Evidence-Based Series 2-25 EDUCATION AND INFORMATION 2013

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

The Role of Bevacizumab (Avastin®) Combined With Chemotherapy in the Treatment of Patients With Advanced Colorectal Cancer: Guideline Recommendations

Members of the Gastrointestinal Cancer Disease Site Group

This Evidence-based Series (EBS) was reviewed in 2013 and put in the Education and Information section by the Gastrointestinal Cancer Disease Site Group on December 2013 (see Section 4- Document Summary and Review Tool for details). The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

Evidence-based Series (EBS) 2-25- consists of four sections:

Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: EBS Development Methods and External Review Process
Section 4: Document Assessment and Review

and is available on the CCO Web site (http://www.cancercare.on.ca)
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S. Welch, W. Kocha, R.B. Rumble, K. Spithoff, J. Maroun, and the Gastrointestinal Cancer Disease Site Group

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Gastrointestinal Cancer Disease Site Group

Original Report Date: December 12, 2005
Current Report Date: May 28, 2008

QUESTION
Should adult patients with advanced (locally advanced non-resectable or metastatic) colorectal cancer who are considered candidates for systemic therapy receive bevacizumab (Avastin®) combined with cytotoxic chemotherapy? Outcomes of interest were overall survival, progression-free survival, response rates, and adverse effects.

TARGET POPULATION
These recommendations apply to adult patients with advanced colorectal cancer who are considered candidates for systemic therapy.

RECOMMENDATIONS
- For patients with advanced colorectal cancer receiving fluoropyrimidine-based chemotherapy as first-line therapy, the addition of bevacizumab is recommended to improve overall survival.
- The addition of bevacizumab to fluoropyrimidine-based chemotherapy is also recommended for patients with advanced colorectal cancer receiving second-line therapy if they did not receive bevacizumab as part of their initial treatment.
The role of continuing bevacizumab after disease progression on a bevacizumab-containing regimen is not clear due to the absence of evidence. Therefore, the continuation of bevacizumab in patients who have progressed on this therapy cannot currently be recommended outside of clinical trials.

QUALIFYING STATEMENTS

- Data from available randomized controlled trials (RCTs) have demonstrated a significant advantage with the addition of bevacizumab to several fluoropyrimidine-based regimens, including regimens of 5-fluorouracil (5FU)/folinic acid (FA), bolus 5FU with irinotecan (IFL), 5FU with oxaliplatin (FOLFOX4), and capecitabine with oxaliplatin (XELOX). These studies have included regimens using 5FU given by intravenous bolus, intravenous infusional and by oral route. Survival benefit has been shown with the addition of bevacizumab to both first- and second-line chemotherapy. A reasonable conclusion is that bevacizumab in combination with any fluoropyrimidine-based chemotherapy is more effective than the same fluoropyrimidine-based chemotherapy alone.

- Given the data supporting the addition of bevacizumab to IFL and to FOLFOX, the Disease Site Group (DSG) finds the addition of bevacizumab to infusional 5FU with irinotecan (FOLFIRI) reasonable, despite the fact that this combination has not been formally evaluated in an RCT. This guideline reflects previous recommendations supporting the use of FOLFIRI over IFL.

- The magnitude of incremental benefit with bevacizumab may change based on the cytotoxic chemotherapeutic regimen it is partnered with. There is insufficient evidence at present to provide any recommendations as to which chemotherapy regimen is optimal in combination with bevacizumab.

- The weight of evidence supports the use of bevacizumab with first-line chemotherapy for patients with advanced colorectal cancer. Although the evidence is less compelling for its use with second-line chemotherapy, this treatment is recommended if bevacizumab is not included in the initial treatment regimen.

- Bevacizumab should not be administered to patients with cerebral metastases, uncontrollable hypertension, severe proteinuria, advanced atherosclerotic disease, bleeding diatheses, or those with non-healing wounds, recent surgery or trauma (i.e., within the previous 28 days), since those patients were excluded from enrolment in clinical trials using bevacizumab. The Gastrointestinal Cancer DSG considers these to be relative contraindications to the use of bevacizumab.

- The addition of bevacizumab to chemotherapy is associated with significant but manageable toxicity, specifically hypertension, bleeding, thromboembolic events, and proteinuria.

KEY EVIDENCE

Three phase III RCTs (1-3) and two phase II randomized trials (4,5) comparing a chemotherapy regimen to the same regimen plus bevacizumab were included in this review. Four of the five clinical trials studied bevacizumab in the first-line treatment of advanced colorectal cancer (1,3-5).

Bevacizumab with Fluoropyrimidines plus Irinotecan

- A phase III RCT compared IFL plus placebo to IFL combined with 5 mg/kg of bevacizumab every two weeks in patients previously untreated for advanced colorectal cancer (1). Patients randomized to IFL combined with bevacizumab had improved median overall survival (OS) (20.3 versus [vs.] 15.6 months; p<0.001), median
progression-free survival (PFS) (10.6 vs. 6.2 months; p<0.001), and overall response rate (RR) (44.8% vs. 34.8%; p=0.004) compared with IFL alone. IFL combined with bevacizumab had comparable toxicity to IFL alone, with an increase in the incidence of grade 3 hypertension (11.0% vs. 2.3%) being the lone exception.

Bevacizumab with Fluoropyrimidines plus Oxaliplatin
- A phase III RCT compared FOLFOX4 to FOLFOX4 plus bevacizumab in the second-line treatment of patients with advanced colorectal cancer (2). FOLFOX4 plus bevacizumab, 10 mg/kg every two weeks, was associated with a statistically significant increase in median OS (12.9 vs. 10.8 months; p=0.0011) and PFS (7.3 vs. 4.7 months; p<0.0001) compared to FOLFOX4 alone. The combination was well tolerated; however, there was a statistically significant increase in grade 3 or 4 toxicity with the combination compared to FOLFOX alone (75% vs. 61%).
- A second phase III RCT randomized untreated patients with advanced CRC to the FOLFOX4 regimen or to a combination of capecitabine and oxaliplatin (XELOX), with a second randomization to bevacizumab or placebo (3). The primary objective of this trial was met, as a statistically significant improvement in PFS was demonstrated with bevacizumab over placebo (median PFS: 9.4 vs. 8.0 months; hazard ratio [HR]=0.83, p=0.0023). OS was prolonged in the bevacizumab arm, but this difference was not statistically significant (median OS: 21.3 vs. 19.9 months; HR=0.89, p=0.0769).

