PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Bevacizumab (Avastin) and Capecitabine for Metastatic Colorectal Cancer

July 21, 2015

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review is to evaluate the safety and efficacy of bevacizumab in combination with capecitabine compared to standard care options or capecitabine, for the first-line treatment of advanced or metastatic colorectal cancer (mCRC) for patients who are not suitable for oxaliplatin or irinotecan-based therapy.

Bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF).[1] The Health Canada recommended dose is 5 mg/kg of body weight given once every 14 days as an intravenous infusion. Bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

The pCODR systematic review included two multicentre phase III, open-label randomized controlled trials (RCTs), the AVEX and MAX studies, which evaluated the efficacy and safety of bevacizumab (BEV) in combination with capecitabine (CAP) compared to CAP alone. In both studies, patients receiving BEV + CAP received IV BEV at a dose of 7.5 mg/kg body weight on day 1 of a 3-weekly cycle and oral CAP 1000 mg/m^2 or 1250 mg/m^2 twice daily on days 1-14 in the AVEX and MAX studies, respectively. Patients in the CAP alone group were treated with the same dose of CAP as the BEV + CAP groups.

The AVEX study randomized patients in a 1:1 ratio between bevacizumab + capecitabine (BEV + CAP; N=140) and capecitabine (CAP; N=140). The MAX study randomized patients between BEV + CAP (N=157), CAP (N=156), and capecitabine plus bevacizumab plus mitomycin (N=158; results for this arm were not reported in this review). Reported patient characteristics appeared to be balanced between the two treatment groups. The ECOG performance status of most patients was 0 or 1 for both studies and the majority of patients was male. In the MAX study, age ranged from 32-86 years while in the AVEX study, only patients who were 70 years or older were included (range 70-87).

Efficacy

The primary endpoint for both studies was progression-free survival (PFS), secondary outcomes included overall survival (OS), overall response rate (ORR), and safety. In the AVEX study, patients in the BEV + CAP group had a significantly longer median PFS than those in the CAP alone group (9.1 versus 5.1 months; HR=0.53, p<0.0001). Similar results were seen in the MAX trial with 8.5 versus 5.7 months (HR=0.63, p=0.03) in the BEV + CAP and CAP alone groups, respectively. In both studies, there was no significant difference in overall survival (OS). The median OS in the AVEX study was 20.7 months for the BEV + CAP group and 16.8 months in the CAP alone group. The median OS was 18.9 months for both the BEV + CAP and CAP alone groups in the MAX study.

In the MAX study, health-related quality of life (HRQoL) was assessed using Euroqol-5D, Utility Based Quality of Life Questionnaire-Cancer, and the Chemotherapy Acceptance Questionnaire. Patients in the BEV + CAP group reported significantly worse outcomes for

sore hands and feet and sore mouth, there were no significant differences for other symptoms, functions, overall QoL, or acceptability of chemotherapy.

Harms

Treatments were generally well tolerated in both studies, with similar treatment-related adverse events (TRAEs) of any grade across treatment groups. The most common TRAEs in patients treated with BEV + CAP in both the AVEX and MAX studies were hand-foot skin reaction, fatigue, diarrhea, and hypertension. In the AVEX study, a higher proportion of patients in the BEV + CAP treatment group compared to the CAP alone group, had a treatment-related serious adverse event (14% versus 8%). A higher proportion of patients in the BEV + CAP group had dose modifications due to toxic effects than the CAP alone group (41% versus 26%).

1.2.2 Additional Evidence

pCODR received input on bevacizumab in combination with capecitabine from one patient advocacy group (Colorectal Cancer Association of Canada). Provincial Advisory Group input was obtained from nine of nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

In addition, two supplemental questions were identified during development of the review protocol as relevant to the pCODR review of bevacizumab in combination with capecitabine for metastatic colorectal cancer and are discussed as supporting information:

- What is the efficacy and safety of bevacizumab (BEV) in combination with 5-fluorouracil (5-FU) for advanced or metastatic colorectal cancer (mCRC)?
- What is the validity of progression-free survival (PFS) as a surrogate outcome for mCRC?

1.2.3 Interpretation and Guidance

For patients whom multi-agent chemotherapy is not suitable, bevacizumab and single-agent fluoropyrimidine chemotherapy (capecitabine or 5-fluorouracil) represent the preferred treatment option. Capecitabine and 5-fluorouracil have shown similar efficacy and safety profiles. Furthermore, treatment with bevacizumab should be considered irrespective of age.

Two well-conducted multicentre RCTs (AVEX and MAX) showed increased progression-free survival with bevacizumab in combination with capecitabine (median of approximately 3-4 months). There were non-significant trends towards improvements in overall survival.

The addition of bevacizumab to single-agent fluoropyrimidine chemotherapy resulted in a modest increase in toxicity. Patients who received combination therapy with bevacizumab had increased rates of hand-foot skin reaction, mucositis, diarrhea, fatigue, and hypertension. These toxicities are similar to what is observed when bevacizumab is added to a multi-agent chemotherapy and are generally considered acceptable and manageable.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a modest net overall clinical benefit from the addition of bevacizumab to single-agent fluoropyrimidine chemotherapy (capecitabine or 5-fluorouracil).

In reaching this conclusion, the Clinical Guidance Panel considered:

- **Effectiveness:** The data reviewed, primarily from two high-quality randomized controlled trials of capecitabine with or without bevacizumab, but also trials adding bevacizumab to 5-fluorouracil and multi-agent chemotherapy in the first and second line setting, show a very consistent modest improvement in progression-free survival, which, in studies powered for it, generally translates into a modest improvement in overall survival.
- **Safety:** The adverse event profiles were modestly increased, similar to those seen in combination with multi-agent chemotherapy where they are generally considered acceptable and in most cases manageable.
- **Need and burden of disease:** Bevacizumab plus a single-agent fluoropyrimidine represents the preferred treatment option for the 5-10% of patients, of any age, who are not able or willing to take multi-agent chemotherapy (for which bevacizumab is generally publicly funded). Regarding issues of equity and accessibility, 5-fluorouracil is an important option for patients without coverage for oral capecitabine in much of the country. Importantly, the clinical outcomes and safety profile of bevacizumab in the treatment of metastatic colorectal cancer appears to be very similar regardless of the chemotherapy backbone. Although the CGP acknowledged that the AVEX and MAX studies included only patients with ECOG 0-2, the CGP concluded that consideration of the appropriateness of treatment with bevacizumab should be a decision between physicians and individual patients.

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 in combination with capecitabine for metastatic colorectal 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.cadth.ca/pcodr.

This Clinical Guidance is based on: a systematic review of the literature regarding bevacizumab in combination with capecitabine for metastatic colorectal cancer conducted by the Gastrointestinal Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from a patient advocacy group; input from the Provincial Advisory Group (PAG); 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 in combination with capecitabine for metastatic colorectal cancer and a summary of submitted PAG Input on bevacizumab in combination with capecitabine for metastatic colorectal cancer are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Colorectal cancer (CRC) is the second and third most common form of cancer among men and women, respectively, in Canada.[2] The Canadian Cancer Society estimated 24,400 newly diagnosed CRC cases in 2014.[2] Twenty to 25% of patients present with metastases at the time of primary diagnosis,[3] and 50% of all CRC patients are estimated to develop metastases over the course of their disease.[4]

Non-surgical treatment options for mCRC include chemotherapy, targeted therapy, and radiation therapy.[5] The primary backbone chemotherapy recommended for advanced CRC is intravenous 5 fluorouracil (5-FU),[6] a fluoropyrimidine which may be used alone or in combination with others including, oxaliplatin and irinotecan. Capecitabine (CAP) is an oral fluoropyrimidine reported to have similar efficacy to 5-FU as first-line treatment of advanced or metastatic colorectal cancer (mCRC).[6,7] It undergoes enzymatic transformation in the body to deliver 5-FU directly to the tumour tissue.[7]

Bevacizumab (BEV) is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF). Endothelial proliferation and the formation of new blood vessels are mediated through VEGF binding. Therefore, VEGF inhibitors, such as BEV reduce the vascularisation of tumours, thereby inhibiting tumour growth.[1] Other Health Canada approved targeted mCRC therapies are cetuximab, and panitumumab, both of which are anti-epidermal growth factor receptor (EGFR) therapies used in patients with KRAS wild-type tumors.[8]

CAP monotherapy, as well as bevacizumab (BEV) in combination with fluoropyrimidine-based chemotherapy, have been approved by Health Canada to be used as first-line treatment of patients with mCRC.[1,9] In addition CAP in combination with oxaliplatin is indicated for the treatment of mCRC following failure of irinotecan-containing combination chemotherapy.[9] The underlying assumption for the BEV + CAP combination which is the subject of this review is that it affords better progression-free survival (PFS) outcomes than CAP alone in mCRC patients for whom combination therapy with IV 5-FU and/or other chemotherapy may be unsuitable, with an acceptable safety profile.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effect of bevacizumab (Avastin) in combination with capecitabine on patient outcomes compared to standard care options or capecitabine, for the first-line treatment of advanced or metastatic colorectal cancer (mCRC) for patients who are not suitable for oxaliplatin or irinotecan-based therapy.

2.1.3 Highlights of Evidence in the Systematic Review

Two multicenter, phase 3, open-label randomized controlled trials, the AVEX[10] and the MAX[11] studies, which evaluated the comparative efficacy and safety of BEV in combination with CAP compared to CAP alone as first-line treatment in patients with mCRC were included in this systematic review. The MAX trial had a third treatment arm which comprised mitomycin in addition to the BEV + CAP combination. However, this systematic review focuses only on outcomes from the BEV + CAP and CAP alone treatment groups. The AVEX study was designed to have 80% power to detect a 31% reduction in the risk of disease progression (HR of 0.69) with a two-sided α of 0.05, and 232 PFS events, while the MAX study had at least 80% power to detect a 33% relative reduction in risk.

Distribution of patient between the treatment groups was balanced across the BEV + CAP group (n=140 and n =157) and the CAP alone group (n=140 and n =156), respectively, for the AVEX and MAX studies. For each study, patients' demographic and disease conditions were generally balanced between treatment groups. While the AVEX study was selective for elderly patients (median age 76 years; range: 70-87), the MAX study was open to adults of ≥18 years, although the median age was 68 years (range: 32-86).[11] The ECOG performance status of most of the patients was 0 or 1 for both studies and the majority (60 to 65%) of patients was male.

In both studies, patients who were randomized to BEV + CAP received IV BEV at a dose of 7. 5mg/kg body weight on day 1 of a 3-weekly cycle and oral CAP 1000 mg/m^2 or 1250 mg/m^2 twice daily on days 1-14 in the AVEX and MAX studies, respectively (Table 1). Patients in the comparator group were treated with similar doses of CAP as in the BEV + CAP group. While the AVEX study reported concomitant drug use by most patients in the two treatment groups, the MAX study did not report any use of concomitant medication. Treatments were pre-specified to continue until disease progression, or intolerable toxic effects, or withdrawal of consent.

The BEV + CAP group in the AVEX study had a median overall duration of exposure to treatment of 5.8 months, with interquartile range (IQR) of 2.6 to 11.1 months, compared with 4.2 months (1.9 to 7.2 months) in the CAP alone group.[10] Although the actual overall duration of exposure was not reported for the MAX study, it might be estimated from the median number of treatment cycles (n = 10 for BEV + CAP; and n = 8 for CAP alone) to be around 7.5 and 6 months for the BEV + CAP and the CAP alone groups, respectively, based on the specified 3-week cycle, and a 4-week month.

Table 1: Summary of Key Characteristics of the Included studies *

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
AVEX[10] 40 centres in 10 countries (Austria, Canada, Hungary, Italy, Mexico, Poland,	Patients aged ≥70 years with previously untreated, unresectable mCRC, who were not deemed to be candidates for oxaliplatin-based or irinotecan-based chemotherapy regimens; and had	BEV, 7.5 mg/kg IV on day 1 with oral CAP 1000 mg/m^2 (1250 mg/m^2 in MAX) twice a day on days 1-14 versus CAP 1000 mg/m^2 (1250 mg/m^2 in MAX) orally twice a day on days 1-14. In MAX, a	*Primary* PFS *Secondary* OS, ORR, and safety

Table 1: Summary of Key Characteristics of the Included studies *

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
Slovenia, South Korea, Spain, and the UK)	at least, one measurable lesion evaluable according RECIST version 1.0; ECOG PS ≤2; creatinine clearance of ≥30 mL/min; and life expectancy ≥3 months;	lower dosage (1000 mg/m^2) was allowed for patients considered at risk for toxicity. Treatments were given every 3 weeks until disease progression, unacceptable toxic effects, or withdrawal of consent.	
MAX[11] 43 centres in 3 countries (Austria, New Zealand, and the UK) Intestinal Trials Group	Patients aged 18 years or older with a diagnosis of colorectal adenocarcinoma, who had measurable or nonmeasurable unresectable metastatic disease with no prior chemotherapy, and considered suitable for capecitabine monotherapy. Eligible patients had to have at least, one measurable lesion; and be evaluable according RECIST v1.0; ECOG PS ≤2; adequate bone marrow, renal function, and hepatic function; Life expectancy ≥3 months (12 weeks);		

ECOG PS = Eastern Cooperative Oncology Group performance status, **ORR** = overall response rate, **OS** = Overall Survival, **PFS** = progression free survival, **RCT** = randomized controlled trial, **RECIST** = Response Evaluation Criteria in Solid Tumors
* See Table 4 for more details

The primary endpoint of both the AVEX and the MAX trials was progression-free survival (PFS), defined as the time from randomization to disease progression or death from any cause, whichever occurred first (Table 1). As shown in Table 2, patients in the BEV + CAP group had a longer median PFS than those in the CAP alone group for both the AVEX trial (9.1 months [95% CI: 7.3, 11.4] versus 5.1 months [4.2, 6.3], respectively) and the MAX trial (8.5 months [95% CI: 7.3, 9.2] versus 5.7 months [5.4, 6.2], respectively). The hazard ratio analysis indicates a 47% and 37% reduction in the risk of disease progression in the AVEX and the MAX studies, respectively among patients in the combination therapy group compared with those in the CAP alone group.

Secondary endpoints of interest to this review included overall survival (OS), health-related quality of life (HRQoL), and disease control (DC). No statistically significant difference was detected between treatment groups for OS in both studies. In the MAX study, for HRQoL, overall QoL was similar except for ratings for sore hands and feet (0.62, 95% CI: 0.19-1.05; p = 0.005), and sore mouth (0.26, 95% CI: 0.00-0.51, p = 0.05); which were worse for those in the BEV + CAP group. In the AVEX study, significantly more patients in the BEV + CAP group achieved disease control than those in the CAP alone group (74% versus 58%; p=0.01). Although the MAX study did not report a DC outcome, a higher proportion of patients in the BEV + CAP group than in CAP alone group attained the related outcome of overall response (OR) in the MAX study (38.3% versus 30.3%). The MAX study did not report on DC directly. It is noteworthy that the studies were not designed or powered to detect differences in these secondary outcomes.

Treatments were generally well tolerated in both studies, with similar treatment-related adverse events (TRAEs) of any grade across treatment groups. However, in the AVEX study, a higher proportion of patients in the BEV + CAP treatment group had their doses modified

because of toxic effects than did those in the CAP alone group (55 (41%) versus 36 (26%), respectively).[10] The MAX study did not report on this specific safety outcome.

