated with chemotherapy alone, 2 (0.9%) developed gastrointestinal-vaginal fistulas and 3 (1.4%) developed genitourinary-vaginal fistulas. The fistulas were not associated with peritonitis, sepsis or death. All patients who had gastrointestinal-vaginal fistulas had received prior pelvic radiation.[10]In addition thromboembolic events of grade 3 or higher were also significantly associated with bevacizumab treatment (8% vs. 1%, P=0.001). Neutropenia of grade 4 or higher, febrile neutropenia of grade 3 or higher, and pain of grade 2 or higher were not significant between the chemotherapy alone and bevacizumab plus chemotherapy groups. Proteinuria of grade 3 or higher, gastrointestinal and genitourinary bleeding was uncommon.[1] The rates of grade 3-5 peripheral sensory neuropathy, nausea, constipation and vomiting were the same between chemotherapy alone and chemotherapy plus bevacizumab.

Table 7: Adverse events

Event	Chemotherapy alone N=219 (%)	Chemotherapy plus Bevacizumab N=220 (%)	Odds Ratio (95%CI)	P value
Gastrointestinal events (excluding fistulas) grade ≥2	96 (44)	114(52)	1.38(0.93-2.04)	0.10
Fistula (grade ≥3)				
Gastrointestinal-vaginal[10]	2 (0.9%)	18 (8.2%)		
Genitourinary-vaginal[10]	3 (1.4%)	4(1.8%)		
Gastrointestinal[10]	NA	1(0.5%)		
Hypertension (grade ≥2)♁ [1]	4(2)	54(25)	17.50(6.23-67.50)	<0.001
Proteinuria (grade ≥3) [1]	0	4(2)	NA (0.90-∞)	0.12
Pain (grade ≥2) [1]	62(28)	71(32)	1.21(0.79-1.85)	0.41
Neutropenia (grade ≥4) [1]	57(26)	78(35)	1.56(1.02-2.40)	0.04
Febrile neutropenia (grade ≥3) [1]	12(5)	12(5)	1.00 (0.40-2.48)	1.00
Thromboembolism (grade ≥3) [1]	3(1)	18(8)	6.42 (1.83-34.3)	0.001
CNS bleeding (grade ≥ 3) [1]	0	0	NA	
Gastrointestinal bleeding (grade ≥3) ∫∫ [1]	1(<1)	4(2)	4.04 (0.39-200.00)	0.37

Event	Chemotherapy alone N=219 (%)	Chemotherapy plus Bevacizumab N=220 (%)	Odds Ratio (95%CI)	P value
Genitourinary bleeding (grade ≥3) ∬[1]	1(<1)	6(3)	6.11(0.73-282.00)	0.12
Fatigue (grades 3-5)[3]	(10)	(14)		
Urinary tract infections (grades 3-5)[3]	(6)	(8)		
Diarrhea (grades 3-5)[3]	(2.7)	(5.5)		

♤ Hypertension of grade 2 or higher was defined as recurrent or continuous hypertension for a period of more than 24 hours or a symptomatic increase in blood pressure by more than 20mm Hg diastolic or to more than 150/100 mmHg if the blood pressure was previously within the normal range

∬ Bleeding was managed primarily with supportive therapy and transfusions of packed red cells, most commonly in the outpatient setting.

CNS= Central nervous system; NA = Not applicable

Deaths

Fatal adverse events were reported in four patients (1.8%) who received chemotherapy alone and in four patients (1.8%) who received chemotherapy plus bevacizumab (P=1.0). These can be seen in table 8.[1] Less than 1% of patients who received bevacizumab with combination chemotherapy died due to a gastrointestinal perforation.[3]

Table 8: Deaths associated with treatment

Treatment	Cause
Cisplatin + paclitaxel	Grade 5 infection with grade 4 neutropenia
Topotecan + paclitaxel	Grade 5 infection with grade 4 neutropenia
Topotecan + paclitaxel	Grade 5 infection with grade 4 neutropenia
Topotecan + paclitaxel	Grade 5 infection with unknown absolute neutrophil count
Topotecan + paclitaxel + bevacizumab	Grade 5 infection with grade 4 neutropenia
Topotecan + paclitaxel + bevacizumab	Grade 5 infection with grade 4 neutropenia
Topotecan + paclitaxel + bevacizumab	Gastrointestinal perforation
Topotecan + paclitaxel + bevacizumab	Adult respiratory distress syndrome

6.4 Ongoing Trials

No ongoing randomized trials comparing bevacizumab plus chemotherapy to chemotherapy in persistent, recurrent and advanced cervical cancer were found.