Bevacizumab with Fluoropyrimidines Alone
- Randomized phase II trials have demonstrated that 5FU/FA plus bevacizumab is associated with improved median survival, improved median time to progression (TTP), and improved response rates compared to 5FU/FA alone (4,5). When the addition to 5FU/FA of a 5mg/kg dose of bevacizumab, given every two weeks, was compared with the addition of a 10 mg/kg dose at the same schedule, the lower dose was associated with improved outcome (median OS: 21.5 vs. 16.1 months; median TTP: 9.0 vs. 7.2 months; RR 40% vs. 24%) (4).

Meta-analysis
- Meta-analysis of reported mortality hazard ratios from four RCTs for which sufficient data were available indicated a significant benefit for the addition of bevacizumab to fluoropyrimidine-based chemotherapy compared with chemotherapy alone (HR 0.79; 95% confidence interval 0.69 to 0.90; p=0.0005).

Treatment Options for Advanced Colorectal Cancer

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FUTURE RESEARCH
Future RCTs should examine the clinical benefit of the continued use of bevacizumab in patients with advanced colorectal cancer who progress on that therapy. RCTs examining the efficacy and toxicity of bevacizumab in combination with other newer agents, such as cetuximab, are also eagerly awaited. Clinical trials are also underway examining the efficacy of bevacizumab in combination with 5FU-based chemotherapy in adjuvant therapy for colorectal cancer.

IMPLICATIONS FOR POLICY
The Food and Drug Administration (FDA) in the United States and Health Canada have approved the use of bevacizumab as part of a fluoropyrimidine-based regimen for the treatment of advanced colorectal cancer.

RELATED GUIDELINES
PEBC Practice Guideline Reports:
• #2-15: Oral capecitabine (Xeloda™) in the First-Line Treatment of Metastatic Colorectal Cancer.
• #2-16: Use of Irinotecan in the Treatment of Metastatic Colorectal Carcinoma.
• #2-16b: Use of Irinotecan (Camptosar®, CPT-11) Combined With 5FU & LV as 1st Line Therapy for Metastatic Colorectal Cancer.
• #2-17: Use of Raltitrexed (Tomudex) in the Management of Metastatic Colorectal Carcinoma.
• #2-22: The Role of Oxaliplatin Combined With 5-Fluorouracil and Folinic Acid in the First and Second-Line Treatment of Advanced Colorectal Cancer.

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Contact Information
For further information about this report, please contact Dr. Jim Biagi, Co-Chair, Gastrointestinal Cancer Disease Site Group, Cancer Centre of Southeastern Ontario, Kingston General Hospital, 25 King St W, Kingston, ON, K7L 5P9; TEL 613-544-2630 ext. 4502; FAX 613-546-8209.

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Phone: 905-527-4322 ext. 42822    Fax: 905-526-6775    E-mail: ccopgi@mcmaster.ca
REFERENCES

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INTRODUCTION
Colorectal cancer is the fourth most common cancer site in both sexes combined, representing 13.1% of all new cancer cases in Ontario (1). Currently, the incidence rates of colorectal cancer in Ontario are in a state of transition. In males, incidence rates increased until 1984, levelled off, then declined by an average 1% per year between 1987 and 1996 (2). In females, incidence rates increased until 1979, levelled off, and then declined an average of 1.6% per year between 1982 and 1996 (2). In males, colorectal cancer is the second most common site, representing 13.9% of all new diagnoses, and, in females, colorectal cancer is the third most common site, representing 12.3% of all new cases (1). In Ontario, colorectal cancer is the second leading cause of cancer death in both sexes combined, representing 12.1% of all cancer deaths (1), despite the fact that mortality rates have been declining in both men and women since 1971 (2). For both males and females, colorectal cancer ranks third as the leading cause of death, after breast and lung in females and after lung and
prostate in males (1). For that reason, there is great interest in improving the treatment results for this group of patients.

Currently, the standard first-line treatment for metastatic colorectal cancer in Canada is either a combination of infusional 5-fluorouracil (5FU), folinic acid (FA; also known as leucovorin calcium [LV]), and irinotecan (CPT-11), known as FOLFIRI (3), or a combination of infusional 5-fluorouracil (5FU), folinic acid (FA), and oxaliplatin (L-OHP) or FOLFOX, in the regimen known as FOLFOX4. An alternative to combination FOLFIRI or FOLFOX4 would be sequential monotherapy with a first-line thymidylate synthase inhibitor (such as 5FU/FA or capecitabine [4]) followed by second-line irinotecan or combination therapy (5).

In recent years, considerable attention has been paid to targeted therapies to improve on the therapeutic ratio of cancer pharmaceuticals. Tumour angiogenesis is associated with invasiveness and the metastatic potential of various cancers. Vascular endothelial growth factor (VEGF), the most potent and specific angiogenic factor identified to date, regulates normal and pathologic angiogenesis. The increased expression of VEGF has been correlated with metastasis, recurrence, and poor prognosis in many cancers, including colorectal cancer.

Bevacizumab (Avastin®) is a recombinant humanized monoclonal antibody to VEGF. It has shown inhibition of growth in several tumour types in animal models and was well tolerated in phase I trials (6,7). Phase II clinical trials have suggested activity of this drug in breast, lung, renal and colorectal cancers in the metastatic setting (8).

On the basis of emerging phase III trials involving bevacizumab in the treatment of advanced colorectal cancer, Cancer Care Ontario’s Program in Evidence-based Care (PEBC) Gastrointestinal Cancer Disease Site Group (DSG) considered a systematic review of the evidence and practice guideline to be necessary.

METHODS

This systematic review was developed by the PEBC using the methods of the Practice Guidelines Development Cycle (9). The evidence selection, approval and review was led by two members of the PEBC’s Gastrointestinal Cancer DSG and consensus on the interpretation of the evidence and the draft recommendations were reached by the entire membership. Review and approval of the draft was also established by the PEBC methodologies secretariat.

This systematic review is a convenient and up-to-date source of the best available evidence on the role of bevacizumab (Avastin®) combined with chemotherapy in the treatment of adult patients with advanced colorectal cancer. The body of evidence in this review is primarily comprised of mature randomized controlled trial data. This systematic review forms the basis of a clinical practice guideline developed by the Gastrointestinal Cancer DSG (Section 1 of this evidence-based series). The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

Entries to MEDLINE (1996 to April 2008), EMBASE (1996 to week 19 2008), and Cochrane Library (2008, Issue 1) databases and abstracts and presentations published in the proceedings of the annual meetings of the American Society of Clinical Oncology (ASCO) (2002 through 2007) were systematically searched for evidence relevant to this evidence-based series.

The keywords “bevacizumab” and “avastin” were used in a multi-purpose search (.mp.) and combined with search terms for colorectal cancer in MEDLINE, including the Medical subject headings (MeSH) search terms “colorectal neoplasms”, “colon neoplasms”, and “rectal neoplasms” and associated text words. These results were combined with search terms to identify randomized controlled trials (RCTs) and meta-analyses. Appropriate
modifications were made to the search strategy for use in EMBASE. Relevant articles and abstracts were selected and reviewed by two reviewers and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles. Disagreements regarding study inclusion were resolved by consensus.