A major limitation to the internal validity of the studies was that it was open-label and thus treatment allocation was not concealed to investigators or patients, leading to a high potential for observer biases. Furthermore, because comorbidity assessments were not done, it was not possible to evaluate the potential impact of comorbidities on reported outcomes, which is especially important in the elderly. In terms of external validity, the exclusion criteria, especially in the AVEX study, seemed too restrictive on medical conditions and medication history, which are commonly associated with elderly patients in real life; this raises uncertainty about the generalizability of the findings to a general population of elderly mCRC patients in actual clinical practice.

Table 2: Summary of Key Outcomes *

	AVEX,[10]		MAX,[11]	
	BEV + CAP (N=140)	CAP (N=140)	BEV + CAP (N=157)	CAP (N=156)
Overall survival, months				
Median (95% CI)	20.7 (17.0, 26.0)	16.8 (12.6, 20.1)	18.9 (NR)	18.9 (NR)
HR* (95% CI)	0.79 (0.57, 1.09)		0.88 (0.68, 1.13)	
p-value	0.18		0.31	
PFS, (months)				
Median (95% CI) in months	9.1 (7.3, 11.4)	5.1 (4.2, 6.3)	8.5 (7.3, 9.2)	5.7 (5.4, 6.2)
HR* (95% CI)	0.53 (0.41, 0.69		0.63 (0.5, 0.79)	
p-value	<0.0001		0.03	
Disease Control, n (%)	104 (74)	81 (58)	NR	NR
p-value	0.01		NR	
Overall response, n (%)	N=140	N=140	N=147	N=142
	27 (19)	14 (10)	56 (38.1)	43 (30.3)
p-value	0.04		0.16	

Harms of Interest	N= 134		N= 136		N= 157		N= 156	
	All grades	Grade 3-5	All grades	Grade 3-5	All grades	Grade 3-5	All grades	Grade 3-5
Bleeding, (%)	25	0	7	0.7	12	1.3	12	2.6
Hypertension, (%)	19	2.2	5	1.5	29	3.8	12	0.6
Thromboembolic disorders, (%)	16	11.9	7	5.1	14.5	12.1	10	7.1
Hand-foot syndrome, (%)	49	15.7	40	6.6	77	26	65	16
Diarrhea, (%)	40	6.7	35	6.6	65	17	62	11
Fatigue, (%)	24	3.7	27	0.7	78	9.6	74	9.6

BEV = bevacizumab, **CAP** = capecitabine, **CI** = confidence interval, **HR** = hazard ratio, **NR** = not reported
* See Tables 7 and 9 for more details

2.1.4 Comparison with Other Literature

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

2.1.5 Summary of Supplemental Questions

What is the efficacy and safety of bevacizumab (BEV) in combination with 5-fluorouracil (5-FU) for advanced or metastatic colorectal cancer (mCRC)?

This section summarized the studies assessing the efficacy and safety of bevacizumab in combination with 5-FU as first-line treatment of advanced or mCRC in patients who are not suitable for oxaliplatin or irinotecan-based therapy. In two phase II randomized-controlled trials,[12,13] BEV in combination with 5-FU and LV showed improvements of 3.7 months in PFS (5.5 months for 5-FU + LV + placebo and 9.2 months for 5-FU + LV + BEV, P = 0.0002), of 23% in RR (17% [95%CI: 7-34%] for 5-FU + LV alone and 40% [95%CI: 24-58%] for 5-FU + LV + BEV) and of 3.8 months in TTP (5.2 months [95%CI: 3.5-5.6 months] for 5-FU + LV alone and 9.0 months [95%CI: 5.8-10.9 months] for 5-FU + LV + BEV). No statistically significant results were observed for OS and duration of response.

Safety concerns associated with BEV included increased occurrences of bleeding, hypertension and thrombosis. Less clinically significant AEs, such as fever, headache, rash, epistaxis, proteinuria and chills, were also more commonly observed in patients who received BEV.

Overall, the use of 5-FU in combination with BEV yielded similar efficacy and safety results to BEV + capecitabine.

See section 7.1 for more information.

What is the validity of progression-free survival (PFS) as a surrogate outcome for mCRC?

The use of PFS shows advantages over OS. PFS is less influenced than OS for competing causes of death and PFS is not influenced by second-line treatments. This section evaluated the validity of using PFS as the primary outcome for mCRC and summarized two publications[14,15] provided by the submitter.

The systematic review reported by Tang et al.[15] was of good overall quality. The authors mentioned that PFS is a more sensitive endpoint than OS for treatment effect. Also with more events at the time of analysis, the use of PFS would result in higher statistical power. The lead time advantage over OS would accelerate the drug development process and save costs. In conclusion, the authors stated that the usage of PFS as a surrogate endpoint in RCTs in first-line chemotherapy for mCRC may be appropriate.

The systematic review conducted by Giessen and colleagues[14] had many reporting and methodologic limitations. The authors concluded that PFS would be justified as a surrogate endpoint in trials using cytotoxic chemotherapy regimen. However, when focusing the analysis on BEV-based therapies, correlation coefficients were lower, albeit with a very wide CI. As high heterogeneity was observed for results with that type of therapy, further research would be needed for validation of PFS as a surrogate endpoint for mCRC.

Overall, the conclusions of these analyses can apply to a general population with mCRC receiving first-line treatment. But more specifically for patients with BEV-based therapies, the utilization of PFS as surrogate outcome for OS appears uncertain.

See section 7.2 for more information.

2.1.6 Other Considerations

Patient Advocacy Group Input

One patient advocacy group, Colorectal Cancer Association of Canada (CCAC), provided input on bevacizumab (Avastin) in combination with capecitabine (Xeloda), for the first-line treatment of advanced or metastatic colorectal cancer (CRC) for patients who are not suitable for oxaliplatin or irinotecan-based therapy, and their input is summarized below.

From a patient perspective, metastatic colorectal cancer (mCRC) is a fatal disease for which there is no known cure other than tumour control or reduction coupled with surgery (in some cases). Respondents expressed their desire to continue accessing therapies to help control their mCRC with respect to quality of life, progression free survival and overall survival. While respondents reported having access to FOLFIRI, FOLFOX and the biologic therapies to help shrink their metastatic disease, respondents reported treatment-related adverse effects with their current therapies. Over 70% of respondents reported pain and neuropathy as being a commonly experienced side effect of their treatments. 50% of respondents reported diarrhea, vomiting, and nausea and 33% of respondents reported fatigue and shortness of breath. Of those respondents that had experienced with bevacizumab and capecitabine, it was reported that 50% of respondents found the therapy was able to shrink or control their colorectal cancer. Some of the therapy's common adverse events included: tiredness, neuropathy, foot pain, dry skin, and nose bleed. Respondents noted that all side effects were considered acceptable, except pain. Respondents also identified an unmet clinical need for the treatment of elderly patients living with mCRC. This is an important issue to patients, especially those patients aged 70 and older. Many mCRC patients aged 70 years and older are deemed unsuitable for irinotecan-based or oxaliplatin-based treatments due to the possibility of their severe toxic effects, especially in patients with comorbidities. According to CCAC, bevacizumab with capecitabine would provide an easier and less toxic regimen when compared to combination chemotherapeutic regimens such as FOLFOX and FOLFIRI.

PAG Input

Input was obtained from eight of the 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 metastatic colorectal cancer (mCRC):

Clinical factors:

- The addition of bevacizumab to capecitabine may have additional benefits for a subgroup of patients.
- Use beyond progression

Economic factors:

- Small subgroup of patients.
- High cost of bevacizumab.

2.2 Interpretation and Guidance

The question being posed by this submission is whether bevacizumab, already generally publicly funded in combination with multi-agent chemotherapy for the first line treatment of metastatic colorectal cancer (mCRC), provides clinical effectiveness and value when combined, for reasons of patient comorbidity, performance status, or preference, with only single-agent fluoropyrimidine chemotherapy.

Effectiveness

Bevacizumab has been shown in two well-conducted multicentre randomized controlled trials (AVEX and MAX) to increase progression free survival (PFS), their primary endpoint, by a median of approximately 3 – 4 months (statistically significant hazard ratios of 0.53 and 0.63), with non-significant trends towards improvement in the secondary, non-powered endpoint of overall survival (OS).

These results are quantitatively similar to what has been seen with the addition of bevacizumab to multi-agent chemotherapy. There have been several meta-analyses of bevacizumab in the first line setting, all with similar findings. For example, a meta-analysis by Cancer Care Ontario's Program in Evidence Based Care found the hazard ratio for OS to be 0.79 and for PFS to be 0.63, both in favour of bevacizumab and statistically significant.[16] In this particular situation, since PFS was associated with an improved OS in larger studies of patients receiving multiagent chemotherapy, it is likely that a similar change in PFS, as seen in smaller studies of patients also with mCRC and receiving first-line treatment with bevacizumab but combined with single agent chemotherapy, would be associated with a similar improvement in OS.

Safety

The addition of bevacizumab to single-agent fluoropyrimidine chemotherapy results in additional but modest toxicity. Patients receiving combined therapy had increased rates of hand-foot skin reaction, mucositis, diarrhea, fatigue, and hypertension. As expected, higher rates of thrombosis, minor bleeding, and proteinuria were observed with the addition of bevacizumab, similar to what is observed when it is added to multi-agent chemotherapy.[16]

Need and Burden of Illness

The alternative for patients not suitable for or preferring not to take multi-agent chemotherapy would be supportive care with or without single-agent fluoropyrimidine alone. Practice pattern studies from the U.S. suggest that approximately 5-10% of patients who receive first line chemotherapy receive single agent fluoropyrimidine treatment with bevacizumab.[17,18] A similar proportion of patients would be expected to be treated this way in Canada.

Combination of bevacizumab with other single-agent fluoropyrimidines

Capecitabine and 5-fluorouracil are considered to be essentially equivalent in terms of effectiveness and tolerability. This is relevant because capecitabine, though preferred because of convenience, is not always accessible to patients due to high out-of-pocket cost in many jurisdictions. Another scenario is patients who start on multi-agent chemotherapy with bevacizumab but then experience dose-limiting toxicity to one of the drugs, the most common example being persistent neuropathy with oxaliplatin. Funding rules in some jurisdictions require discontinuation of bevacizumab when one of the other drugs is stopped. Consequently, although not part of the initial submission, relevant clinical trials of combining bevacizumab with 5-fluorouracil were identified. A small randomized phase II study comparing 5-fluorouracil with or without bevacizumab at a biologically equivalent dose of 2.5 mg/kg/week demonstrated similar trends and magnitude of benefit in PFS and OS and response rates that favoured the bevacizumab-containing regimen, with a similar toxicity profile as well.[13] Extending this assessment to include intravenous 5-fluorouracil should be considered, especially to patients without insurance, of limited financial means, or who have experienced toxicity with other drugs.

Effect of age

Although the AVEX trial limited enrolment to patients 70 years of age and older, analyses of both trials (AVEX and MAX) indicate that efficacy and toxicity results are similar regardless of age.

Treatment with bevacizumab beyond progression

In the second-line setting, after progression, the addition of bevacizumab has been associated with a significant increase in overall survival (HR=0.81) in one randomized trial,[19] and in another powered only for PFS (HR=0.70).[20] It should be noted that these values are consistent with what has been observed in the first line setting in combination with both single- and multi-agent chemotherapy.

Patients not receiving multi-agent chemotherapy in the first line setting are probably less likely to receive it in second line, unless treatment resulted in an improvement in performance status that made such a consideration possible. In any event, the public funding rules around second-line treatment should not be different whether patients have received bevacizumab with single- or multi-agent chemotherapy in first line.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a modest net overall clinical benefit from the addition of bevacizumab to single-agent fluoropyrimidine chemotherapy (capecitabine or 5-fluorouracil).

In reaching this conclusion, the Clinical Guidance Panel considered:

- **Effectiveness:** The data reviewed, primarily from two high-quality randomized controlled trials of capecitabine with or without bevacizumab, but also trials adding bevacizumab to 5-fluorouracil and multi-agent chemotherapy in the first and second line setting, show a very consistent modest improvement in progression-free survival, which, in studies powered for it, generally translates into a modest improvement in overall survival.
- **Safety:** The adverse event profiles were modestly increased, similar to those seen in combination with multi-agent chemotherapy where they are generally considered acceptable and in most cases manageable.
- **Need and burden of disease:** Bevacizumab plus a single-agent fluoropyrimidine represents the preferred treatment option for the 5-10% of patients, of any age, who are not able or willing to take multi-agent chemotherapy (for which bevacizumab is generally publicly funded). Regarding issues of equity and accessibility, 5-fluorouracil is an important option for patients without coverage for oral capecitabine in much of the country. Importantly, the clinical outcomes and safety profile of bevacizumab in the treatment of metastatic colorectal cancer appears to be very similar regardless of the chemotherapy backbone. Although the CGP acknowledged that the AVEX and MAX studies included only patients with ECOG 0-2, the CGP concluded that consideration of the appropriateness of treatment with bevacizumab should be a decision between physicians and individual patients.

3 BACKGROUND CLINICAL INFORMATION

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

3.1 Description of the Condition

In 2014 the Canadian Cancer Society estimates that there were 24,400 new cases of colorectal cancer diagnosed, and 9,300 people died from the disease. Most of this latter group would have had spread of their cancer from the colon into vital organs, most commonly the liver or lungs. In a minority of patients with a few isolated sites of metastatic disease, surgery can sometimes be curative. Unfortunately, for the majority metastatic disease is incurable.

3.2 Accepted Clinical Practice

When colorectal cancer is at an incurable stage, the primary treatment is with systemic therapy. This is given with goals of extending survival and ameliorating or delaying symptoms, but it is with only palliative intent. With supportive care alone, the median survival is approximately 6–12 months. Recent studies involving treatment with multiple lines of chemotherapy routinely report median survivals of over 24 months.[21] The standard first line of therapy is fluoropyrimidine-based chemotherapy combined with bevacizumab.

Chemotherapy

Fluroropyrimidines available in Canada are intravenous 5-fluorouracil and its oral prodrug, capecitabine. Many studies in different clinical situations have shown capecitabine to be a more convenient substitute for intravenous fluorouracil that is equivalent in terms of efficacy and side-effect profile,[21-23] although the incidence of hand-foot syndrome is higher and doses need to be reduced in the setting of renal dysfunction.[24] Drug acquisition costs are higher for capecitabine but may be partially offset by the costs associated with central venous access and infusion needed for current fluorouracil schedules. These drugs can be combined with oxaliplatin and/or irinotecan to make 'combination chemotherapy.' Sequencing oxaliplatin and irinotecan in first- versus second-line regimens are considered to be equivalent approaches.[25,26]

As many clinical guidelines, such as the 2014 Cancer Care Ontario Guideline 2-5 (Strategies of Sequential Therapies in Unresectable, Metastatic Colorectal Cancer Treated with Palliative Intent), note, the decision to use fluoropyrimidine monotherapy as opposed to combination chemotherapy "should be made on a case-by-case basis based on considerations that include patient and tumour characteristics, toxicity of each strategy and patient preference."[27] Older patients and those with significant comorbidity or poor performance status may be more appropriately treated with fluoropyrimidine monotherapy.

Bevacizumab

As described in the Health Canada Fact Sheet on the drug, bevacizumab is a "monoclonal antibody (that)… attacks the blood vessels that surround the tumour.[28] In order to grow and spread, tumours need a constant supply of oxygen and other nutrients. Tumours get this supply by creating their own network of blood vessels. This process is called angiogenesis….(Bevacizumab) works by blocking angiogenesis" through binding to the vascular endothelial growth factor (VEGF) receptor. Reflecting standard practice, bevacizumab's approval by Health Canada is for use "in combination with

fluoropyrimidine-based chemotherapy … for first-line treatment of patients with metastatic carcinoma of the colon or rectum."