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 cervical cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

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

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

The Gynecologic Clinical Guidance Panel is comprised of three clinical oncologists.The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). 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

1. Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE (R) Daily Update, Ovid EMBASE and Ovid CDSR.

1. avastin.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw, tn, dm, mf, dv, nm, kf, px, rx, an, ui]
2. bevacizumab.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw, tn, dm, mf, dv, nm, kf, px, rx, an, ui]
3. rhuMAb-VEGF.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw, tn, dm, mf, dv, nm, kf, px, rx, an, ui]
4. rhuMAb - VEGF.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw, tn, dm, mf, dv, nm, kf, px, rx, an, ui]
5. rhuMAbVEGF.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw, tn, dm, mf, dv, nm, kf, px, rx, an, ui]
6. (cervix or cervical).mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw, tn, dm, mf, dv, nm, kf, px, rx, an, ui]
7. 1 or 2 or 3 or 4 or 5
8. 6 and 7
9. remove duplicates from 8
10. random:.af.
11. 9 and 10

2. Literature Search via PubMed

1. (((bevacizumab) OR avastin) OR rhuMAb-VEGF) OR rhuMAb - VEGF
2. (((neoplasms) AND cervix)) OR cervical cancer
3. publisher[sb]

3. Grey Literature Searches

Clinical Trial Registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov
Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: ibrutinib OR imbruvica OR PCI-32765 OR PCI - 32765 OR PCI 32765 OR PCI32765

Select International Agencies:

Food and Drug Administration (FDA):
www.fda.gov

European Medicines Agency (EMA):
www.ema.europa.eu

Search terms: bevacizumab OR avastin OR rhuMAb-VEGF) OR rhuMAb - VEGF

4. Conference Abstracts:

American Society of Clinical Oncology (ASCO)
via the *Journal of Clinical Oncology* search portal: http://jco.ascopubs.org/search

Search terms: bevacizumab OR avastin OR rhuMAb-VEGF) OR rhuMAb - VEGF

REFERENCES

1. Tewari KS, Sill MW, Long IHJ, Penson RT, Huang H, Ramondetta LM, et al. Improved survival with bevacizumab in advanced cervical cancer. New England Journal of Medicine. 2014;370(8):734-43.
2. Tewari KS, Huang H, Ramondetta LM, Landrum LM, Oaknin A, Reid TJ, et al. Final overall survival analysis of the phase III randomized trial of chemotherapy with and without bevacizumab for advanced cervical cancer: A NRG Oncology - Gynecologic Oncology Group Study. Ann Oncol 2014;25(Suppl 6):abstract LBA26.
3. Avastin (bevacizumab) [US prescribing information]. Mississauga (ON): Hoffmann-La Roche Limited; November 2014.
4. Monk BJ, Sill MW, McMeekin DS, Cohn DE, Ramondetta LM, Boardman CH, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: A Gynecologic Oncology Group study. Journal of Clinical Oncology. 2009;27(28):4649-55.
5. Kitagawa R, Katsumata N, Ando M, et al. A multi-institutional phase II trial of paclitaxel and carboplatin in the treatment of advanced or recurrent cervical cancer. Gynecol Oncol 2012;125(2):307-11.
6. Canadian Cancer Society, Statistics Canada. Candian Cancer Statistics 2014. . [January 22. 2015]; Available from: http://www.cancer.ca/~/media/cancer.ca/CW/cancer information/cancer 101/Canadian cancer statistics/Canadian-Cancer-Statistics-2014-EN.pdf.
7. Rose PG, Blessing JA, Gershenson DM, McGehee R. Paclitaxel and cisplatin as first-line therapy in recurrent or advanced squamous cell carcinoma of the cervix: a gynecologic oncology group study. Journal of Clinical Oncology. 1999;17(9):2676-90.
8. American Cancer Society. Survival rates for cervical cancer, by stage. [February 3, 2015]; Available from: http://www.cancer.org/cancer/cervicalcancer/detailedguide/cervical-cancer-survival.
9. pan-Canadian Oncology Drug Review Manufacturer Submission: Avastin (bevacizumab); Company: Hoffmann-La Roche Limited. Mississauga (ON): Hoffmann-La Roche Limited: 2014 December 29.
10. Willmott LJ, Java JJ, Monk BJ, Shah J, Husain A, Tewari KS. Fistulae in women treated with chemotherapy with and without bevacizumab for persistent, recurrent or metastatic cervical cancer in GOG-240. International Gynecologic Cancer Society; November 8-11, 2014; Melbourne, Australia2014.
11. Cancer Care Ontario. Ontario Cervical Screening Report 2012. [February 3, 2015]; Available from: https://http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=295748.
12. Monk BJ, Willmott LJ, Sumner DA. Anti-angiogenesis agents in metastatic or recurrent cervical cancer. Gynecologic Oncology. 2010;116(2):181-6.
13. Tomao F, Papa A, Rossi L, Zaccarelli E, Caruso D, Zoratto F, Panici PB, Tomao S. Angiogenesis and antiangiogenic agents in cervical cancer. OncoTargets and Therapy 2014;7:2237-2248.
14. Eskander RN Tewari K. Targeting angiogenesis in advanced cervical cancer. Therapeutic Advances in Medical Oncology 2014;6(6)):280-292.
15. Monk BJ, Sill MW, Burger RA, Gray HJ, Buekers TE, Roman LD. Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: A gynecologic oncology group study. Journal of Clinical Oncology. 2009;27(7):1069-74.
16. The Blue Book and overview of gynecologic oncology. Available from: http://www.pathology.med.umich.edu/gynonc/bluebook/appendix/appen2.html.
17. Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