The Canadian Medical Association Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) were searched for existing evidence-based practice guidelines.

**Study Selection Criteria**

**Inclusion Criteria**

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of:

1. Randomized controlled trials (RCTs) comparing chemotherapy plus bevacizumab with chemotherapy alone in the treatment of adult patients with advanced colorectal cancer. Overall survival, progression-free survival, and/or response rate had to be reported.
2. Syntheses of evidence in the form of meta-analyses of RCTs meeting the above criteria.

**Exclusion Criteria**

The following were not considered for inclusion in this report:

1. Phase I and single-arm phase II studies.
2. Abstract reports of RCTs presenting preliminary or interim data only.
3. Results of RCTs reported in letters or editorials.
4. Papers published in a language other than English, as translation services were not available.

**Trial Quality Assessment**

Assessment of trial quality was performed by extracting key items from published trial reports, including declaration of funding source, randomization method, patients' baseline characteristics, statistical power, follow-up, and type of analysis (e.g. intention-to-treat (ITT)). As the published trial reports were used to determine quality, this assessment was limited by the detail of the study methods that were reported by the authors.

**Synthesizing the Evidence**

Where possible, the data were pooled to estimate the overall effect on survival of chemotherapy with bevacizumab versus chemotherapy alone. Since hazard ratios (HRs), rather than the number of events at a certain time point, are the preferred statistic for pooling time-to-event outcomes (10), these were extracted directly from the reported trial results. The variances of the HR estimates were calculated from the reported confidence intervals (CI) or log-rank $p$ values where available. A fixed effects model could not be used because the included trials dealt with different treatment regimens and patient groups, violating the necessary assumption of a common treatment effect. Therefore, a random effects model was used for all summary estimates, as it provides the more conservative estimate of effect (11). The study results were pooled using Review Manager 4.2.7 (RevMan Analyses 1.0.2; version date: May 2004; © 2004 the Cochrane Collaboration), which is freely available through the Cochrane Collaboration.

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Statistical heterogeneity was calculated using the $\chi^2$ test for heterogeneity and the $I^2$ percentage. A probability level for the $\chi^2$ statistic less than or equal to 10% (p≤0.10) or an $I^2$ greater than 50% were considered indicative of statistical heterogeneity. Results are expressed as HRs with 95% CI. An HR >1.0 indicates that patients receiving chemotherapy with bevacizumab had a higher probability of experiencing death compared with chemotherapy without bevacizumab; conversely, an HR <1.0 suggests that patients receiving bevacizumab experienced a lower probability of death.

RESULTS

Literature Search Results

Three phase III RCTs (12-14) and two randomized phase II trials (15,16) comparing chemotherapy to chemotherapy plus bevacizumab were included in this review. A third treatment arm of one of the phase III RCTs (12) is published separately from the parent trial (17). A pooled analysis (18) of individual patient data from three RCTs (12,14,15) was also included in this review.

Four of the included trials were of first-line therapy (12,14-16) while one trial included only patients previously treated with irinotecan and a fluoropyrimidine for advanced or metastatic disease (13). Two trials investigated the addition of bevacizumab to 5FU/FA (15,16), two to an oxaliplatin-containing regimen (13,14) and one to an irinotecan-containing regimen (12).

Study Quality and Characteristics

Selected characteristics of included trials, including treatment regimens, are reported in Appendix 1. Four trials were supported by industry grants (12,14-16), whereas one was led by a cooperative group (13). Method of randomization was reported for only three trials and allocation concealment was adequate in all three trials (12,14,16). Patient stratification was by Eastern Cooperative Oncology Group (ECOG) Performance Score (PS), site of primary disease, and number of metastatic sites in two trials (12,16), by ECOG PS and prior radiotherapy in one trial (13), and by region, ECOG PS, liver as a metastatic site, alkaline phosphatase level, and number of metastatic sites in another trial (14). Three of the trials were double-blinded and placebo-controlled with regard to bevacizumab (12,14,16). One trial reported that primary analyses were performed by a blinded independent review committee but blinding of patients was not discussed (15). The fifth trial was open-label (13). Statistical power to detect a significant difference between groups for primary outcomes was reported in four trials (12,13,14,16). One trial allowed patients in the control arm to cross over to receive bevacizumab at disease progression (15); however, all trials used an intention-to-treat analysis approach.

Two of the included reports were on randomized phase II studies (15,16). The results of these studies must be interpreted with caution due to the methodological limitations associated with phase II studies. Both randomized phase II studies included in this review were designed to evaluate the efficacy and safety of bevacizumab with 5FU/FA compared to 5FU/FA alone, using statistical comparisons between groups; however, these studies had relatively small sample sizes, were imbalanced in baseline prognostic characteristics between treatment groups, and were statistically powered to detect only large differences between groups with regard to primary endpoints.

Outcomes

**Randomized Clinical Trials**

**Bevacizumab with 5FU / Irinotecan (IFL)**
A phase III placebo-controlled RCT by Hurwitz et al (12) was designed to investigate the efficacy and tolerability of bevacizumab in combination with the Saltz regimen of bolus 5FU/FA and irinotecan (CPT-11), known as IFL, as first-line treatment of patients with advanced colorectal cancer. 5FU/FA and irinotecan were given weekly for four out of six weeks, and bevacizumab was given every two weeks at a dose of 5 mg/kg. A third treatment arm of 5FU/FA and bevacizumab (without irinotecan) was abandoned after the safety of the addition of bevacizumab to irinotecan was established. Results of this treatment arm are discussed in the ‘5FU / Folinic Acid’ section of this systematic review. Treatment was continued for 36 weeks or until disease progression, whichever occurred first. Patients with cerebral metastases, significant atherosclerotic disease, proteinuria, or a history of coagulopathy were excluded from that study. The primary endpoint was overall survival (OS), whereas progression-free survival (PFS), objective response rate (RR), and duration of response were all secondary endpoints.

A total 815 patients were randomized to receive IFL with bevacizumab (n=403) or IFL with placebo (n=412). Results are summarized in Table 1. Improvements in median survival (20.3 vs. 15.6 months; p<0.001), PFS (10.6 vs. 6.2 months; p<0.001), overall RR (45% vs. 35%; p=0.004), and response duration (10.4 vs. 7.1 months; p=0.0014) were detected with IFL combined with bevacizumab compared with IFL alone.