Chemotherapy + bevacizumab

Bevacizumab has been shown in multiple studies to increase overall survival when given with combination chemotherapy by approximately 1.5 months[16,24,29] to as many as 4.7 months.[30] A randomized phase II study of intravenous fluorouracil monotherapy with or without bevacizumab found that it improved progression-free survival, but the increase observed in median overall survival from 12.9 to 16.6 months did not reach statistical significance.[12]

3.3 Evidence-Based Considerations for a Funding Population

The relevant funding population for bevacizumab + capecitabine is patients undergoing first-line chemotherapy for metastatic colorectal cancer who are not suitable for, or decline, combination chemotherapy. As mentioned in Section 3.1, approximately 9,300 patients die from colorectal cancer in Canada each year and most of these would at some point have been eligible to consider palliative chemotherapy. Practice pattern studies from the U.S. suggest that approximately 5-10% of patients who receive first line chemotherapy receive single agent fluoropyrimidine treatment with bevacizumab.[17,18] There are no biomarkers or diagnostic tests to identify this subpopulation, but increased age and poor performance status are empirically observed to be important clinical predictors.[18]

Because angiogenesis inhibition can interfere with healing, bevacizumab should not be used in patients within 4 weeks of surgery or with conditions such as active bleeding or fistulae that require angiogenesis to heal. In terms of relative contraindications, bevacizumab may increase the risk of arterial and venous thrombosis, leading to myocardial infarction, stroke, or venous thrombosis and embolism.[16] Consequently, patients at increased risk for these conditions should weigh the risks versus benefits. It can also cause or exacerbate hypertension and proteinuria, although these can generally be managed medically.

3.4 Other Patient Populations in Whom the Drug May Be Used

Aside from the combination with fluoropyrimidine-based chemotherapy as described here, there are no other populations for whom bevacizumab should be used in the first line setting. Data do not support its use as a single agent. There is evidence that continuing bevacizumab into second line further improves survival.[19]

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Colorectal Cancer Association of Canada (CCAC), provided input on bevacizumab (Avastin) in combination with capecitabine (Xeloda), for the first-line treatment of advanced or metastatic colorectal cancer (mCRC) for patients who are not suitable for oxaliplatin or irinotecan-based therapy, and their input is summarized below.

CCAC conducted an online survey on February 10 – February 22, 2015 of colorectal cancer patients and caregivers in Canada and abroad to gather information about patient and caregiver experiences with the drug under review, and received 111 responses. Three respondents reported having experienced with bevacizumab and capecitabine in first line therapy. These patients were contacted through CCAC's database of registered colorectal cancer patients and their respective caregivers. The survey used free-form commentary and scoring options (ten point scale) and limited closed-ended questions (agree/disagree, yes/no, patient/caregiver). In addition, to better provide the patient and caregiver perspective, CCAC conducted interviews with patients and caregivers from the CCAC support groups as well as obtaining publications focusing on the therapy in question. Specifically, two patient respondents were interviewed for the purpose of this submission and have offered their input, herein referenced as Patient I and Patient II. CCAC also included a Quality of Life (QoL) survey of 1,001 Canadians aged 18 and over that was conducted in March 2011.

From a patient perspective, metastatic colorectal cancer (mCRC) is a fatal disease for which there is no known cure other than tumour control or reduction coupled with surgery (in some cases). Respondents expressed their desire to continue accessing therapies to help control their mCRC with respect to quality of life, progression free survival and overall survival. While respondents reported having access to FOLFIRI, FOLFOX and the biologic therapies to help shrink their metastatic disease, respondents reported treatment-related adverse effects with their current therapies. Over 70% of respondents reported pain and neuropathy as being a commonly experienced side effect of their treatments. 50% of respondents reported diarrhea, vomiting, and nausea and 33% of respondents reported fatigue and shortness of breath. Of those respondents that had experienced with bevacizumab and capecitabine, it was reported that 50% of respondents found the therapy was able to shrink or control their colorectal cancer. Some of the therapy's common adverse events included: tiredness, neuropathy, foot pain, dry skin, and nose bleed. Respondents noted that all side effects were considered acceptable, except pain. Respondents also identified an unmet clinical need for the treatment of elderly patients living with mCRC. This is an important issue to patients, especially those patients aged 70 and older. Many mCRC patients aged 70 years and older are deemed unsuitable for irinotecan-based or oxaliplatin-based treatments due to the possibility of their severe toxic effects, especially in patients with comorbidities. According to CCAC, bevacizumab with capecitabine would provide an easier and less toxic regimen when compared to combination chemotherapeutic regimens such as FOLFOX and FOLFIRI.

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 mCRC

CCAC indicated that depending upon the metastatic site impacted, symptoms of metastatic colorectal cancer (mCRC) include severe abdominal pain, vomiting, dizziness, shortness of breath, coughing, fatigue, loss of appetite and bloating. CCAC noted that the most frequently reported disease-related symptoms from the recent survey included but are not limited to: pain, bloody stools, fatigue, bowel obstructions, diarrhea/constipation, weight loss, and nausea.

According to CCAC, approximately 97% of respondents identified the following aspects colorectal cancer as being the most important and difficult to control were:

- Pain
- Fatigue
- Shortness of breath
- Weakness
- Mobility
- Nausea/vomiting/dizziness
- Loss of normal bowel function

Survey respondents stated the limitations resulting from those symptoms included but are not limited to the following:

- Work cessation
- Cessation of physical activity
- Investing too much time in management of disease
- Inability to socialize
- Sexual dysfunction
- Ostomy leakage

Respondents were also provided with an opportunity to list any physical or psychological limitations resulting from their colorectal cancer. CCAC reported that 34% of respondents reported mobility issues, difficulty being active and difficulty participating in daily activities, while 28% of respondents expressed their fear of a recurrence as occupying their every thought; and 23% of respondents reported fatigue and weakness. The balance of responses included the following:

- Pain and neuropathy
- Depression and anxiety
- Nausea and dizziness
- Hernia and ileostomy
- Change of eating habits
- Loss of normal bowel habits
- Sexual dysfunction

4.1.2 Patients' Experiences with Current Therapy for mCRC

According to CCAC, standard treatment for mCRC, which affects approximately 50% of the total colorectal cancer population, involves chemotherapy based on fluoropyrimidines, oxaliplatin, and irinotecan used in combination i.e. FOLFIRI and FOLFOX, used sequentially; and monoclonal antibodies (MAB) targeting vascular endothelial growth factor (VEGF) such as bevacizumab. In patients with KRAS wild type tumours, the therapies generally include monoclonal antibodies targeting epidermal growth factor receptor (EGFR) such as cetuximab and panitumumab.

CCAC stated that due to the presence of comorbidities and age-related decline in organ function, a high proportion of the elderly patient population (>70 years) is not eligible for these combination therapies. Because they are generally unsuitable for upfront oxaliplatin-based or irinotecan-based combination regimens, they would be considered an undertreated subset of the mCRC population.

According to the survey results, respondents did have access FOLFIRI, FOLFOX and the biologic therapies to help shrink their metastatic disease. 65.4% of respondents maintained these therapies were effective at controlling the following symptoms resulting from their colorectal cancer:

- Pain reduction
- No more symptoms
- Cancer remission
- Bowel obstruction resolved

Notwithstanding, respondents reported treatment-related adverse effects with their current therapies. Over 70% of respondents reported pain and neuropathy as being a commonly experienced side effect of their treatments. 50% of respondents reported diarrhea, vomiting, and nausea and 33% of respondents reported fatigue and shortness of breath.

83% of respondents surveyed maintained that some of those treatment-related adverse events were more difficult to tolerate than others. Over 90% of respondents reported pain, neuropathy, diarrhea, vomiting and nausea as the most difficult adverse effects to control. Furthermore, based on the dialogue with respondents from CCAC's support groups, respondents reported tingling or a feeling of pins and needles in their hands and feet with severe numbness and found it difficult to do small tasks with their hands like buttoning a shirt. In some cases, neuropathy can cause pain and difficulty with daily life, including walking or balancing. This has led to cessation of treatment which respondents have found quite stressful in their treatment journey. Diarrhea, nausea, and vomiting were the most frequently reported side effects of irinotecan which can cause severe dehydration and necessitate cessation of therapy as well.

When respondents were asked if they could choose a treatment based on each drug's known toxicity profile, 70% of respondents reported that it would be very important to do so.

CCAC found that disparities exist across Canada as they relate to access to treatments both to the therapy itself and in some cases, the line of treatment in which it is available. This is evidenced in the QoL Survey results which show regional disparities in the confidence levels of Canadians regarding access to therapies. Over 50% of respondents surveyed believe that geographical location impacts their quality of treatment when diagnosed with cancer.

Respondents reported that it would be very important to access additional treatments whose benefits might only be short term despite treatment adverse effects. A survey conducted by the CCAC in March 2011 indicated that respondents were interested in treatment even in end of life situations when the benefit was just a few weeks, provided, there was good QoL.

64% of respondents surveyed reported out of pocket expenses associated with the management of their disease. They cited travel related, parking costs, and loss of work as the most highly incurred expenditures when accessing their drug therapies.

When asked if patients would be willing to pay out of pocket to access new drug therapies for the treatment of their mCRC, 55.6% of respondents replied "Yes". Some of the open ended replies are reported below:

- Yes, because I would do anything to be cancer free
- Yes, if it meant a better chance of survival
- Yes, if I could afford it

When respondents were asked if some of their needs were not being met, the following open ended replies were noted:

- Treatments are ineffective
- More information on combining drug treatments with nutrition and natural therapies
- Better discussion on availability of clinical trials

Based on discussion with the CCAC support group, respondents identified an unmet clinical need for the treatment of elderly patients living with mCRC. This is an important issue to patients, especially those patients aged 70 and older, because the majority of patients diagnosed with mCRC are elderly. Many mCRC patients aged 70 years and older are deemed unsuitable for irinotecan-based or oxaliplatin-based treatments due to the possibility of their severe toxic effects, especially in patients with comorbidities. Despite the fact that this age group accounts for approximately half of the mCRC population, these patients continue to be undertreated. A suitable and effective treatment option is required for this subset of the mCRC population.

4.1.3 Impact of mCRC and Current Therapy on Caregivers

CCAC indicated that the impact of mCRC on caregivers and families is significant. Caregivers provide supportive care to the patient in managing adverse side effects, providing emotional support and assuming additional unpaid work duties in the home.

Additionally, caregivers of mCRC patients are fraught with financial challenges relating to disability and cost of accessing treatments in those provinces that have reimbursement restrictions. Travel and parking costs are also assumed by the caregiver when accessing drug therapies.

83% of respondents surveyed identified the following difficulties in caring for patients with colorectal cancer:

- Emotional impact (fear, guilt, not feeling able to cope)
- Taking care of the patient and family at the same time
- Balancing work life
- Lack of emotional support for caregivers
- Financial pressures
- Stress, anxiety

72% of respondents surveyed reported the following challenges in dealing with adverse effects from the current therapies:

- Not knowing how to support the patient
- Difficulty taking care of the family
- Not knowing how to cope, lack of help

In addition to the above, respondents reported that accessing drug therapies significantly impacts a caregiver's daily routine. This included:

- Taking time off work
- Time to accompany patient to treatments

- Emotional impact/stress
- Limited social activities
- Difficulties in balancing family care with patient care
- Difficulties related to travel

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Bevacizumab in combination with Capecitabine

Based on the information collected by CCAC, respondents expressed their desire to continue accessing therapies to help control their mCRC with respect to quality of life, progression free survival and overall survival. For patients who do not qualify for combination therapy, accessing an additional therapeutic option would allow for increased PFS and extended disease control (tumour shrinkage or disease stability) with anticipated side effects. Additionally, as an oral therapy in late stage disease, capecitabine would provide elderly patients with QoL and the ability to access treatment at home which are important factors.

71% of respondents expressed a desire to be afforded the opportunity to have choice in the selection of the best therapeutic option in the treatment of their mCRC.

According to CCAC, bevacizumab with capecitabine would provide an easier and less toxic regimen when compared to combination chemotherapeutic regimens such as FOLFOX and FOLFIRI. Elderly patients may not be optimal candidates for irinotecan or oxaliplatin-based chemotherapy because of the drugs' toxicity profiles which may prove harmful, especially in the presence of comorbidities. As such, the bevacizumab and capecitabine combination may be an effective and well tolerated therapeutic regimen in the previously untreated mCRC patients 70 years or older.

In addition, CCAC submit that oral capecitabine provides an easily administered chemotherapeutic option which is generally well tolerated by patients in the comfort of their homes (i.e. fewer hospital visits, travel costs). Moreover, CCAC indicated that bevacizumab is also a generally well tolerated therapy easily administered through intravenous injection (in less than 30 minutes) capable of enhancing efficacy when combined with oral capecitabine.

According to CCAC's survey, three respondents reported having experienced with bevacizumab and capecitabine in first line therapy. The therapy was funded:
- As a part of a clinical
- Through private insurance
- Through self-pay

Respondents reported the following positive and negative effects with their treatment:

Positive effects included:
- Shrunk tumours for 6 months
- Shrinking and stopped spreading

Negative effects included:
- New tumour on liver after 6 months
- Dry skin, nose bleeding

When asked about the respondent's personal experience with bevacizumab in combination with capecitabine, it was reported that 50% of respondents found the therapy was able to shrink/control their colorectal cancer. Some of the therapy's common adverse events reported by respondents included:

- Tired, neuropathy
- Foot pain
- Dry skin, nose bleeding

According to CCAC, all side effects were considered acceptable, except pain. One respondent qualified their statement with following quote: "*They (side effects) are all acceptable if they help shrink cancer*".

All respondents confirmed the therapy was easy to administer/receive. 83% (n= 5/6) of respondents reported their overall experience with bevacizumab and capecitabine was much better when compared to other drugs/therapies. 56% (n= 4/7) of respondents stated they were able to maintain a normal QoL while taking bevacizumab and capecitabine. With respect to a patient's long term health and well-being, respondents stated the therapy will be capable of "*keeping the cancer at bay*" and "*slowing (cancer) growth*".

CCAC also conducted extensive interviews with two mCRC patients from one of the CCAC support groups. Patient #1 is a 74 year old female who currently has no evidence of disease status from the mCRC diagnosis she received in August 2008 (metastatic disease to lungs). In her words, she was considered "*palliative*" and was "*sentenced to receive chemo for the next year or two until she succumbed to the disease*". Patient #1 reported that she was in excellent health, and found her prognosis to be unacceptable and sought to advocate for herself to access additional therapies which could ultimately render her a surgical candidate.

In her own words, patient #1 stated: "*I wanted to access Avastin with chemo which I had heard so much about at our support group meetings. I changed oncologists and with his help, I did. It shrank those tumours and I had the life-saving surgery I needed. Today, years later, I am still cancer free! I believe it was my age that was preventing the doctors from being more aggressive with me. That's just wrong. We need more therapies designed to address the needs of this population and if there's a therapy that can do that, the cancer experts owe it to everyone to make it available*!"