18. Organization IAfRoCWH. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. 2012; Available from: http://globocan.iarc.fr/old/FactSheets/cancers/cervix-new.asp.
19. Saito I, Kitagawa R, Fukuda H, Shibata T, Katsumata N, Konishi I, et al. A phase III trial of paclitaxel plus carboplatin versus paclitaxel plus cisplatin in Stage IVB, persistent or recurrent cervical cancer: Gynecologic cancer study group/Japan clinical oncology group study (JCOG0505). Japanese Journal of Clinical Oncology. 2010;40(1):90-3.
20. Tewari KS, Sill M, Long HJ, Ramondetta LM, Michelle Landrum L, Oaknin A, et al. Incorporation of bevacizumab in the treatment of recurrent and metastatic cervical cancer: A phase III randomized trial of the Gynecologic Oncology Group. Journal of Clinical Oncology. 2013;1).
21. Penson RT, Huang H, Wenzel LB, Monk BJ, Stockman S, Long HJ, et al. Bevacizumab for advanced cervical cancer: patient-reported outcomes for a randomized, phase 3 trial (NRG Oncology-Gynecologic Oncology Group protocol 240). Lancet Oncology. 2015;January 29, 2015 [epub ahead of print].
22. Kuznar W. Bevacizumab an effective new treatment option for relapsed cervical cancer. American Health and Drug Benefits. 2013;6(6 SPL.ISS).
23. Salomon-Perzynska M, Perzynski A, Rembielak-Stawecka B, Michalski B, Skrzypulec-Plinta V. VEGF - targeted therapy for the treatment of cervical cancer - literature review. [Polish]Terapia celowana ukierunkowana na VEGF w leczeniu raka szyjki macicy - przegl^d pismiennictwa. Ginekologia Polska. 2014;85(6):461-5.
24. Minion L, Tewari KS, Chan JK, Penson RT, Cohn DE, Monk BJ. A trial-based economic assessment of bevacizuamb and chemotherapy versus chemotherapy alone for advanced cervical cancer: Cost-effective analysis of gynecologic oncology group (GOG) protocol 240. International Journal of Gynecological Cancer. 2013;1):241.
25. Penson RT, Huang H, Tewari KS, Long HJ, Ramondetta LM, Landrum LM, et al. Patient reported outcomes in a practice changing randomized trial of bevacizumab in the treatment of advanced cervical cancer: A Gynecologic Oncology Group study. European Journal of Cancer. 2013;49:S18.
26. Kehoe S. Bevacizumab and treatment of cervical cancer. Maturitas. 2014.
27. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000 Feb 29-. Identifier NCT00803062, Paclitaxel and Cisplatin or Topotecan With or Without Bevacizumab in Treating Patients With Stage IVB, Recurrent, or Persistent Cervical Cancer; 2008 Dec 4[Last updated 2015 January 13; cited 2015 January 22]. Avaliable from: https://clinicaltrials.gov/show/NCT00803062.
28. Hoffmann-La Roche Limited. Response to checkpoint meeting questions [internal report]. Mississauga (ON): Hoffmann-La Roche Limited.