The combination of IFL and bevacizumab was generally well tolerated; however, an increase in grade 3 or 4 toxicity with IFL combined with bevacizumab (85% vs. 74%) compared to IFL alone was observed. This discrepancy can be attributed to an increase in grade 3 hypertension (10.9% vs. 2.3%), which was treated with oral medications. There was no significant difference in bleeding, thrombosis, or proteinuria between the two arms. Gastrointestinal perforation was a rare complication observed in the IFL plus bevacizumab arm. See Table 2 for a summary of toxicity data.

**Bevacizumab with 5FU or capecitabine / Oxaliplatin (FOLFOX or XELOX)**

Two phase III RCTs were identified that investigated the addition of bevacizumab to an oxaliplatin-containing regimen, one as first-line therapy (14) and one in previously treated patients (13). Results of a previous randomized controlled trial, N9741, demonstrated the superiority of FOLFOX4 (infusional 5FU plus oxaliplatin) over IFL in terms of progression-free and overall survival (19).

A phase III RCT by Giantonio et al was designed to evaluate the efficacy of the addition of bevacizumab to FOLFOX4 as second-line therapy for patients with metastatic colorectal cancer (13). Patients were eligible for the study if they had previously received irinotecan and a fluoropyrimidine for advanced disease. The study investigators chose to use high-dose bevacizumab in the experimental arm at a dose of 10 mg/kg every two weeks. A third trial arm consisted of bevacizumab as a single agent. An independent data-monitoring committee closed this arm early due to inferior efficacy. Treatment was continued until disease progression in patients who tolerated treatment. The primary endpoint was OS, and secondary endpoints included RR, PFS, and toxicity.

A total 820 eligible patients were randomized to receive FOLFOX4 alone (n=291), FOLFOX4 plus bevacizumab (n=286), or bevacizumab alone (n=243). Results of the first two arms are summarized in Table 1. After a median follow-up of 28 months, a statistically significant improvement in overall and progression-free survival has been shown with the addition of bevacizumab to FOLFOX4 (median OS: 12.9 vs. 10.8 months; HR for death = 0.75, p=0.0011; median PFS: 7.3 vs. 4.7 months; HR for progression = 0.61, p<0.0001).

The combination of FOLFOX4 and bevacizumab was generally well tolerated; however, there was more frequent grade 3 or 4 toxicity related to the experimental arm of the trial compared to the control arm (75% vs. 61%; see Table 2). The increase in grade 3 neuropathy
was likely a consequence of longer oxaliplatin exposure in the experimental arm. Thrombosis, hemorrhage, and bowel perforation were rare events, seen primarily in patients receiving bevacizumab.

A second trial by Saltz et al evaluated the addition of bevacizumab to fluoropyrimidines with oxaliplatin (14). The NO16966 trial was initiated as an international open-label, randomized phase III trial with the primary objective of confirming the noninferiority of capecitabine / oxaliplatin (XELOX) versus FOLFOX4. Capecitabine is an oral pro-drug of 5FU, which has a similar efficacy and toxicity profile to infusional 5FU. In 2004, with the regulatory approval of bevacizumab in advanced colorectal cancer, the protocol was amended to include a second randomization to bevacizumab or placebo. The study became double-blinded with regards to the addition of bevacizumab or placebo to the chemotherapy regimens. Fourteen hundred patients were recruited to the amended protocol. The results have been reported both in terms of XELOX vs. FOLFOX (20) and in terms of bevacizumab vs. placebo (14) (Table 1). The primary endpoint for the latter analysis was improvement in PFS with bevacizumab over placebo. Although response rates were similar (47% vs. 49%), there was a statistically significant improvement in PFS favouring bevacizumab over placebo (median PFS: 9.4 vs. 8.0 months; HR=0.83, p=0.0023). Overall survival was prolonged in the bevacizumab arm, but this difference was not statistically significant (median OS: 21.3 vs. 19.9 months; HR=0.89, p=0.0769).

The investigators noted that fewer patients in the bevacizumab arm were treated until progression compared to the placebo arm (14). Thirty percent of patients discontinued treatment due to adverse events in the experimental arm, compared to only 21% in the control arm. The majority of these discontinuations were due to events classically associated with chemotherapy rather than bevacizumab, such as neurotoxicity, gastrointestinal and hematologic events. As with previous bevacizumab trials in colorectal cancer, the incidence of thrombosis, bowel perforation and thrombosis was rare. There was no significant difference in 60-day mortality between the bevacizumab arm and the placebo arm. The relatively modest improvements in PFS and OS associated with bevacizumab may be explained by the inability to continue treatment until progression in the majority of patients and has led to the hypothesis that continuing bevacizumab alone until disease progression may be necessary.

**Bevacizumab with 5FU / Folinic acid alone**

Two randomized phase II trials by Kabbinavar et al have investigated the efficacy and safety of bevacizumab in addition to 5FU/FA versus 5FU/FA alone in patients previously untreated for advanced colorectal cancer (15,16). In both trials, 5FU/FA was given using the Roswell Park regimen (bolus infusions weekly for six of eight weeks), while bevacizumab was given every two weeks. Treatment was continued until disease progression in patients who tolerated treatment.

A total 104 patients were randomized in one trial to receive 5FU/FA combined with 10 mg/kg bevacizumab (n=33), 5FU/FA combined with 5-mg/kg bevacizumab (n=35) or 5FU/FA alone (n=36) (15). Patients in the 5FU/FA arm were allowed to receive bevacizumab alone after disease progression but were analyzed in the group to which they were randomized. The primary endpoints of the trial were time to disease progression (TTP) and tumour RR. Secondary endpoints were OS and duration of response. Results are summarized in Table 1. Compared with 5FU/FA alone, 5FU/FA plus bevacizumab at both dose levels was associated with significant improvements in median TTP (low dose, 9.0 months; high dose, 7.2; control, 5.2; p=0.005 for low-dose arm) and RR (low dose, 40%; high dose, 24%; control 17%; p=0.029 for low-dose arm). There was no significant improvement in median survival (low dose, 21.5 months; high dose, 16.1; control, 13.8); however, this study did not have statistical power to
detect a difference in overall survival between groups. In order to increase power to detect a significant treatment effect, data from both bevacizumab arms were pooled in a retrospective analysis (reported in Table 1). Partial response was seen in two out of 22 patients who crossed over to receive bevacizumab after progression.

Grade 3 or 4 toxicity was seen more frequently in both bevacizumab arms compared to the 5FU/FA arm (low dose, 74%; high dose 78%; control, 54%) (14). Bleeding, hypertension, and thrombosis were observed at greater frequency in the bevacizumab arms in this trial compared to control.