Patient #2 is a 70 year old male with metastasis to the liver, and is actively undergoing second line systemic therapy. Patient #2 exhausted first line bevacizumab + FOLFOX and was then required to proceed to FOLFIRI without bevacizumab because of funding restrictions for bevacizumab in second line. The patient believes this funding restriction as the first clinical challenge in the management of his mCRC. "*Access to Avastin should be readily available in both first and second line therapy so that my cancer is optimally managed*". Patient #2 also expressed concerns with FOLFIRI-induced toxicity necessitating a dose reduction and at times treatment cessation. Patient #2 was frequently hospitalized for irinotecan-induced diarrhea and vomiting which ultimately caused severe dehydration requiring hydration therapy over the course of several days. CCAC believed that bevacizumab and capecitabine would be an ideal therapy for patients such as Patient #2 who needs to avoid the toxic effects of either Irinotecan or Oxaliplatin-based chemotherapy.

In his own words, patient #2 stated: "*I have been so ill for so long because of the FOLFIRI. My oncologist had to reduce the Irinotecan and when that didn't work, he had to take me off of it altogether. I was then on just 5FU only to discover that the tumours in my liver grew. I requested they add the Avastin but it was denied. I believe the Avastin with the 5FU would make*

for a less toxic yet more effective combination! And if they can switch the 5FU to the pill that would be great!"

4.3 Additional Information

According to CCAC, patients and caregivers are in agreement that an additional line of therapy is required for the treatment-refractory mCRC population. Specifically, an additional therapeutic option is required for the first-line treatment of elderly patients (>70 years) with mCRC, particularly in those who are not candidates for oxaliplatin-based or irinotecan-based combination regimens. CCAC believes that elderly patients continue to be an undertreated population and, therefore, underserved. With a positive funding recommendation, the elderly population would greatly benefit from bevacizumab and capecitabine therapy in upfront therapy.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for bevacizumab in combination with capecitabine for metastatic colorectal cancer. The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.cadth.ca/pcodr).

Overall Summary

Input was obtained from eight of the 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 metastatic colorectal cancer (mCRC):

Clinical factors:

- The addition of bevacizumab to capecitabine may have additional benefits for a subgroup of patients.
- Use beyond progression

Economic factors:

- Small subgroup of patients.
- High cost of bevacizumab.

Please see below for more details.

5.1 Factors Related to Comparators

PAG noted that the current standard of care in the first-line treatment of mCRC is oxaliplatin or irinotecan based combination chemotherapy with bevacizumab. For patients who cannot receive oxaliplatin or irinotecan, capecitabine monotherapy is commonly used and the comparator in the AVEX trial is appropriate.

5.2 Factors Related to Patient Population

PAG identified that the number of the patients with mCRC who cannot receive irinotecan or oxaliplatin based chemotherapy is relatively small. The combination of bevacizumab and capecitabine provides a treatment option that may have added benefits for this group of patients over capecitabine alone.

PAG has concerns for use of bevacizumab beyond progression and is requesting clarity on timing of treatment discontinuation. PAG noted that the trial was conducted in elderly patients and is seeking guidance on the generalization of using capecitabine and bevacizumab in younger patients who cannot receive irinotecan or oxaliplatin based chemotherapy.

5.3 Factors Related to Dosing

PAG noted that dose and the treatment schedule for bevacizumab are the same as in other treatment combinations for mCRC. This is an enabler to implementation.

5.4 Factors Related to Implementation Costs

There is familiarity amongst health care providers with the preparation, administration and monitoring bevacizumab. This is an enabler to implementation.

The addition of bevacizumab to the current oral chemotherapy will increase preparation and administration times. Although the 30 minute infusion time for bevacizumab is fairly short, additional nursing, lab, physician and pharmacy are required to monitor for adverse effects (infusion reactions, blood pressure, proteinuria, etc.).

PAG noted that this is a small number of patients and anticipate a small incremental budget impact.

5.5 Factors Related to Health System

PAG noted that bevacizumab is already being used in the first line setting for mCRC and there is familiarity with the drug. These are enablers to implementation.

As bevacizumab is an add-on for this subgroup of patients with mCRC, PAG noted that an intravenous infusion may not be as acceptable or as accessible geographically as oral therapy for this subgroup of patients.

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 bevacizumab (BEV) and capecitabine (CAP) on patient outcomes compared to capecitabine alone, as first-line treatment of advanced or metastatic colorectal cancer (mCRC) in patients who are not suitable for oxaliplatin or irinotecan-based therapy. (See Table 1 in Section 6.2.1 for outcomes of interest).

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 Table 3. 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 and unpublished RCTs	Patients with mCRC who are not suitable for oxaliplatin or irinotecan-based therapy and who have not received prior chemotherapy **Subgroups:** • Patients who are ≥ 70 years old, • Patients who are < 70 years old,	BEV, 7.5 mg/kg IV given on day 1; plus CAP, 1000 mg/m^2 twice daily on days 1-14 on a 3 week cycle	CAP, 1000 mg/m^2 twice daily on days 1-14 on a 3 week cycle	**Efficacy** • **OS** • **PFS** • **HRQoL** • **TTP** • DCR • Post-PFS therapy [a] **Safety** • SAE • AE • WDAE AEs of interest to BEV o **Bleeding** o **Heart attack** o **Hypertension** o **Proteinuria** o **Thromboembolic disorders** AEs of interest to CAP o Asthenia o **Diarrhea** o **Fatigue** o **HFS** o **Nausea** o Mucositis/Stomatitis

AE = adverse event; **BEV** = bevacizumab; **CAP** = capecitabine; **DCR** = disease control rate; **HFS** = hand food syndrome; **HRQoL**= health-related quality of life; **mCRC** = metastatic colorectal cancer; **OS** = overall survival; **PFS** = progression-free survival; **RCT** = randomized controlled trial; **SAE** = serious adverse event; **TTP** = time to progression; **WDAE** = withdrawal due to adverse event

[a] Post-PFS therapy refers to subsequent treatment after disease progression.

** 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-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Avastin, bevacizumab, Xeloda, capecitabine and colorectal 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. The search was also limited to English language documents, but not limited by publication year. The search is considered up to date as of June 5, 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 – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

6.2.3 Study Selection

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

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

6.2.4 Quality Assessment

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

6.2.5 Data Analysis

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

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.

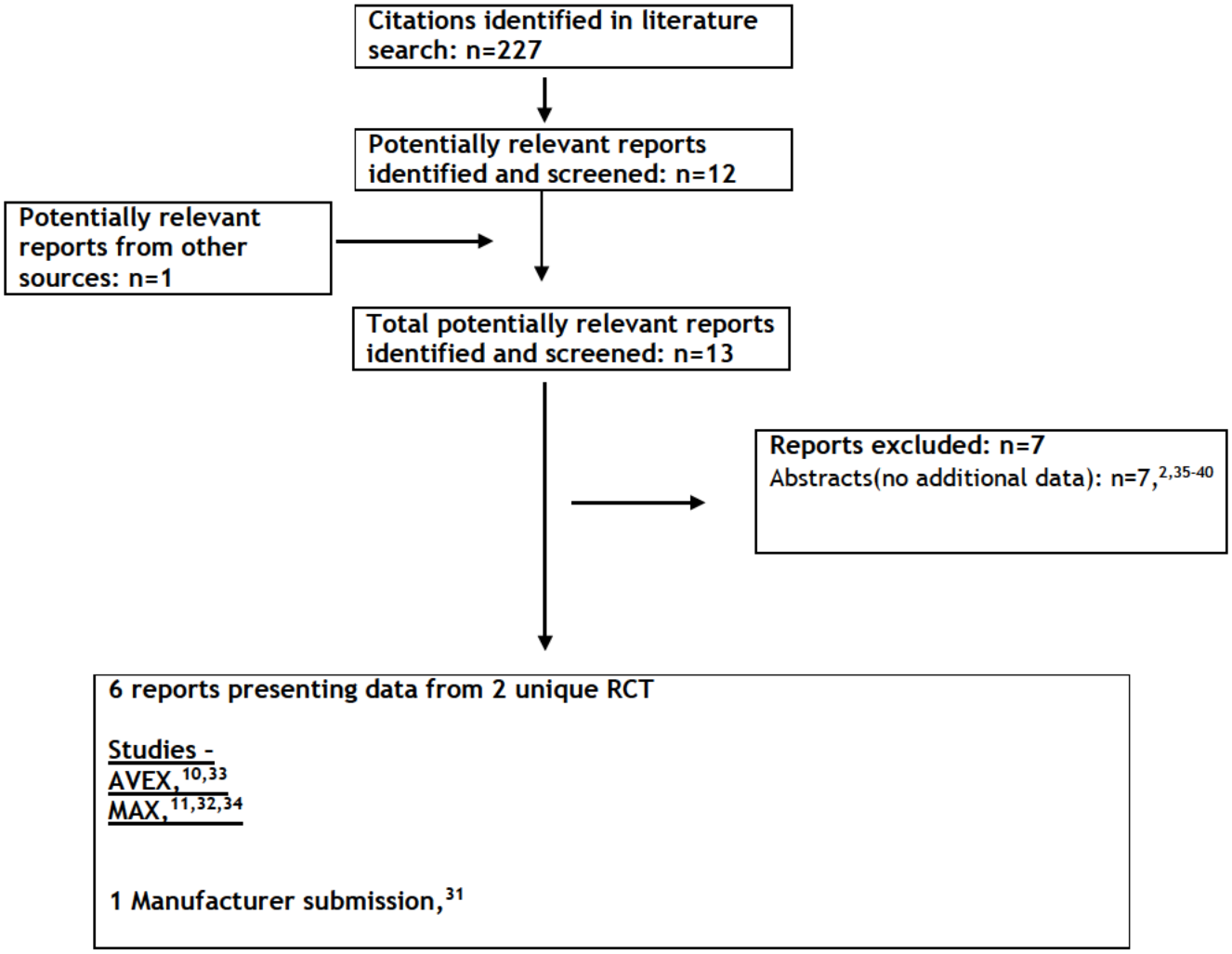
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided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

6.3 Results

6.3.1 Literature Search Results

Two hundred and twenty-seven citations were identified through literature search, of which 12 were considered potentially relevant. Together with the collective manufacturer submission for review, a total of 13 potentially relevant references were identified. Six reports, presenting data from 2 unique RCTs, were selected for inclusion in this pCODR systematic review.[10,11,31-34] Reports were excluded because they were abstracts which did not provide additional data.

QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

Two clinical trials, the AVEX[10] and the MAX[11] studies met the inclusion criteria for this systematic review. Both were multicenter, phase III, open-label randomized controlled trials which evaluated the comparative efficacy and safety of CAP alone and CAP in combination with BEV as first-line treatment in patients with metastatic colorectal cancer. In the MAX trial, there was a third treatment arm which comprised mitomycin in addition to the BEV + CAP combination. However, this systematic review focuses only on outcomes from the CAP alone and the BEV + CAP treatment groups. Table 4 presents a summary of the included studies.

6.3.2.1 Detailed Trial Characteristics

Table 4: Summary of Trial Characteristics of the Included studies

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
AVEX[10] 40 centres in 10 countries (Austria, Canada, Hungary, Italy, Mexico, Poland, Slovenia, South Korea, Spain, and the UK) Patient enrollment: July 9, 2007 to December 14, 2010. Data cut-off for efficacy analyses was on Jan 12, 2012 Data cut-off for safety analyses was on Mar 08, 2013 n=280 randomized, n=270 treated Phase III, open-label, RCT Sponsored by Hoffmann-La Roche	Patients aged 70 years or older with previously untreated, unresectable mCRC, who were not deemed to be candidates for oxaliplatin-based or irinotecan-based chemotherapy regimens. Eligible patients had to have • histologically or cytologically confirmed carcinoma of the colon, rectum, or both; with evidence of metastases; • diagnosis of colorectal cancer ≤6 before start of study treatment; • at least, one measurable lesion; and be evaluable according RECIST v1.0; • ECOG PS ≤2; • creatinine clearance of ≥30 mL/min; and • Life expectancy ≥3 months; Patients with a history of other cancers in the previous 5 years were excluded.	BEV, 7.5 mg/kg IV on day 1 with CAP 1000 mg/m² orally twice a day on days 1-14 versus CAP 1000 mg/m² orally twice a day on days 1-14. Treatments were given every 3 weeks until disease progression, unacceptable toxic effects, or withdrawal of consent.	<u>Primary</u> PFS <u>Secondary</u> OS, ORR, DCR, safety
MAX[11] 43 centres in 3 countries (Austria, New Zealand, and the UK) Patient enrollment: July, 2005 to June, 2007. Data cut-off for efficacy analyses was on Feb 27, 2009 Data cut-off for safety- NR n=471 randomized, n=468 treated Phase III, open-label, RCT Sponsored by the Australasian Gastro-Intestinal Trials Group	Patients aged 18 years or older with a histologic diagnosis of colorectal adenocarcinoma, who had measurable or nonmeasurable unresectable metastatic disease with no prior chemotherapy, and considered suitable for capecitabine monotherapy. Eligible patients had to have • diagnosis of colorectal cancer ≤6 before start of study treatment; • at least, one measurable lesion; and be evaluable according RECIST v1.0; • ECOG PS ≤2; • Adequate bone marrow, renal function, and hepatic function; • Life expectancy ≥3 months (12 weeks);	CAP, 1250 mg/m² orally twice a day on days 1-14 versus • BEV, 7.5 mg/kg IV on day 1 plus CAP 1250 mg/m² orally twice a day on days 1-14 ,or • *BEV, 7.5 mg/kg IV on day 1 plus CAP 1250 mg/m² orally twice a day on days 1-14 plus Mitomycin 7 mg/m² on day 1, BEV and CAP were administered every 3 weeks until disease progression, while mitomycin was given every 6 week for only 24 weeks to minimize the risk of HUS. Treatment was planned to continue until confirmed disease progression occurred. Patients considered at risk of toxicity could be nominated by investigators to start at a lower dosage (1000 mg/m² twice daily).	<u>Primary</u> PFS <u>Secondary</u> OS, toxicity, QOL

DCR = disease control rate, **ECOG PS** = Eastern Cooperative Oncology Group performance status, **HUS** = hemolytic uremic syndrome; **NR** = not reported, **ORR** = overall response rate, **OS**= Overall Survival, **PFS** = progression free survival, **QOL**= quality of life, **RCT**= randomized controlled trial, **RECIST**= Response Evaluation Criteria in Solid Tumors

* This review focuses on Comparison between CAP alone and CAP plus BEV only, without reporting outcomes for CAP + BEV + Mitomycin treatment.

a) Trials

Patients were randomized in a 1:1 ratio between the BEV + CAP group and CAP alone group in both the AVEX (N=280) and MAX (N=471) studies,[10,11] Major eligibility criteria for inclusion into the studies have been listed in Table 4. In addition, patients who had previously received adjuvant chemotherapy were eligible for both studies if the therapy had been completed 6 months or longer before the start of study treatment.[10] Patients were excluded if they had previous chemotherapy for mCRC or adjuvant anti-VEGF treatment. Other exclusion criteria included clinically significant cardiovascular disease, hypertension, a history of thromboembolic events within previous 6 months; a history of proteinuria; and clinical evidence of brain metastases or a history of CNS disease. Furthermore, patients who used aspirin regularly (at >325 mg per day), or those with a present or recent (within 10 days) medication history involving daily use of aspirin, other NSAIDs, or full-dose therapeutic anticoagulants on thrombolytic drugs were also excluded.[10]

The AVEX study was designed to have 80% power to detect a 31% reduction in the risk of disease progression (HR of 0.69) with a two-sided α of 0.05, and 232 PFS events, while the MAX study had at least 80% power to detect a 33% relative reduction in risk. Thus, at their sample sizes, the AVEX and MAX studies were sufficiently powered to detect improvement of at least 2 months and 2.5 months in median PFS, respectively, between the treatment groups.