A second randomized, placebo-controlled, phase II trial of 209 patients was designed for patients thought unsuitable for first-line irinotecan (16). The mean age was 71 years in both arms. The primary endpoint was OS and secondary endpoints were PFS, RR, response duration, and quality of life. The trial was designed with 80% power to detect a 39% reduction in hazard of death using a two-tailed log-rank test at the 0.05 level of significance. At disease progression, patients were unblinded to treatment allocation and could receive any second-line treatment, although only patients randomized to the bevacizumab treatment arm could receive bevacizumab as part of second-line therapy. Results for the primary endpoint of OS showed no significant benefit for bevacizumab over control (median 16.6 vs. 12.9 months, HR=0.79, p=0.160); however, a significant improvement in PFS (median 9.2 vs. 5.5 months, hazard ratio [HR] =0.50, p<0.05) was seen for patients receiving 5FU/FA combined with bevacizumab compared to those receiving 5FU/FA with placebo. While RR was higher in patients who received bevacizumab, the difference between groups was marginally non-significant (26% vs. 15%, p=0.055). Although more grade 3 and 4 toxicities were seen in the 5FU/FA/bevacizumab arm (87% vs. 71%), the 60-day mortality was higher in the 5FU/FA alone arm (13.5% vs. 5%). Sixteen percent of the 5FU/FA/bevacizumab group suffered grade 3 hypertension compared to 2.9% of the 5FU/FA–alone group (16). Gastrointestinal perforation occurred in two patients receiving bevacizumab.

In the previously discussed trial by Hurwitz et al (12), a third treatment arm consisting of 5FU/FA /bevacizumab was discontinued after interim safety analysis confirmed the tolerability of irinotecan plus bevacizumab. The median OS and PFS in the third treatment arm (5FU/FA/bevacizumab) were 18.3 months and 8.8 months, respectively. The overall RR of the combination of 5FU/FA and bevacizumab in that trial was 39% (17). Analysis of that cohort suggests comparable efficacy to IFL.
Table 1. Randomized trials of bevacizumab in advanced colorectal cancer.

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Treatment allocation</th>
<th>Evaluable patients</th>
<th>Median survival (months)</th>
<th>1-year survival (%)</th>
<th>HR for death</th>
<th>Median PFS (months)</th>
<th>HR for progression</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bevacizumab with fluoropyrimidines plus irinotecan</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hurwitz (12,17)</td>
<td>IFL/placebo</td>
<td>411</td>
<td>15.6</td>
<td>63.4</td>
<td>0.66, p&lt;0.001</td>
<td>6.2</td>
<td>0.54, p&lt;0.001</td>
<td>34.8</td>
</tr>
<tr>
<td></td>
<td>IFL/BV</td>
<td>402</td>
<td>20.3</td>
<td>74.3</td>
<td></td>
<td>10.6</td>
<td></td>
<td>44.8</td>
</tr>
<tr>
<td></td>
<td>5FU/FA/BV</td>
<td>110</td>
<td>18.3</td>
<td>68</td>
<td></td>
<td>8.8</td>
<td></td>
<td>p=0.004</td>
</tr>
<tr>
<td><strong>Bevacizumab with fluoropyrimidines plus oxaliplatin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giantonio (13) (2nd-line)</td>
<td>FOLFOX4</td>
<td>291</td>
<td>10.8</td>
<td>43</td>
<td>4.7</td>
<td>7.3</td>
<td>0.61, p&lt;0.0001</td>
<td>8.6</td>
</tr>
<tr>
<td></td>
<td>FOLFOX4/BV</td>
<td>286</td>
<td>12.9</td>
<td>56</td>
<td>0.75, p=0.0011</td>
<td>7.3</td>
<td>0.61, p&lt;0.001</td>
<td>22.7</td>
</tr>
<tr>
<td></td>
<td>BV</td>
<td>243</td>
<td>10.2</td>
<td>44</td>
<td></td>
<td>2.7</td>
<td></td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Saltz (14)</td>
<td>XELOX/FOLFOX4/placebo</td>
<td>701</td>
<td>19.9</td>
<td>72</td>
<td>0.89 (95% CI 0.76-1.03), p=0.0769</td>
<td>8.0</td>
<td>0.83 (95% CI 0.72-0.95), p=0.0023</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>XELOX/FOLFOX4/BV</td>
<td>699</td>
<td>21.3</td>
<td>79</td>
<td></td>
<td>9.4</td>
<td></td>
<td>47</td>
</tr>
<tr>
<td><strong>Bevacizumab with fluoropyrimidines alone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kabbinavar (15)</td>
<td>5FU/FA</td>
<td>36</td>
<td>13.8</td>
<td></td>
<td></td>
<td>5.2</td>
<td></td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>5FU/FA/BV (5mg/kg)</td>
<td>35</td>
<td>21.5</td>
<td>NR</td>
<td>0.63</td>
<td>9.0</td>
<td>0.46, p=0.005</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>5FU/FA/BV (10mg/kg)</td>
<td>33</td>
<td>16.1</td>
<td>1.17</td>
<td></td>
<td>7.2</td>
<td>0.66, p=0.217</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>5FU/FA/BV (pooled)</td>
<td>68</td>
<td>18.0</td>
<td>0.86</td>
<td></td>
<td>7.4</td>
<td>0.54, p=0.013</td>
<td>32</td>
</tr>
<tr>
<td>Kabbinavar (16)</td>
<td>5FU/FA/placebo</td>
<td>105</td>
<td>12.9</td>
<td>53</td>
<td></td>
<td>5.5</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>5FU/FA/BV</td>
<td>104</td>
<td>16.6</td>
<td>63</td>
<td>0.79 (95% CI 0.56-1.10), p=0.159</td>
<td>9.2</td>
<td>0.50 (95% CI 0.34-0.73)</td>
<td>26</td>
</tr>
</tbody>
</table>

Notes: PFS, progression-free survival; ORR, objective response rate; 5FU, 5-fluorouracil; BV, bevacizumab; FA, folinic acid; FOLFOX4, infusional 5FU, bolus FA, oxaliplatin; IFL, bolus 5-FU/FA/CPT-11; NR, not reported; CI, confidence interval.

a Estimated from Kaplan-Meier survival curves.
Table 2. Adverse events reported in randomized trials of bevacizumab in advanced colorectal cancer.

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Hurwitz (12)</th>
<th>Giatonio (13)</th>
<th>Saltz (14)b</th>
<th>Kabbinavar (15)b</th>
<th>Kabbinavar (16)a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IFL (n=397)</td>
<td>IFL+BV (n=393)</td>
<td>FOLFOX4 (n=287)</td>
<td>FOLFOX4 +BV (n=285)</td>
<td>FOLFOX / XELOX (n=675)</td>
</tr>
<tr>
<td>All grade III/IV toxicity</td>
<td>74</td>
<td>85^a</td>
<td>61</td>
<td>75^a</td>
<td>75</td>
</tr>
<tr>
<td>60-day all-cause mortality</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Leukopenia Grade III/IV</td>
<td>31</td>
<td>37</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea Grade III/IV</td>
<td>25</td>
<td>32</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neuropathy Grade III/IV</td>
<td>-</td>
<td>-</td>
<td>9</td>
<td>16^a</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension Grade III/IV</td>
<td>8</td>
<td>22^a</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thrombosis Grade III/IV</td>
<td>16</td>
<td>19</td>
<td>-</td>
<td>-</td>
<td>2.5</td>
</tr>
<tr>
<td>Hemorrhage Grade III/IV</td>
<td>-</td>
<td>-</td>
<td>2.5</td>
<td>3</td>
<td>1^c</td>
</tr>
<tr>
<td>Proteinuria Grade III/IV</td>
<td>3</td>
<td>3</td>
<td>&lt;1</td>
<td>3^a</td>
<td>1</td>
</tr>
<tr>
<td>GI perforation Grade III</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Notes: 5FU, 5-fluorouracil; FA, folinic acid; IFL, bolus 5FU/FA + irinotecan; FOLFOX4, infusional 5FU, bolus FA + oxaliplatin; BV, bevacizumab; XELOX, capecitabine and oxaliplatin.

^a Data is statistically significant (p<0.05) compared to control group.

^b Description of statistical significance not published.

^c Data for arterial thrombosis. Venous thrombosis was 8% in the bevacizumab group compared with 5% in the control group.
Meta-analyses

Kabbinavar et al (18) published a pooled analysis of individual patient data from the three RCTs investigating the addition of bevacizumab to 5FU/FA compared to 5FU/FA-based chemotherapy alone. For the Hurwitz trial (12), patients who received IFL plus placebo were included in the chemotherapy-alone control group, whereas the two bevacizumab-containing arms were included in the experimental arm. The pooled analysis indicated a significant benefit in median survival (17.9 vs. 14.6 months), mortality HR (0.742 [95% CI, 0.59 to 0.93]), median PFS (8.77 vs. 5.55 months), progression HR (0.63 [95% CI, 0.5 to 0.78]), and objective response rate (34.1% vs. 24.5%, p=0.019), for patients who received 5FU/FA-based chemotherapy plus bevacizumab compared to patients who received 5FU/FA-based therapy alone.

The Gastrointestinal Cancer DSG performed its own meta-analysis of four RCTs that reported mortality HRs and sufficient data to calculate variance estimates (12-14,16). Insufficient data were reported in the publication of the smaller randomized phase II trial by Kabbinavar et al to be included in the meta-analysis (15). Pooled results from the four trials indicated a significant reduction in mortality for patients receiving bevacizumab, with an overall HR of 0.79 (95%CI; 0.69 to 0.90; p=0.0005) compared with patients who received fluoropyrimidine-based chemotherapy alone (Figure 1). No significant statistical heterogeneity was detected between studies (p=0.14). A sensitivity analysis of only the first-line therapy trials (12,14,16) demonstrated a similar benefit for the addition of bevacizumab to chemotherapy, with a mortality HR of 0.79 (95%CI, 0.65 to 0.96; p=0.02).

Figure 1. Mortality hazard ratios in randomized trials of chemotherapy plus bevacizumab versus chemotherapy alone in patients with advanced colorectal cancer.

### DISCUSSION

Two phase III RCTs have demonstrated improved survival in patients with advanced colorectal cancer when bevacizumab was added to standard 5FU-based chemotherapy regimens, which incorporate IFL and oxaliplatin (FOLFOX4) (12,13). A third RCT involving two oxaliplatin-based regimens did not demonstrate improved survival with the addition of bevacizumab; however, progression-free survival was significantly improved in the bevacizumab-containing arms of all three studies (14). Survival and response rates were similarly improved in randomized phase II trials comparing 5FU/FA combined with bevacizumab to 5FU/FA alone in advanced colorectal cancer (15,16). A meta-analysis of mortality hazard ratios reported in four of the RCTs demonstrated a significant survival benefit for patients receiving bevacizumab. Survival benefit has been shown when
bevacizumab is added to 5FU regimens given by bolus injection (IFL) and by continuous infusion (FOLFOX). Bevacizumab in combination with 5FU-based chemotherapy has been shown to be effective in both first- and second-line treatment of advanced colorectal cancer.

Despite the fact that bevacizumab has not been shown to add benefit to all available 5FU-based combination therapies in an RCT (e.g., FOLFIRI), it is reasonable to believe that bevacizumab in combination with any fluoropyrimidine-based chemotherapy is more effective than any fluoropyrimidine-based chemotherapy alone. This conclusion is supported by two large observational registry trials in first-line metastatic colorectal cancer - the BRiTE trial in the United States (21) and the First B.E.A.Trial conducted in Europe and Canada (22). These trials were designed to evaluate safety events of bevacizumab used in combination with a variety of chemotherapy regimens in a broad community-based population of patients with metastatic colorectal cancer. Nearly 4000 patients have been enrolled in these two studies to date. Although preliminary, data from these observational studies suggest that bevacizumab in combination with a variety of fluoropyrimidine-based chemotherapy regimens is safe, with efficacy similar to that seen in the pivotal trial by Hurwitz et al (12).

The FDA and other regulatory agencies approved bevacizumab in 2004, leading to sequential studies where the first cohort compared two or more chemotherapy regimens without bevacizumab and the second cohort evaluated the same regimens with bevacizumab. Although patients were not randomized to receive bevacizumab or not, three sets of sequential randomized trials provide supporting evidence for the safety and efficacy of the use of bevacizumab with a variety of chemotherapy regimens in the treatment of advanced colorectal cancer (23-26) (See Appendix 2). Historical comparisons between the Bowel Oncology with Cetuximab Antibody (BOND) trial (23) (cetuximab plus irinotecan compared with cetuximab alone in irinotecan-refractory patients) and the BOND-2 trial (24), which added bevacizumab to both arms, suggested improved RR and TTP with the addition of bevacizumab both to cetuximab alone and the combination of cetuximab and irinotecan. The TREE-1 study randomized patients to receive oxaliplatin with infusional 5FU (FOLFOX), bolus 5FU (bFOL), or oral 5FU (CapeOx), and the TREE-2 study added bevacizumab to all three study arms (25). The addition of bevacizumab in the TREE-2 study caused more grade 3/4 hypertension, wound healing and bowel perforation in each arm; however, there appeared to be significant improvements in RR, TTP, and OS for all three treatment arms. Similarly, historical comparison of two cohorts of the BICC-C trial suggested that all measures of efficacy were improved with the addition of bevacizumab to both modified IFL and FOLFIRI (26).