The participants in the studies were randomized on to the treatment groups without masking of the allocated treatment. Randomization was stratified by ECOG performance status (0 or 1 versus 2) and geographical region in the AVEX study; and by age (<65 years versus ≥65 years), ECOG performance status (0 or 1 versus 2), the dose of CAP (1000mg versus 1250 g/m^2 twice daily), and institution in the MAX study.

b) Populations

Distribution of patient between the treatment groups was balanced across the BEV + CAP group (n=140 and n =157) and the CAP alone group (n=140 and n =156), respectively, for the AVEX and MAX studies. Demographic and disease characteristics of patients were generally similar across treatment groups at baseline (Table 5). While the AVEX study was selective for elderly patients (median age 76 years; range: 70- 87), the MAX study was open to adults of ≥18 years, although the median age was 68 years (range: 32-86).[11]

The majority (60 to 65%) of patients were male in both studies, with the AVEX study reporting a predominantly (85%) white population. The MAX study did not report the race distribution of its study population. The ECOG performance status of most of the patients was 0 or 1 for both studies. In the AVEX study, most patients were on concomitant drugs for comorbidities. No detail of patients' comorbidities was provided in the MAX study. For the AVEX study, the proportion of patients in the BEV + CAP group who had previous adjuvant therapy or who had undergone surgical resection of the primary tumour was ≥10% than those in the CAP group who had received these interventions (32% versus 19% or 74% versus 64%, respectively). Although in the MAX study, more patients in the BEV + CAP group than in the CAP group had previous adjuvant chemotherapy or surgical resection, the differences between the groups were smaller in magnitude compared to those reported in the AVEX study (see Table 5).

Table 5: Summary of Patient's Baseline Characteristics (ITT)				
	AVEX,[10]		MAX,[11]	
Characteristics	BEV + CAP (N= 140)	CAP (N= 140)	BEV + CAP (N= 157)	CAP (N= 156)
Age in years, n (range)	76 (70-87)	77 (70-87)	67 (32-85)	69 (37-86)
Male, n (%)	84 (60)	84 (60)	102 (65)	98 (63)
Race, n (%):				
White	118 (84)	119 (85)	NR	NR
Other	22 (16)	21 (15)	NR	NR
ECOG PS, n (%):				
0	70 (50)	60 (43)	91 (58)	90 (58)
1	58 (41)	67 (48)	54 (34)	59 (38)
2	10 (7)	11 (8)	12 (8)	7 (4)
3	0	1 (1)	0	0
Missing data	2 (1)	1 (1)	0	0
Location of Primary Tumour, n (%)				
Colon	81 (58)	76 (54)	100 (64)	93 (60)
Rectum	44 (31)	35 (25)	29 (18)	41 (26)
Colon and Rectum	15 (11)	27 (19)	NR	NR
Other	0	0	27 (17)	19 (12)
Unknown	0	1 (1)	1 (<1)	3 (2)
Missing Data	0	1 (1)	0	0
Site of metastatic disease, n (%)				
Liver	88 (63)	95 (68)	117 (75)	112 (72)
Lung	50 (36)	57 (41)	62 (39)	61 (39)
Other	49 (35)	32 (23)	125 (80)	127 (81)
Liver only	52 (37)	54 (39)	NR	NR
Time (months) since diagnosis of primary disease, Median (range)	4.0 (1.7-21.5)	2.5 (1.3-21.3)	NR	NR
Time (months) since diagnosis of metastatic disease, Median (range)	1.4 (0.7-2.6)	1.4 (0.7-2.1)	NR	NR
Previous adjuvant treatment, n (%)	45 (32)	26 (19)	68 (43)	53 (34)
Surgical resection, n (%)	103 (74)	89 (64)	127 (81)	124 (79)
History of medical condition, n (%)				
Arterial hypertension	79 (56)	68 (49)	NR	NR
Myocardial infarction	9 (6)	8 (6)	NR	NR
Thromboembolic events	10 (7)	2 (1)	NR	NR
Neurological disorders	8 (6)	8 (6)	NR	NR
Chronic gastrointestinal inflammation	4 (3)	8 (6)	NR	NR
Stroke	5 (4)	1 (1)	NR	NR
Use of any concomitant drugs*, n (%)	129 (92)	127 (91)	NR	NR

BEV = bevacizumab; **CAP** = capecitabine; **ECOG PS** = Eastern Cooperative Oncology Group performance status, **NR =** not reported

Table 5: Summary of Patient's Baseline Characteristics (ITT)				
	AVEX,[10]		MAX,[11]	
Characteristics	BEV + CAP (N= 140)	CAP (N= 140)	BEV + CAP (N= 157)	CAP (N= 156)
*Concomitant drugs included proton-pump inhibitors, calcium-channel blockers, angiotensin-converting-enzyme inhibitors, ß-adrenoceptor antagonists, statins, corticosteroids, anticoagulants, and antihypertensive drugs.				

c) Interventions

Randomized patients in both the AVEX and MAX studies[10,11] received BEV administered intravenously (IV) at 7.5 mg/kg on day 1 of a 3-weekly cycle with or without CAP (depending on treatment allocation) administered orally twice daily on days 1-14. The dose of CAP was 1000 mg/m^2 and 1250 mg/m^2 in the AVEX and MAX studies, respectively, although investigators in the MAX study could choose to use a 1000 mg/m^2 starting dose for patients they considered at risk of toxicity. It was reported that the AVEX study allowed pre-specified dose modifications of CAP, but not of BEV, after the occurrence and resolution of predefined grade 3-4 haematological or grade 2-4 non-haematological toxic effects.[10] In addition, continuation of treatment with only one of the combination drugs (BEV + CAP) was permissible if toxic effects due to the other required temporary or definitive interruption of its use.

Ten patients in the AVEX study (n=6, BEV + CAP; n=4, CAP alone) and three patients in the MAX study (n=1, BEV + CAP; n=2, CAP alone) did not receive their allocated treatment. Most of the patients in the two treatment groups of the AVEX study used concomitant drugs (see Table 5). The MAX study did not report any details of patients' use of concomitant medication, although it is very likely that patients of the reported median age (68 years) would be using other medications beside the study drugs.[11] Treatments were pre-specified to continue until disease progression, or intolerable toxic effects, or withdrawal of consent.

d) Outcome Measures

Efficacy Outcomes

Efficacy outcomes of interest for this review include overall survival (OS), defined as the time from random assignment to death from any cause, and progression-free survival (PFS), defined as the time from randomization to disease progression or death from any cause, whichever occurred first.[10] The primary endpoint of both the AVEX and MAX studies was PFS which was assessed radiologically or clinically using the Response Evaluation Criteria in Solid Tumors (RECIST) instrument. Other outcomes included: patients' health related quality of life (HRQoL), time to disease progression (TTP) and disease control rate (DCR). Although DCR was not specifically defined in the articles included in this review, it is commonly defined as the proportion of patients with advanced or metastatic cancer who have achieved complete response, partial response and stable disease to a therapeutic intervention in clinical trials of anticancer agents.[17-19]

Tumour assessment of disease response was conducted every 9 weeks for the first 27 weeks of the AVEX study, and every 12 weeks thereafter until progressive disease.[10] However, unscheduled assessment was performed if progressive disease was suspected before the next scheduled assessment.[10] Details of tumour assessment schedules were not provided for the MAX study.[11] All efficacy analyses were based on the intention-to-treat population (ITT) defined as all patients randomly assigned, irrespective of whether any dose of study treatment was given.[10]

The AVEX study did not report assessing patients' health-related quality of health (HRQoL). In the MAX study, quality of life was assessed using Euroqol-5D, Utility Based Quality of

Life Questionnaire-Cancer, and the Chemotherapy Acceptance Questionnaire. Patients completed the questionnaire at baseline and every 3 weeks till week 12, and thereafter, 6-weekly until progression. The differences between treatment groups, with 95% confidence interval (CI) and p-values were calculated using generalized estimation equation regression models which accounted for baseline values, repeat measurements, and treatment duration.

Safety outcomes

Patients were monitored for adverse events (AEs) at baseline and before the start of each treatment cycle according to the National Cancer Institute Common Terminology Criteria for Adverse Events.[10,11] Analyses of safety outcomes were based on patients who received at least one dose of study treatment, and compared the proportions of patients who reported AEs according to severity.

In the AVEX study, safety data were reported as the numbers and proportions of patients in each treatment group who experienced any treatment-related adverse event (TRAE), any treatment-related serious AE (TRSAE), any AE of grade ≥3, and any AE leading to withdrawal/discontinuation of treatment (WDAE).[10] Furthermore, the AVEX study reported any AEs leading to dose interruption or dose modification or death, as well as all AEs of special interest to bevacizumab or capecitabine. In addition to the overall safety/toxicity assessments, patients were assessed for specific AEs (AEs of interest) known to be associated with treatment with BEV or chemotherapy with CAP.

The MAX study did not report overall TRAEs, TRSAEs, or WDAEs for the study as a whole or its individual treatment groups.[11] However, as was done in the AVEX study, graded toxicity data for selected AEs associated with the use of BEV as well as CAP were reported.[11]

e) Exposure

The median number of treatment cycles (IQR) in the AVEX study was 9 (4 to 15) for the BEV + CAP group and 6 (3 to 10) for the CAP alone group. The MAX study reported the median number of treatment cycles (range) as 10 (1 to 46) and 8 (1 to 57) for the BEV + CAP and the CAP alone groups, respectively, which is slightly higher than in the AVEX study. The BEV + CAP group in the AVEX study had a median overall duration of exposure to treatment of 5.8 months, with interquartile range (IQR) of 2.6 to 11.1 months, compared with 4.2 months (1.9 to 7.2) in the CAP alone group.[10] Although the actual overall duration of exposure was not reported for the MAX study, it might be estimated from the median number of treatment cycles to be around 7.5 and 6 months for the BEV + CAP and the CAP alone groups, respectively, based on the specified 3-week cycle. In the AVEX study, dose interruption or modifications were made for 74 (55%) of 134 patients in the combination group and 59 (43%) of 136 patients in the CAP alone group.[10] The MAX study did not report any data for dose interruptions or modifications.

f) Patient Disposition

Discontinuation rates were reported in the AVEX study but not the MAX study. The overall proportion of patients who discontinued treatment was similar across the BEV + CAP and the CAP alone treatment groups. However, discontinuation due to disease progression was more than 10% higher among patients in the CAP alone group than among those who received the combination therapy (Table 6). A higher proportion of patients in the BEV + CAP group than in than CAP alone group discontinued treatment due to adverse event.

Table 6: Patient Population and Disposition				
	AVEX,[10]		MAX,[11]	
	BEV + CAP, n (%)	CAP, n (%)	BEV + CAP, n (%)	CAP, n (%)
Randomized	140 (100)	140 (100)	157 (100)	156 (100)
Received treatment	134 (95.7)	136 (97.1)	156 (99.4)	154 (98.7)
Efficacy analysis	140 (100)	140 (100)	157 (100)	156 (100)
Safety analysis	134 (95.7)	136 (97.1)	157 (100)	156 (100)
Discontinued	131 (93.6)	133 (95)	NR	NR
• Disease progression	68 (48.6)	88 (62.9)	NR	NR
• AE	23 (16.4)	13 (9.3)	NR	NR
• Withdrawal of consent	18 (12.9)	9 (6.4)	NR	NR
• Death	8 (5.7)	12(8.6)	NR	NR
• Protocol violation	3 (2.1)	3 (2.1)	NR	NR
• Other	11 (7.9)	8 (5.7)	NR	NR
• Lost to follow-up	0	2 (1.4)	NR	NR
AE = adverse event, **BEV** = bevacizumab, **CAP** =capecitabine, **NR** = not reported				

g) Limitations/Sources of Bias

- A major limitation to the internal validity of the studies was that they were open-label trials. The allocated study treatment was not blinded from the patients or the investigators. Although the primary endpoint, PFS, is an objective measure which would normally not be susceptible to unblinded conditions, the protocol provision which permits unscheduled assessment of progressive disease carries the potential for unbalanced assessment frequencies between treatment arms. Therefore, in the absence of analysis to evaluate the sensitivity of outcomes to unscheduled assessment of disease progression, the potential for observer bias owing to the open-label design of the study cannot be ruled out.
- The proportion of patients in the BEV + CAP group who had undergone surgical resection of the primary tumour, or received previous adjuvant treatment (with or without radiotherapy) was higher than in the CAP alone group, in both studies, especially in the AVEX study. It is unknown how these previous interventions contributed to the differences in outcomes between the treatment groups.
- The exclusion criteria was too restrictive and may have denied entry into the study to many participants on the basis of medical conditions and medication history commonly associated with the target population in real life. Thus the generalizability of the findings to a general population of elderly mCRC patients in actual clinical practice is unclear.
- Comorbidity assessments were not done as part of the trials. Therefore, the distribution of patients with comorbid conditions across treatment groups is unknown and the potential impact of comorbidities on the reported outcomes is uncertain.
- According to their product monographs,[1,9] the recommended doses of BEV and CAP are 5 mg/kg once every 14 days, and 1250 mg/m^2 twice daily, respectively; with no need for adjustment of the starting dose for geriatric patients for either drug. Both trials used a higher dose of BEV (7.5 mg/kg) with the AVEX study mandating a lower starting dose of CAP (1000 mg/m^2 twice daily doses) while the MAX trial permitted the use of this lower dose at investigators discretion. Therefore it is unknown whether at optimal doses BEV + CAP would retain the trial-reported comparative efficacy advantages relative to CAP alone, while still maintaining a tolerable safety profile. However, higher doses of BEV have

been recommended by its product monograph for other cancers,[1] and according to the investigators, CAP at 1000 mg/m² twice daily doses has been found to be effective and safe for elderly patients.[10]

- In the AVEX trial, it was permissible to continue treatment with one drug in the combination group (BEV + CAP) if toxic effects required temporary or definitive interruption of the second study drug. While this seems to have the potential to reduce the efficacy advantage of the group, a sensitivity analysis to confirm this would be informative, especially, if it also considered the safety outcomes among patients who had to use one instead of the two drugs at any time and compared it to those who used the two products through the entire study.
- Tumor assessment data for PFS were reported missing for a significant proportion of the study population (51 [18%]) in the AVEX.[10] While there seems to be a balance of missing data across treatment groups, the impact of the magnitude on the reported outcome is uncertain.
- The statistical analysis of both studies was silent on handling of missing data, which is a common significant source of bias in trials. However, data reported as missing applied to a small number of the study population and the distribution across the study arms was fairly balanced. Thus it is unlikely that missing data would have resulted in significant biases in these studies.
- The AVEX study was funded by the manufacturer whose employee/stock-holders were also involved in the study design as well as the collection, analysis, and interpretation of data. In addition, the manufacturer provided third-party writing support for the report. Thus the benefit of independent objective investigators is uncertain, and it is unknown to what extent the apparent conflict of interest influenced the findings and reportage of the study.

6.3.2.3 Detailed Outcome Data and Summary of Outcomes

a) Efficacy Outcomes

At the cut-off date for efficacy analysis in the AVEX study,[10] the median follow-up period for the BEV + CAP group was 24.8 month with IQR of 15.1 to 37.7 months, and 21.6 (12.8-31.9) for the CAP group. For the MAX study, the overall median follow up was reported as 30.8 month for data used for the main analysis.[11]

Overall Survival

The median OS in the AVEX study was 20.7 months (95% CI: 17.0, 26.0) in the BEV + CAP group and 16.8 months (95% CI: 12.6, 20.1) in the CAP alone group, this was not statistically significant (HR, 0.79; 95% CI: 0.57, 1.09; p=0.18). However, as shown by OS rates in Table 7, a numerically greater proportion of patient in the combination treatment group than in the CAP alone group survived at both years 1 and 2 in the AVEX study. In the MAX study, both the BEV + CAP and CAP groups had median OS of 18.9 months. Overall survival rates were not reported in the MAX study. It should be noted that the studies were not designed or powered to detect differences in overall survival.[10,11]

Progression free survival (PFS)

The median PFS was longer for patients in the BEV + CAP group than in the CAP alone group for both the AVEX and MAX studies (Table 7). In the AVEX study, the median PFS was 9.1 months for the BEV + CAP group and 5.1 months for the CAP group, this was statistically significant with a difference of 4 months (HR, 0.53; 95% CI: 0.41, 0.69; p<0.0001). In the MAX study, the median PFS was 8.5 months for the BEV + CAP group and 5.7 months for the CAP group, this was statistically significant with a difference of 2.8 months (HR, 0.63; 95% CI: 0.50, 0.79; p=0.03). Median PFS for BEV + CAP and CAP groups were similar in the AVEX and

MAX studies. Data from the AVEX study also shows that a higher proportion of patients in the BEV + CAP group had PFS at months 6, 12, and 18 than those in the CAP alone group (Table 7).

Table 7: Summary of Key Efficacy Outcomes				
	AVEX,[10]		MAX,[11]	
	BEV + CAP (N=140)	CAP (N=140)	BEV + CAP (N=157)	CAP (N=156)
Overall survival, months				
Median (95% CI)	20.7 (17.0, 26.0)	16.8 (12.6, 20.1)	18.9 (NR)	18.9 (NR)
HR* (95% CI)	0.79 (0.57, 1.09)		0.88 (0.68, 1.13)	
p-value	0.18		0.31	
Overall Survival rates, % (95% CI)				
Year 1	73.6 (64.8, 80.6)	60.0 (50.5, 68.2)	NR	NR
Year 2	44.3 (34.3, 53.8)	35.1 (25.4, 45.0)	NR	NR
PFS, (months)				
Median (95% CI) in months	9.1 (7.3, 11.4)	5.1 (4.2, 6.3)	8.5 (7.3, 9.2)	5.7 (5.4, 6.2)
HR* (95% CI)	0.53 (0.41, 0.69)		0.63 (0.5, 0.79)	
p-value	<0.0001		0.03	
PFS rates, % (95% CI)				
6 months	66.7 (57.7, 74.2)	44.2 (35.5, 52.5)	NR	NR
12 months	34.8 (26.6, 43.2)	10.3 (5.8, 16.3)	NR	NR
18 months	16.2 (10.1, 23.6)	3.6 (1.2, 8.1)	NR	NR
Disease Control, n (%)	104 (74)	81 (58)	NR	NR
p-value	0.01		NR	
Duration of response, median (95% CI)	9.0 (8.3, 10.0)	9.4 (6.2, 12.6)	NR	NR
Overall response, n (%)	N=140	N=140	N=147	N=142
	27 (19)	14 (10)	56 (38.1)	43 (30.3)
p-value	0.04		0.16	
-Complete response	3 (2)	2 (1)	3 (2)	1 (<1)
-Partial response	24 (17)	12 (9)	53 (36.1)	42 (29.6)
-Stable disease	77 (55)	67 (48)	80 (54.4)	70 (49.3)
-Progressive disease	14(10)	30 (21)	4 (2.7)	24 (16.9)
Post-PFS Therapy, n (%)				
-Any Additional treatment	52 (37.1)	52 (37.1)	NR (62)	NR (68)
-Antimetabolites	43 (30.7)	39 (27.9)	NR	NR
-FOLFIRI	8 (5.7)	4 (2.9)	NR	NR
-FOLFOX	3 (2.1)	1 (0.7)	NR	NR
-XELIRI	1 (0.7)	0	NR	NR
-Active chemotherapy [a]	NA	NA	NR (17)	NR (22)

BEV = bevacizumab, CAP = capecitabine, CI = confidence interval, FOLFIRI = fluorouracil/folinic acid/irinotecan, FOLFOX = fluorouracil/folinic acid/oxaliplatin, HR = hazard ratio, NR = not reported, XELIRI = capecitabine/irinotecan

[a] Active chemotherapy refers to treatment involving oxaliplatin, irinotecan and a fluoropyrimidine in combination or as monotherapy without specifying how they were combined, if they were.

Subgroup analysis of efficacy outcomes

The AVEX study included only patients who were ≥70 years. Therefore, it had no data to support subgroup analysis of younger patients as defined in the review protocol. However, a forest plot of a subgroup analysis of PFS in the MAX study showed that patients who were <65 years had improved PFS benefits with BEV + CAP than those who were older, although the difference between the two groups was not statistically significant.[11] In other subgroup analyses comparing patients who were <75 years to those who were ≥75 years in both the AVEX and MAX studies showed that the addition of BEV to CAP improved PFS benefits significantly in both groups, with similar benefits to those who are ≥75 years, as well those <75 years (Table 8).[10,32] In the MAX study, an interaction test for OS, response rate, and PFS revealed no statistically significant effect on age.[32]

Table 8: Subgroup Analysis of Efficacy Outcomes						
The AVEX study,[10,33]						
	70-74 years		**75-80 years**		**≥80 years**	
	BEV + CAP, N=55	**CAP, N=46**	**BEV + CAP, N=57**	**CAP, N=66**	**BEV + CAP, N=28**	**CAP, N=28**
OS, Months (95% CI)	20.7 (13.7, 26.1)	22.2 (9.7, 42.7)	19.8 (13.8, 27.3)	17.4 (11.9, 23.0)	19.7 (7.5, 26.9)	12.6 (6.6, 17.0)
OS HR (95% CI)	0.91 (0.50, 1.66)		0.79 (0.48, 1.30)		0.62 (0.31, 1.24)	
Log-rank P-value	0.55		0.37		0.24	
PFS, Months (95% CI)	7.6 (6.0, 11.80	5.0 (4.0, 6.5)	9.8 (7.1, 11.4)	5.1 94.1, 7.4)	10.5 (5.0, 14.5)	5.1 (2.2, 7.1)
PFS, HR (95% CI)	0.52 (0.32, 0.83)		0.60 (0.40, 0.89		0.36 (0.19, 0.71)	
Log-rank P-value	<0.001		0.016		0.003	
ORR (%)	25.5	10.9	15.8	12.1	14.3	3.6
Fisher's exact p-value	0.076		0.607		0.352	
The MAX study,[11,32,38]						
	<75 years			**≥75 years**		
	BEV + CAP, N=125	**CAP, N=119**		**BEV + CAP, N=32**	**CAP, N=37**	
OS, Months	20.4	20.0		15.7	13.4	
HR (95% CI)	0.90 (0.67, 1.20)			0.80 (0.47, 1.36)		
P-value	0.47			0.41		
PFS, Months	8.5	5.8		8.8	5.6	
PFS, HR (95% CI)	0.65 (0.50, 8.84)			0.52 (0.32, 0.86)		
P-value	0.001			0.01		

BEV = bevacizumab, **CAP** = capecitabine, **CI** = confidence interval, **HR** = hazard ratio, **ORR** = overall response rate, **OS** = overall survival, **PFS** = progression-free survival

Health related quality of life (HRQoL)

Patients' quality of life (QoL) outcomes were reported in the MAX study,[11] but not in the AVEX study.[10] Majority of patients (87%) in the MAX study completed QOL assessments questionnaire. Between group differences were calculated with estimating equation regression models as 0.62 (95% CI: 0.19, 1.05; p = 0.005) for sore hands and feet, and 0.26 (95% CI 0.00, 0.51, p = 0.05) for sore mouth. In each case of difference, patients in the BEV + CAP group reported worse outcomes than those in the CAP alone group.[34] No other significant differences between the two treatment groups were observed in other symptoms, functions, overall QoL, or acceptability of chemotherapy.[34]

Disease control rate (DCR)

As shown in Table 7, the AVEX study reported significantly more patients in the BEV + CAP group that achieved disease control than those in the CAP group (74% versus 58%; p=0.01). However, the median duration of response was similar between the treatment groups (BEV + CAP: 9.0 months [95 CI: 8.3, 10.0] versus CAP alone: 9.4 months [95% CI: 6.2, 12.6]). Disease control and duration of response were not endpoints reported in the MAX study. However, a higher proportion of patients in the BEV + CAP group than in CAP alone group attained the related outcome of overall response (OR) in both the AVEX and MAX studies. Although the OR rates were higher in each treatment group in the MAX study than in the AVEX study, the difference between treatment groups reached the level of statistical significance (p=0.04) in only the AVEX study.

Post-PFS therapy

As shown in Table 7, equal proportions of patients (37.1 %) in the two treatment arms of the AVEX study used at least one subsequent treatment after disease progression. There was a trend of a slightly higher percentage of patients in the BEV + CAP arm than the CAP alone arm when individual chemotherapy regimens were considered, however the clinical significance of this observation is unclear. The proportion of patients who received subsequent therapy in MAX study was fairly balanced across treatment groups, although a slightly higher percentage of patients in the CAP group than in the BEV + CAP group used subsequent treatment (see Table 7), which is inconsistent with what was observed in the AVEX study. Details of treatment regimen were not provided in the MAX study.

b) Harms Outcomes

Safety analyses in the AVEX study was based on patients who had received at least one dose of treatment and excluded randomized patients who did not receive their allocated treatment (n=10).[10] The median duration of follow-up by the final safety analyses cut-off date was 34.4 months (IQR: 23.9-48.5) for the BEV + CAP group and 29.2 months (IQR: 25.5-42.4) for the CAP group.[10] The MAX study reported interim treatment-related toxicity after 60 and 150 patients had received at least two cycles of study treatment.[11] Therefore, a direct comparison of safety outcomes reported by the two studies may be inappropriate at this time. Adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0[10,11]. Both the AVEX and MAX studies reported on selected AEs of interest detailing overall as well as grade ≥3 AEs (Table 9).

Table 9: Selected AEs of special interest occurring in ≥ 5% of patients

Event category	AVEX,[10]				MAX,[11]			
	BEV + CAP (N = 134) (%)		CAP (N = 136) (%)		BEV + CAP (N = 157) (%)		CAP (N = 156) (%)	
	All grades	Grade 3-5	All grades	Grade 3-5	All grades	Grade 3-5	All grades	Grade 3-5
AEs common to BEV use								
Hypertension	19	2.2	5	1.5	29	3.8	12	0.6
Congestive heart failure	0	0	1	0	NR	NR	NR	NR
Thromboembolic disorders	16	11.9	7	5.1	14.5	12.1	10	7.1
-Venous	12	8.2	5	4.4	10	8.9	10	7.1
-Arterial	4	3.7	2	0.7	4.5 †	3.2	0	0
Bleeding	25	0	7	0.7	12	1.3	12	2.6
Proteinuria	7	1.5	0.7	0	31	3.2	12	0.6
Gastrointestinal perforation	1	0	0	0	1.9	1.9	0.6	0.6
AEs Common to CAP								
Asthenia	22	5.2	16	3.7	NR	NR	NR	NR
Diarrhea	40	6.7	35	6.6	65	17	62	11
Fatigue	24	3.7	27	0.7	78	9.6	74	9.6

Table 9: Selected AEs of special interest occurring in ≥ 5% of patients								
Event category	AVEX,[10]				MAX,[11]			
	BEV + CAP (N = 134) (%)		CAP (N = 136) (%)		BEV + CAP (N = 157) (%)		CAP (N = 156) (%)	
	All grades	Grade 3-5	All grades	Grade 3-5	All grades	Grade 3-5	All grades	Grade 3-5
Hand-foot syndrome	49	15.7	40	6.6	77 †	26	65	16
Nausea	24	0.7	27	0	67	5.1	54	5.8
Vomiting	21	2.2	12	0.7	38	5.1	31	5.1
AEs= adverse events, BEV = bevacizumab, CAP = capecitabine, NR = not reported † According to the investigators, grades 3 to 4 AEs were significantly higher in the BEV + CAP group compared with the CAP alone group (unadjusted for duration of treatment; all P=0.03).								

While the AVEX study categorized safety outcomes into serious adverse events (SAEs), adverse events (AEs) and adverse events leading to dose modification or disruption, the MAX study bundled safety outcomes as toxicity. Treatment-related SAEs in the AVEX study occurred in 19 (14%) patients in the BEV + CAP group compared with 11 (8%) patients in the CAP alone group.

As shown in Table 10, treatment-related adverse events (TRAEs) of any grade were similar between treatment groups. However, a higher proportion of patients in the combined treatment group had grade ≥3 TRAES than did those in the CAP alone group. The most frequently occurring TRAE in patients treated with BEV + CAP in both the AVEX and MAX studies were hand-foot skin reaction, fatigue, diarrhea, and hypertension (Table 9).

AEs leading to dose interruption or modifications were not categorized as related or unrelated to treatment (Table 10) in the AVEX study. A higher proportion of patients in the BEV + CAP treatment group had their doses modified because of toxic effects than did those in the CAP alone group (55 (41%) versus 36 patients (26%), respectively).[10]

Treatment discontinuation due to AEs occurred more in the combination treatment group than in the CAP alone group (25% versus 15%). No particular AE was identified as the main cause of treatment discontinuation.

Table 10: Summary of Overall Safety Outcomes		
Harms Category	AVEX,[10]	
	BEV +CAP (N=134) n (%)	CAP (N=136) n (%)
TRSAE	19 (14)	11 (8)
TRAE (Any grade)	112 (84)	110 (81)
Grade ≥3 TRAE (Any kind)	53 (40)	30 (22)
AEs leading to any dose interruption or modification	74 (55)	59 (43)
WDAE	34 (25)	20 (15)
AEs = adverse events, BEV = bevacizumab, CAP = capecitabine, CI = confidence interval, HR = hazard ratio, TRAE = treatment related adverse events, TRSAE = treatment related serious adverse events, WDAE = withdrawal due to adverse events		

6.4 Ongoing Trials

Although no ongoing trials were identified which are relevant to the current review, an approved study which has not yet begun was found. The purpose of this randomized phase III clinical trial (identifier NCT01279681), sponsored by North Central Cancer Treatment Group, is to study how well combination chemotherapy plus bevacizumab with or without oxaliplatin works in treating older patients with metastatic colorectal cancer.[41] According to the latest verified information by the National Cancer institute (NCI), the study was not yet recruiting as at December 2012.[41]

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of bevacizumab in combination with capecitabine for metastatic colorectal cancer:

- What is the efficacy and safety of bevacizumab (BEV) in combination with 5-fluorouracil (5-FU) for advanced or metastatic colorectal cancer (mCRC)?
- What is the validity of progression-free survival (PFS) as a surrogate outcome for mCRC?

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 What is the efficacy and safety of bevacizumab (BEV) in combination with 5-fluorouracil (5-FU) for advanced or metastatic colorectal cancer (mCRC)?