Although the meta-analysis of available comparisons of chemotherapy versus chemotherapy with bevacizumab suggests a survival advantage with the addition of bevacizumab, the magnitude of benefit is not consistent across trials. The magnitude of incremental benefit with bevacizumab may change based on the cytotoxic chemotherapeutic regimen it is partnered with. There is insufficient evidence at present to recommend which chemotherapy regimen is optimal in combination with bevacizumab.

There is no evidence to support the use of bevacizumab as monotherapy in advanced colorectal cancer. In addition, the combination of 5FU and bevacizumab failed to show significant efficacy in patients with advanced colorectal cancer that progressed on both irinotecan-containing and oxaliplatin-containing regimens (27). Thus, bevacizumab should not be seen as an alternative in the third-line setting of systemic treatment of advanced colorectal cancer.

All patients in the aforementioned clinical trials were bevacizumab-naïve at the start of the trial. There is no available evidence to answer the question of whether bevacizumab, when used as a part of first-line therapy, should be continued upon progression as part of a second-line regimen. Further randomized clinical trials are required to answer this question.
Dosing and Toxicity

Bevacizumab has a demonstrated efficacy in combination with 5FU-based chemotherapy at a dose of 5 mg/kg and 10 mg/kg given intravenously every two weeks. The regimens used in clinical trials are summarized in Appendix 1. The only comparison of the two doses available in the literature demonstrated an advantage to the 5-mg/kg dose. Thus, a reasonable conclusion is that the most effective dose of bevacizumab is 5 mg/kg given intravenously every two weeks. The higher dose of bevacizumab (10 mg/kg q2w) was used in combination with FOLFOX in the phase III trial described previously. The protocol did allow for reduction of dose down to 5 mg/kg for toxicity deemed related to bevacizumab. Over one-half of patients (55.8%) had such a reduction in bevacizumab. Dose reduction of bevacizumab did not impact on PFS or OS (28), suggesting that the lower dose is at least as effective as the higher dose, when used in combination with FOLFOX.

Due to concerns for hypersensitivity, bevacizumab has been administered by a slow infusion in clinical trials to date. The initial infusion should be a 90-minute infusion, with a second infusion reduced to 60 minutes if tolerated, and subsequent infusions reduced further to 30 minutes if tolerated. Investigators at Memorial Sloan Kettering Cancer Centre have experimented with an infusion rate of 0.5 mg/kg/minute (i.e. 10 minutes for the 5 mg/ kg dosage) with reported success (29). Until further information becomes available, the recommended infusion time of bevacizumab, if tolerated, is initially 90 minutes, 60 minutes for a second dose, and 30 minutes for all subsequent dosing.

Commonly observed adverse effects in clinical trials with bevacizumab included bleeding, thrombosis, hypertension, and proteinuria. Hypertension seen in clinical trials has been manageable with oral anti-hypertensives; however, frequent monitoring of blood pressure is necessary. Reported and ongoing phase III trials have excluded patients with cerebral metastases, advanced atherosclerotic disease, or proteinuria; thus, those conditions should be considered contraindications to the use of bevacizumab. Gastrointestinal perforation and poor wound healing are consistently seen in association with bevacizumab across clinical trials; however, their incidence is rare (30).

In September 2006, Genentech and the FDA released a warning that bevacizumab can result in rare instances of reversible posterior leukoencephalopathy syndrome (RPLS) (incidence <0.1%) and nasal septum perforation.

A minority of patients with advanced or metastatic colorectal cancer present with resectable metastatic disease, which can be treated with curative intent by a multimodality approach. The safety of bevacizumab in perioperative chemotherapy has been questioned, due to concerns of impaired wound healing and liver regeneration. Data on the safety of bevacizumab in this setting are limited to evidence from the observational registry trials (21,22), and a phase II study, reported recently by European investigators. In this study, 54 patients were treated with XELOX/bevacizumab for 5 cycles prior to resection of their hepatic metastases, followed by a sixth cycle with XELOX alone (31). The overall response rate to the neoadjuvant chemotherapy was high, 74%, and this included 11% of patients who had a pathological complete response. Potentially curative surgery was performed in 91% of the cohort. Long-term follow-up is necessary to determine any detriment to liver function associated with the neoadjuvant chemotherapy which included bevacizumab. Available evidence suggests the feasibility of using bevacizumab in preoperative chemotherapy prior to liver resection, however, further studies have been planned to answer this question more definitively. If bevacizumab is to be used as part of preoperative chemotherapy prior to resection of metastases, the Gastrointestinal Cancer DSG recommends that bevacizumab be held for at least five weeks preoperatively, although results from further prospective studies may alter this recommendation.
Future Research
Future RCTs should examine the clinical benefit of the continued use of bevacizumab in patients with advanced colorectal cancer who progress on that therapy. Additional randomized controlled trials examining the efficacy and toxicity of bevacizumab in combination with other newer agents, such as capecitabine, cetuximab and panitumumab, are also eagerly awaited. Clinical trials are also underway examining the efficacy of bevacizumab in combination with 5FU-based chemotherapy in adjuvant therapy for colorectal cancer.

ONGOING TRIALS
The National Cancer Institute (NCI) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/), the 2002 through 2007 conference proceedings of ASCO were searched for reports of new or ongoing trials in May 2008. See Appendix 3 for a summary table of relevant trials.

CONCLUSIONS
For patients with advanced colorectal cancer receiving fluoropyrimidine-based chemotherapy as first-line therapy, the addition of bevacizumab is recommended to improve overall survival. The addition of bevacizumab to fluoropyrimidine-based chemotherapy is also recommended for patients with advanced colorectal cancer receiving second-line therapy if they did not receive bevacizumab as part of their initial treatment.

Data from available randomized clinical trials have demonstrated a survival benefit with the addition of bevacizumab to several fluoropyrimidine-based regimens, including regimens of 5FU/FA, 5FU with irinotecan (IFL), 5FU with oxaliplatin (FOLFOX4) and capecitabine with oxaliplatin (XELOX). Regimens using 5FU given by bolus, infusional and oral means have been represented in those studies. Survival benefit has been shown with the addition of bevacizumab to both first- and second-line chemotherapy. It is reasonable to conclude that bevacizumab in combination with any fluoropyrimidine-based chemotherapy is more effective than that fluoropyrimidine-based chemotherapy alone.

The role of continuing bevacizumab after disease progression on a bevacizumab-containing regimen is not clear due to the absence of evidence. Therefore, the continuation of bevacizumab in patients who have progressed on that therapy cannot currently be recommended outside of clinical trials.