7.1.1 Objective

Avastin (BEV) in combination with fluoropyrimidine-based chemotherapy is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum. As bevacizumab in combination with capecitabine was indicated in the funding request of this submission, other fluoropyrimidines were not included as comparators in the review protocol and only this combination was reviewed in the systematic review. However, 5-FU is an active fluoropyrimidine metabolite of capecitabine that is also used in chemotherapy regimens. Although its oral administration may be preferred because of convenience, capecitabine is not always accessible to patients due to out-of-pocket cost in many jurisdictions. Consequently, the use of bevacizumab in combination with 5-FU for the treatment of mCRC is of interest for this review. This section will summarize studies assessing the efficacy and safety of bevacizumab in combination with 5-FU, an intravenously administered drug, as first-line treatment of advanced or mCRC in patients who are not suitable for oxaliplatin or irinotecan-based therapy.

7.1.2 Findings

A supplemental literature search was performed to identify trials in which capecitabine was substituted by 5-FU in combination with BEV for mCRC. Two randomized-controlled trials[12,13] were identified.

Kabbinavar et al. 2003[13]

The authors conducted a phase II RCT which investigated the safety and efficacy of two doses of BEV in combination with 5-FU and leucovorin (LV) versus 5-FU + LV alone as first-line therapy in patients with mCRC. The study enrolled 104 previously untreated patients with measurable mCRC, an ECOG PS of 0 or 1, and a life expectancy of more than 3 months. Patients were randomly assigned (1:1:1) to the following three treatment groups: 5-FU + LV, 5-FU + LV + low dose BEV 5 mg/kg, and 5-FU + LV + high dose BEV 10 mg/kg. 5-FU (500 mg/m^2 intravenous bolus) and LV (500 mg/m^2 intravenous infusion) were administered weekly for the first 6 weeks of each 8-week cycle until the completion of 6 cycles (48 weeks) or disease progression. BEV (intravenous infusion) was administered every two weeks until 48 weeks or disease progression. The primary efficacy endpoints were response rates (RR) and time to progression (TTP). Secondary endpoints included overall survival (OS) and duration of response. Tumour status was

blindly assessed every 8 weeks by an independent review facility. The study was sponsored by Genentech Inc.

Imbalances in baseline characteristics of the treatment arms were observed by treatment arms. These imbalances suggested that more patients in the control group had previous surgery for cancer compared to patients who received BEV. Also, patients who received BEV had more metastases, both in liver and lung, and had lower serum albumin. Baseline characteristics at baseline disfavored the investigational drug.

Results for efficacy outcomes are reported in Table 1.

Table 1: Kabbinavar et al 2003[13] - Efficacy outcomes

Endpoint	5-FU + LV N = 36	5-FU + LV + BEV (5 mg/kg) N = 35	5-FU + LV + BEV (10 mg/kg) N = 33
Response rate (RR), %			
Value (95% CI)	17 (7 to 34%)	40 (24 to 58)	24 (12 to 43)
P value vs control	--	0.029	0.434
Time to progression (TTP), months			
Median (95% CI)	5.2 (3.5 to 5.6)	9.0 (5.8 to 10.9)	7.2 (3.8 to 9.2)
HR vs control, unadjusted	--	0.46	0.66
P value vs control	--	0.005	0.217
Overall survival (OS), months			
Median (95% CI)	13.8 (9.1 to 23.0)	21.5 (17.3 to UND)	16.1 (11.0 to 20.7)

BEV = bevacizumab, CI = confidence interval, 5-FU = 5-fluorouracil, HR = hazard ratio, LV = leucovorin, OS = overall survival, RR = response rate, TTP = time to progression, UND = undetermined.

As per protocol, twenty-two patients from the control group crossed over after disease progression to receive BEV (10 mg/kg every two weeks) in monotherapy. Two of these patients had a partial response to BEV. No information was provided for subsequent therapies.

Adverse events (AEs) are reported in Table 2. Among the fifty deaths reported during the study, three patients, one in each group, presumably died from a cause other than disease progression. Statistically more ($P = 0.042$) patients in the BEV treatment arms had grade 3 or 4 AEs, but this may be due to longer stay in the study as the HR was not statistically different when comparing BEV to control (HR = 1.15, $P = 0.61$). BEV was associated with fever, headache, rash, epistaxis, proteinuria and chills. Moreover, increased occurrences of bleeding, hypertension and thrombosis have been observed in the BEV arms of this trial. Twelve percent of patients discontinued the study due to AEs, 2 were in the control arm, 1 was a cross-over patient, 4 were in the low dose BEV arm, and 6 were in the high dose BEV arm.

Table 2: Kabbinavar et al 2003[13] -Adverse Events						
Adverse events, n (%)	5-FU + LV N = 35		5-FU + LV + BEV (5 mg/kg) N = 35		5-FU + LV + BEV (10 mg/kg) N = 32	
	All events	Grade 3/4	All events	Grade 3/4	All events	Grade 3/4
Any Event	35 (100)	19 (54)	35 (100)	26 (74)	32 (100)	25 (78)
Diarrhea	29 (83)	13 (37)	32 (91)	10 (29)	24 (75)	10 (31)
Leukopenia	1 (3)	1 (3)	4 (11)	2 (6)	1 (3)	1 (3)
Stomatitis	6 (17)	0	8 (23)	0	6 (19)	0
Fever	4 (11)	0	13 (87)	0	11 (34)	1 (3)
Headache	5 (14)	0	11 (31)	0	12 (38)	1 (3)
Rash	7 (20)	0	16 (46)	1 (3)	11 (34)	0
Chills	1 (3)	0	5 (14)	0	5 (16)	0
Abdominal pain	19 (54)	1 (3)	16 (46)	3 (9)	15 (47)	4 (13)
Weight loss	8 (23)	0	5 (14)	1 (3)	3 (9)	0
GI hemorrhage	0 (0)	0	2 (6)	0	5 (16)	3 (9)
Epistaxis	4 (11)	0	16 (46)	0	17 (53)	0
Hypertension	1 (3)	0	4 (11)	3 (9)	9 (28)	8 (25)
Infection	7 (20)	0	14 (40)	0	8 (25)	1 (3)
Thrombotic events	3 (9)	1 (3)	9 (26)	5 (14)	4 (13)	2 (6)
BEV = bevacizumab, 5-FU = 5-fluorouracil, GI = gastrointestinal, LV = leucovorin.						

The authors concluded that the results suggest that BEV in combination with 5-FU + LV increases response rate, prolongs time to progression and prolongs survival compared with 5-FU + LV alone in patients with mCRC.

Kabbinavar et al. 2005[12]

The authors conducted a multicentre phase II RCT which compared BEV in combination with 5-FU and LV to placebo with 5-FU and LV as first-line therapy in patients with mCRC who were deemed not optimal candidates for first-line irinotecan-containing regimens. In addition, patients had to have one of the following characteristics: be 65 years or older, have an ECOG PS of 1 or 2, have a serum albumin level ≤ 3.5 g/dL, or have prior abdominal/pelvic radiotherapy. The study enrolled 209 patients who were randomly assigned (1:1) to 5-FU + LV + placebo or to 5-FU + LV + BEV. 5-FU (500 mg/m^2 intravenous bolus) and LV (500 mg/m^2 intravenous infusion) were administered weekly for the first 6 weeks of each 8-week cycle. BEV 5 mg/kg was administered every two weeks. The study duration was 96 weeks. Patients were blinded to their treatment assignment until disease progression. The primary endpoint was overall survival (OS).

Secondary endpoints were progression-free survival (PFS), response rate (RR), response duration (RD) and quality of life (QoL) assessed with the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) instrument. Tumour status was evaluated by CT scan at baseline and every 8 weeks thereafter by the investigator and by a blinded independent radiology facility.

Baseline characteristics were reasonably balanced between treatment groups, except for the number of metastasis sites and the number of patients with low serum albumin that both were numerically higher in the 5-FU/LV/BEV group.

The median duration of the therapy was 23 weeks in the 5-FU + LV/placebo group and 31 weeks in the 5-FU + LV + BEV group. Subsequent therapies were used in approximately 50% of patients in both groups, although more patients in the placebo group were treated with irinotecan and oxaliplatin.

Results for efficacy outcomes are displayed in Table 3.

Table 3: Kabbinavar et al 2005[12] - Efficacy outcomes

Endpoint	5-FU + LV + placebo N = 105	5-FU + LV + BEV N = 104
Overall survival (OS), months		
Median	12.9	16.6
HR (95% CI)	0.79 (0.56 to 1.10)	
P-value	0.16	
Progression-free survival (PFS), months		
Median	5.5	9.2
HR (95% CI)	0.50 (0.34 to 0.73)	
P-value	0.0002	
Overall response rate (RR), %		
Value	15.2	26.0
Complete response	0	0
Partial response	15.2	26.0
P-value	0.055	
Duration of response, months		
Median	6.8	9.2
HR (95% CI)	0.42 (0.15 to 1.17)	
P-value	0.088	

BEV = bevacizumab, CI = confidence interval, 5-FU = 5-fluorouracil, LV = leucovorin, OS = overall survival, PFS = progression-free survival, RR = response rate.

Treatment with BEV had no statistically significant effect on QoL as determined by time to deterioration of QoL (TDQ) based on the colon cancer-specific FACT-C subscale score (CCS). The median TDQ was 3.0 months in the 5-FU + LV + placebo group and 3.1 months in the 5-FU + LV + BEV group (HR = 0.79; *P* = 0.188). As secondary QoL measures, TDQ was also determined based on the trial outcome index (TOI-C), i.e. the sum of CCS, physical and functional well-being, and

based on total FACT-C. Median secondary TDQ measures were 2.3 and 3.2 months for TOI-C (HR = 0.71; *P* = .048) and 2.6 and 3.6 months for total FACT-C (HR = 0.66; *P* = .016), for placebo-treated and BEV-treated patients, respectively. Due to a multiplicity of tests, the relevance of the result for TOI-C is not clear.

Adverse events (AEs) are reported in Table 4. BEV appeared to be associated with a higher rate of grade 3-4 AEs, in particular, hypertension, arterial thrombotic events, proteinuria, but to a lower rate of mortality of all causes at 60 days.

Table 4: Kabbinavar et al 2005[12] - Occurrence (%) of Adverse Events

Adverse Event (%)	5-FU + LV + placebo N = 104	5-FU + LV + BEV N = 100
Any grade 3 or 4 adverse event	71	87
Adverse event leading to study discontinuation	12	10
Adverse event leading to death	7	4
All-cause mortality at 60 days	14	5
Diarrhea (grade 3 or 4)	40	39
Leukopenia (grade 3 or 4)	7	5
Hypertension (any) • Hypertension (grade 3)*	5 3	32 16
Thrombotic events (any) • Deep thrombophlebitis • Pulmonary embolus • Arterial thrombotic event (any)	18 9 2 5	18 6 3 10
Bleeding (grade 3 or 4)	3	5
Proteinuria (any) • Grade 2 • Grade 3	19 4 0	38 7 1
Gastrointestinal perforation	0	2
BEV = bevacizumab, 5-FU = 5-fluorouracil, LV = leucovorin.		
Note: * No grade 4 hypertension events were reported		

The authors concluded these data demonstrated that BEV, when combined with bolus 5-FU + LV, provides substantial clinical benefit for patients with previously untreated mCRC who were not considered optimal candidates for first-line irinotecan treatment.

Critical appraisal

Kabbinavar et al. 2003[13] conducted their study in 104 patients with mCRC without specifying their eligibility for oxaliplatin or irinotecan-based therapy. Thus, it is unclear if this patient population was relevant for the present review. Patients were not blinded, but disease progression was assessed by blinded investigators. An expectation bias was possible on the patient side. Kabbinavar et al. 2005[12] conducted their study in 209 patients who were deemed

not optimal candidates for first-line irinotecan-containing regimens. These patients and the assessors of tumor response were blinded, but investigators were unblinded. The two studies investigated a dose of BEV similar to the dose used in the MAX and AVEX trials, i.e. 2.5 mg/kg/week. The populations of these two studies do not overlap with one another.

7.1.3 Summary

This section summarized the studies assessing the efficacy and safety of bevacizumab in combination with 5-FU as first-line treatment of advanced or mCRC in patients who are not suitable for oxaliplatin or irinotecan-based therapy. In two phase II randomized-controlled trials,[12,13] BEV in combination with 5-FU and LV showed improvements of 3.7 months in PFS (5.5 months for 5-FU + LV + placebo and 9.2 months for 5-FU + LV + BEV, *P* = 0.0002), of 23% in RR (17% [95%CI: 7-34%] for 5-FU + LV alone and 40% [95%CI: 24-58%] for 5-FU + LV + BEV) and of 3.8 months in TTP (5.2 months [95%CI: 3.5-5.6 months] for 5-FU + LV alone and 9.0 months [95%CI: 5.8-10.9 months] for 5-FU + LV + BEV). No statistically significant results were observed for OS and duration of response.

Safety concerns associated with BEV included increased occurrences of bleeding, hypertension and thrombosis. Less clinically significant AEs, such as fever, headache, rash, epistaxis, proteinuria and chills, were also more commonly observed in patients who received BEV.

Overall, the use of 5-FU in combination with BEV yielded similar efficacy and safety results to BEV + capecitabine.

7.2 What is the validity of progression-free survival (PFS) as a surrogate outcome for mCRC?

7.2.1 Objective

In order to evaluate the validity of using PFS as the primary outcome for trials investigating mCRC, this section will summarize two publications provided by the submitter. The publications of Tang et al. 2007[15] and Giessen et al. 2012[14] analyzed the use of PFS in mCRC based on published literature.

7.2.2 Findings

The Tang et al. 2007 Study[15]

The aim of the authors was to perform a comprehensive literature-based analysis to determine whether progression-free survival (PFS), time to progression (TTP) or response rate (RR) were correlated with OS and whether improvements in PFS, TTP and RR with first-line therapies were associated with improvements in OS in mCRC.

Tang and colleagues conducted a systematic literature search of randomized controlled trials of first line therapy in mCRC published up to 2005 that included more than 100 patients per arm. Exclusion criteria were locally advanced unresectable disease; intermittent as opposed to continuous chemotherapy; and hepatic chemotherapy infusion.

A total of 45 trials were identified, but 6 were further excluded based on exclusion criteria. Therefore, 39 trials with 87 treatment arms and 18,668 patients were included. All treatment arms reported RR, 55 reported PFS, and 32 reported TTP. The median follow-up duration ranged from 12 to 57.6 months. All trials that reported a statistically significant difference in OS also reported a significant difference in TTP or PFS.

There was a strong correlation between PFS and OS, which did not appear to depend on the chemotherapy regimen (See Table 5). The Spearman rank correlation coefficient (r_s) values were 0.79 (95%CI: 0.65-0.87) between PFS and OS, 0.24 (95%CI: –0.13-0.55) between TTP and OS, and 0.59 (95% CI: 0.42-0.72) between RR and OS. When comparing these coefficients, the r_s for PFS and OS was found to be statistically significantly higher than that for TTP and OS (P = 0.001).

Table 5: Tang et al 2007[15] - Correlation Between Surrogate Endpoints and OS

Surrogate End Point	Nonparametric Spearman Rank Correlation Coefficient	95% CI
PFS vs OS	0.79	0.65 to 0.87
TTP vs OS	0.24	–0.13 to 0.55
RR vs OS	0.59	0.42 to 0.72
ΔPFS vs ΔOS	0.74	0.47 to 0.88
ΔTTP vs ΔOS	0.52	0.004 to 0.81
ΔRR vs ΔOS	0.39	0.08 to 0.63

CI = confidence interval, OS = overall survival, PFS = progression-free survival, RR = response rate, TTP = time to progression.

Note: Δ is the difference between treatment arms within a trial.

For each trial, the differences in endpoints (ΔPFS, ΔTTP, ΔRR, ΔOS) were calculated as the estimate in the experimental arm(s) minus the estimate in the control arm. Within trials, there was a strong correlation between ΔPFS and ΔOS. The r_s values were 0.74 (95%CI: 0.47-0.88) between ΔPFS and ΔOS, 0.52 (95% CI: 0.004-0.81) between ΔTTP and ΔOS, and 0.39 (95% CI: 0.08-0.63) between ΔRR and ΔOS. No statistically significant difference was found between coefficients.

A linear regression analysis through the origin of the plot evaluated ΔOS as a function of ΔPFS. This analysis was used to determine a conversion factor between ΔPFS and ΔOS and to obtain the proportion of variability explained (R^2). The conversion factor from ΔPFS to ΔOS was estimated at 1.02 ± 0.16 and the R^2 was 0.65.

Fifteen trials reported 18 pairs of hazard ratios (HR) for PFS and OS between treatment arms. Based on the HRs, a linear regression analysis was performed through the origin of the plot to determine the percent risk reduction of OS as a function of percent risk reduction of PFS. There was a highly statistically significant relationship between risk reductions for PFS and OS (P = <0.0001). The slope of the regression line was 0.54 ± 0.10, meaning that a 10% risk reduction for PFS would yield an estimated 5.4% risk reduction for OS.

The length of lead time that could be gained by using PFS instead of OS as the primary endpoint was estimated. The difference between the median OS and median PFS was plotted as a function of median OS. The lead time is estimated to increase from approximately 4 to 5 months for a median OS of 9 months, to close to 1 year for a median OS of 1.5 years.

In their conclusions, the authors mentioned that PFS is a more sensitive endpoint than OS for treatment effect. Also with more events at the time of analysis, the use of PFS will result in higher statistical power. The lead time advantage over OS would accelerate the drug development process and save costs. Therefore, the usage of PFS as a surrogate endpoint in RCTs in first-line chemotherapy for mCRC may be appropriate.

Critical Appraisal

The AMSTAR tool[42] has been used to critically appraise the systematic review conducted by Tang et al.[15]. A pre-determined protocol as well as a duplicated study selection and data extraction were used for the systematic review. The literature search was adequate. Grey literature search was included. The list of included and excluded trials was provided. Some characteristics of the included studies were disclosed, but much information was missing. The studies were not assessed for quality. The methods for combining the findings were adequate. The likelihood of publication bias was not assessed. Conflicts of interest were only reported for the author of the systematic review, not for the authors of the included studies. Among factors limiting their analysis, the authors mentioned that their review was not based on individual patient data, the low reporting of HRs in 55 of 87 treatment arms, the heterogeneous definition of progression, the equal assessment of progression in all treatment arms of a same trial, and the lack of information on subsequent treatments potentially confounding OS. In patients opting for single-agent chemotherapy in the first line setting, however, subsequent treatment would be expected to be less likely than in the general colorectal cancer population.

The Giessen et al.2012 Study[14]

The aim of the authors was to conduct a comprehensive literature-based quantitative, systematic review to determine whether PFS is correlated with OS in first-line chemotherapy trials for mCRC.

Giessen and his colleagues conducted a systematic review of randomized controlled trials for patients who underwent first-line chemotherapy for mCRC published up to January 2012. Inclusion criteria included a sample size of at least 100 patients per trial and the reporting of either PFS or TTP along with OS. Exclusion criteria were trials which enrolled patients with locally advanced unresectable disease or with previous chemotherapy, trials investigating surgical resection of resectable/unresectable metastatic disease, trials limited to elderly or younger population, pooled data reports or noninterventionnal trials, trials using additional hepatic chemotherapy infusion, treatment with intermittent chemotherapy, and trials involving nonapproved drugs by EMA at the time of review.

Data from 50 trials representing 22,736 patients were included. Seven trials used TTP as the primary endpoint, but both TTP and PFS were referred to as PFS.

When all treatment regimens were analyzed, treatment effects on PFS (ΔPFS) and OS (ΔOS) were found to be correlated with a coefficient of 0.87 (95%CI: 0.67-0.93) (see Table 6). Within treatment arms, PFS was also correlated with OS with a coefficient of 0.86 (95%CI: 0.79-0.91).

Table 6: Giessen et al 2012[14] - Correlation Between Surrogate Endpoints and OS

Treatments	Number of patients	N of trials; N of trial arms	Correlation ΔPFS and ΔOS	95% CI	Correlation PFS and OS	95% CI
All treatments	22,736	50; 102	0.87	0.67 to 0.93	0.86	0.79 to 0.91
Chemotherapy-only	17,887	40; 74	0.93	0.49 to 0.97	0.81	0.71 to 0.88
Oxaliplatin-based	10,060	31; 44	0.68	0.41 to 0.85	0.69	0.36 to 0.87
Irinotecan-based	7,301	24; 36	0.82	0.52 to 0.95	0.74	0.59 to 0.86
Chemotherapy and antibody	4,849	19; 28	0.47	0.05 to 0.72	0.52	0.09 to 0.88

Table 6: Giessen et al 2012[14] - Correlation Between Surrogate Endpoints and OS						
Treatments	**Number of patients**	**N of trials; N of trial arms**	**Correlation ΔPFS and ΔOS**	**95% CI**	**Correlation PFS and OS**	**95% CI**
Chemotherapy and bevacizumab	3,310	11; 17	0.84	0.05 to 0.94	0.45	0.00 to 0.84
Chemotherapy and cetuximab or panitumumab	1,335	7; 9	0.28	–0.87 to 0.92	0.96	–0.76 to 1.00
CI = confidence interval, OS = overall survival, PFS = progression-free survival.						
Note: Δ is the difference between treatment arms within a trial.						

When narrowing the analysis to the 17,887 patients and 40 trials who received only cytotoxic therapy, correlation coefficients were similar with 0.93 (95%CI: 0.49-0.97) between ΔPFS and ΔOS and 0.81 (95%CI: 0.71-0.88) between PFS and OS.

By including only the 4,849 patients from 19 trials who had antibody-based regimens, lower correlation coefficients between ΔPFS and ΔOS (0.47, 95% CI 0.05 to 0.72) and between PFS and OS (0.52, 95%CI: 0.09-0.88) were found.

When subgrouping for BEV-based therapies used in 3,310 patients from 11 trials, a high correlation was found between ΔPFS and ΔOS (0.84, 95%CI: 0.05-0.94), but a low correlation was observed between PFS and OS (0.45, 95%CI: 0.00-0.84). However, as suggested by CIs, there was a high heterogeneity between these studies. Further research is then needed on BEV-based therapies.

Critical Appraisal

The AMSTAR tool[42] has been used to critically appraise the systematic review conducted by Giessen et al.[14]. Their review had several limitations mainly due to missing information. A pre-determined protocol and duplicated study selection and data extraction were not mentioned in the systematic review. The literature search appeared adequate. Grey literature search was included. The list of included studies was provided, but excluded studies were not. Some characteristics of the included studies were disclosed, but much information was missing. The studies were not assessed for quality. The methods for combining the findings was adequate, but data for PFS and TTP were pooled, although they were different measures. Also, data were very heterogeneous for specific subgroups. The likelihood of publication bias was not assessed. Conflicts of interest were only reported for the author of the systematic review, but not for the authors of the included studies. Among factors limiting their analysis, the authors noted the heterogeneous definition of progression, the equal assessment of progression in all treatment arms of a same trial and the lack of information on subsequent treatments potentially confounding OS. The limitations of aggregated data compared to individual patient-level analyses were also acknowledged.

7.2.3 Summary

The use of PFS shows advantages over OS. PFS is less influenced than OS for competing causes of death and PFS is not influenced by second-line treatments. This section evaluated the validity of using PFS as the primary outcome for mCRC and summarized two publications[14,15] provided by the submitter.

The systematic review reported by Tang et al.[15] was of good overall quality. The authors mentioned that PFS is a more sensitive endpoint than OS for treatment effect. Also with more events at the time of analysis, the use of PFS would result in higher statistical power. The lead time advantage over OS would accelerate the drug development process and save costs. In conclusion, the authors stated that the usage of PFS as a surrogate endpoint in RCTs in first-line chemotherapy for mCRC may be appropriate.

The systematic review conducted by Giessen and colleagues[14] had many reporting and methodologic limitations. The authors concluded that PFS would be justified as a surrogate endpoint in trials using cytotoxic chemotherapy regimen. However, when focusing the analysis on BEV-based therapies, correlation coefficients were lower, albeit with a very wide CI. As high heterogeneity was observed for results with that type of therapy, further research would be needed for validation of PFS as a surrogate endpoint for mCRC.

Overall, the conclusions of their analysis can apply to a general population with mCRC receiving first-line treatment. But more specifically for patients with BEV-based therapies, the utilization of PFS as surrogate outcome for OS appears uncertain.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Gastrointestional 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) in combination with capecitabine for metastatic colorectal cancer. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

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

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

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

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** January 2015, **Embase** 1974 to 2015 Feb 23, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

#	Searches	Results
1	216974-75-3.rn,nm.	28885
2	(Bevacizumab* or avastin* or altuzan* or nsc-704865 or nsc704865 or rhuMAb-VEGF or rhumabvegf or anti-vegf or antivegf or immunoglobulin-G1 or immunoglobulinG1).ti,ab,rn,nm,sh,hw,ot.	65202
3	or/1-2	65202
4	154361-50-9.rn,nm.	15624
5	(capecitabin* or Xeloda or Capiibine or capibine or Caxeta or Xabine or apecitab or arxeda or capebina or capetero or cipatin or intacape or naprocap or xalvobin or xelobig or xelocan or Ro-09-1978 or ro-091978 or ro09-1978 or ro091978).ti,ab,rn,nm,sh,hw,ot.	24254
6	or/4-5	24254
7	exp Colorectal Neoplasms/	172999
8	((Cancer* or neoplasia or neoplasm* or tumor* or tumour* or carcinoma* or cyst or cysts or polyp or polyps or sigmoid) adj3 (Colorectal or colo-rectal or rectum or rectal or rectums or anus or anal or colon or colonic or colons or bowel or bowels or intestinal or intestine or intestines)).ti,ab.	382064
9	or/7-8	429888
10	3 and 6 and 9	2978
11	10 use pmez	371
12	10 use cctr	83
13	*Bevacizumab/	9859
14	(Bevacizumab* or avastin* or altuzan* or nsc-704865 or nsc704865 or rhuMAb-VEGF or rhumabvegf or anti-vegf or antivegf or immunoglobulin-G1 or immunoglobulinG1).ti,ab.	33659
15	or/13-14	34479
16	*capecitabine/	4107

17	(capecitabin* or Xeloda or Capiibine or capibine or Caxeta or Xabine or apecitab or arxeda or capebina or capetero or cipatin or intacape or naprocap or xalvobin or xelobig or xelocan or Ro-09-1978 or ro-091978 or ro09-1978 or ro091978).ti,ab.	12036
18	or/16-17	12484
19	exp colon tumor/	220444
20	exp rectum tumor/	165809
21	((Cancer* or neoplasia or neoplasm* or tumor* or tumour* or carcinoma* or cyst or cysts or polyp or polyps or sigmoid) adj3 (Colorectal or colo-rectal or rectum or rectal or rectums or anus or anal or colon or colonic or colons or bowel or bowels or intestinal or intestine or intestines)).ti,ab.	382064
22	or/19-21	460931
23	15 and 18 and 22	1115
24	23 use oemezd	756
25	(Randomized Controlled Trial or Controlled Clinical Trial).pt.	899554
26	Randomized Controlled Trial/	749295
27	Randomized Controlled Trials as Topic/	167518
28	"Randomized Controlled Trial (topic)"/	66253
29	Controlled Clinical Trial/	479089
30	Controlled Clinical Trials as Topic/	8798
31	"Controlled Clinical Trial (topic)"/	3721
32	Randomization/	167513
33	Random Allocation/	167513
34	Double-Blind Method/	353915
35	Double Blind Procedure/	120599
36	Double-Blind Studies/	315135
37	Single-Blind Method/	52115
38	Single Blind Procedure/	19582
39	Single-Blind Studies/	52115
40	Placebos/	319971
41	Placebo/	265670
42	Control Groups/	73650

43	Control Group/	73562
44	(random* or sham or placebo*).ti,ab,hw.	2841227
45	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	589266
46	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	1416
47	(control* adj3 (study or studies or trial*)).ti,ab.	918827
48	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.	67815
49	allocated.ti,ab,hw.	118358
50	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.	66769
51	or/25-50	3597759
52	and/11,51	106
53	and/12,50	76
54	and/24,51	260
55	or/52-54	442
56	limit 55 to english language	420
57	remove duplicates from 56	303

2. Literature search via PubMed

Search	Query	Items found
#9	Search **#7 AND #8**	1
#8	Search **publisher[sb]**	471336
#7	Search **#1 AND #2 AND #5 AND #6**	102
#6	Search **randomized controlled trial[pt] OR randomized controlled trials as topic[mh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR random*[tw] OR "Placebos"[Mesh] OR placebo[tiab] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw] OR dumm*[tw]))**	1036418
#5	Search **#3 OR #4**	258788
#4	Search **(Cancer*[tiab] OR neoplasia[tiab] OR neoplasm*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR cyst[tiab] OR cysts[tiab] OR polyp[tiab] OR polyps[tiab] OR sigmoid[tiab]) AND (Colorectal[tiab] OR colo-rectal[tiab] OR rectum[tiab] OR rectal[tiab] OR rectums[tiab] OR anus[tiab] OR anal[tiab] OR colon[tiab] OR colonic[tiab] OR colons[tiab] OR bowel[tiab] OR bowels[tiab] OR intestinal[tiab] OR intestine[tiab] OR intestines[tiab])**	224234
#3	Search **Colorectal Neoplasms[mh]**	151096
#2	Search **capecitabine [Supplementary Concept] OR capecitabin*[tiab] OR Xeloda[tiab] OR Capiibine[tiab] OR capibine[tiab] OR Caxeta[tiab] OR Xabine[tiab] OR apecitab[tiab] OR arxeda[tiab] OR capebina[tiab] OR capetero[tiab] OR cipatin[tiab] OR intacape[tiab] OR naprocap[tiab] OR xalvobin[tiab] OR xelobig[tiab] OR xelocan[tiab] OR Ro-09-1978[tiab] OR ro- 091978[tiab] OR ro09-1978[tiab] OR ro091978[tiab]**	4403

Search	Query	Items found
#1	Search **bevacizumab [Supplementary Concept] OR bevacizumab*[tiab] OR avastin*[tiab] OR altuzan*[tiab] OR nsc-704865[tiab] OR nsc704865[tiab] OR rhuMAb-VEGF[tiab] OR rhuMabVEGF[tiab] OR anti-VEGF[tiab] OR anti-VEGF[tiab] OR immunoglobulin-G1[tiab] OR immunoglobulinG1[tiab]**	13600

Cochrane Central Register of Controlled Trials (Central)

Searched via Ovid (see section 1 above)

4. **Grey Literature search via:**

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search terms: Avastin/bevacizumab and Xeloda/capecitabine

Select international agencies including:

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

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

Search terms: Avastin/bevacizumab and Xeloda/capecitabine

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

European Society for Medical Oncology (ESM0)
http://www.esmo.org/

Search terms: Avastin/bevacizumab and Xeloda/capecitabine last 5 years

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