Bevacizumab should not be administered to patients with cerebral metastases, uncontrollable hypertension, severe proteinuria, advanced atherosclerotic disease, bleeding diatheses, or to those with non-healing wounds or recent surgery or trauma (i.e. within the previous 28 days). These patients were excluded from enrolment in clinical trials using bevacizumab.

CONFLICT OF INTEREST
Authors of this evidence-based series were polled for conflicts of interest. No conflicts were declared.

JOURNAL REFERENCE
The following systematic review based on this guideline has been published in the Annals of Oncology (http://annonc.oxfordjournals.org) by Oxford University Press on behalf of the European Society for Medical Oncology:

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For a complete list of the Gastrointestinal Cancer Disease Site Group members, please visit the CCO Web site at: http://www.cancercare.on.ca

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Contact Information
For further information about this report, please contact Dr. Jim Biagi, Co-Chair, Gastrointestinal Cancer Disease Site Group, Cancer Centre of Southeastern Ontario, Kingston General Hospital, 25 King St W, Kingston, ON, K7L 5P9; TEL 613-544-2630 ext. 4502; FAX 613-546-8209.

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca
REFERENCES


### Appendix 1. Selected characteristics of included randomized controlled trials.

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Treatment allocation</th>
<th>Treatment Dose and schedule</th>
<th>Selected Patient Inclusion Criteria</th>
<th>Statistical Power</th>
<th>Follow-up</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hurwitz (12,17)</td>
<td>IFI/placebo</td>
<td>IFI/BV</td>
<td>Histologically confirmed mCRC Age ≥18 ECOG PS 0 or 1 Life expectancy &gt;3 months No prior CT or biologic therapy for metastatic disease</td>
<td>80% power to detect HR of 0.75 for death with 385 deaths, two-sided p values, α=0.05, one interim analysis of efficacy</td>
<td>NR</td>
<td>50% of pts received 2nd-line therapy. 25% of patients received oxaliplatin. Only pts randomized to a BV arm could receive BV as 2nd-line therapy.</td>
</tr>
<tr>
<td></td>
<td>5FU/FA/BV</td>
<td>5FU: 500 mg/m², IV bolus, FA: 20 mg/m², IV over 2 hrs, Irinotecan: 125 mg/m², given first 4 wks of 6-wk cycle. BV: 5 mg/kg IV every 2 wks. 5FU: 500 mg/m², FA: 500 mg/m², given first 6 wks of 8-wk cycle. BV: as above.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Giantonio (13)</td>
<td>FOLFOX4</td>
<td>FOLFOX4/BV</td>
<td>Prior CT with irinotecan and a fluoropyrimidine required Histologically confirmed advanced or mCRC</td>
<td>95% power to detect 50% difference in overall survival with 13 months follow-up</td>
<td>Median 28 months</td>
<td>Open label trial.</td>
</tr>
<tr>
<td></td>
<td>5FU: 400 mg/m² IV bolus, then 600 mg/m² by 22 hr infusion, days 1 and 2, FA: 200 mg/m² IV over 2hrs, days 1 and 2, Oxaliplatin: 85 mg/m² IV, day 1, BV: 10 mg/kg IV, day 1, All agents given every 2 wks.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Saltz (14)</td>
<td>XELOX/FOLFOX4 + placebo</td>
<td>XELOX/FOLFOX4 + BV</td>
<td>Histologically confirmed mCRC Age ≥18 ECOG PS 0 or 1 No prior systemic therapy for advanced or mCRC No prior oxaliplatin or bevacizumab</td>
<td>NR</td>
<td>Median 28 months</td>
<td>29% of pts in BV arm and 47% of pts in the placebo arm continued treatment until progression.</td>
</tr>
<tr>
<td></td>
<td>FOLFOX: 5FU: 400 mg/m² IV bolus, then 600 mg/m² by 22 hr infusion, days 1 and 2, FA: 200 mg/m² IV over 2hrs, days 1 and 2, Oxaliplatin: 85 mg/m² IV, day 1, BV: 5 mg/kg IV, day 1, All agents given every 2 wks. XELOX: Capecitabine: 1000 mg/m² orally, twice daily, days 1-14, Oxaliplatin: 130 mg/m² IV day 1, BV: 7.5 mg/kg IV day 1, All agents given every 3 wks.</td>
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</tr>
<tr>
<td>Kabbnavar (15)</td>
<td>5FU/FA</td>
<td>5FU/FA/BV (5mg/kg)</td>
<td>Histologically confirmed mCRC with metastases &gt;1cm² Age ≥18 ECOG PS 0 or 1 Life expectancy &gt;3 months</td>
<td>NR</td>
<td>NR</td>
<td>Imbalance in men, ECOG PS, pts with liver/lung metastases, low serum albumin at baseline. 61% of pts in the control arm received single-agent BV (10mg/kg) as crossover therapy.</td>
</tr>
<tr>
<td></td>
<td>5FU/FA/BV (10mg/kg)</td>
<td>5FU: 500 mg/m², IV bolus, FA: 500 mg/m² IV over 2 hrs, given first 6 wks of 8-wk cycle. BV: 5 or 10 mg/kg IV, given every 2 wks.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author (reference)</td>
<td>Treatment allocation</td>
<td>Treatment Dose and schedule</td>
<td>Selected Patient Inclusion Criteria</td>
<td>Statistical Power</td>
<td>Follow-up</td>
<td>Comments</td>
</tr>
<tr>
<td>-------------------</td>
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<td>----------</td>
</tr>
<tr>
<td>Kabbinavar (16)</td>
<td>5FU/FA/placebo</td>
<td>5FU: 500 mg/m², IV bolus,</td>
<td>Histologically confirmed mCRC</td>
<td>80% power to</td>
<td>NR</td>
<td>Approximately 50% of pts in each arm received subsequent therapies following assigned therapy Only pts in BV arm could receive BV as a component of 2nd-line treatment</td>
</tr>
<tr>
<td></td>
<td>5FU/FA/BV</td>
<td>FA: 500 mg/m² IV over 2 hrs, given first 6 wks of 8-wk cycle. BV: 5 mg/kg IV every 2 wks.</td>
<td>Not optimal candidates for 1st-line irinotecan-containing therapy One of the following characteristics: age ≥65, ECOG PS 1 or 2, serum albumin ≤ 3.5 g/dL, or prior RT to abdomen or pelvis</td>
<td>detect HR of 0.61 for death with 133 deaths, two-sided p values, α=0.05, two interim analyses</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: 5FU, 5-fluorouracil; BV, bevacizumab; FA, folinic acid; FOLFOX4, infusional 5FU, bolus FA, oxaliplatin; IFL, bolus 5-FU/FA/irinotecan; NR, not reported; ITT, intention-to-treat; wk, weeks; mCRC, metastatic colorectal cancer; CT, chemotherapy; pts, patients; IV, intravenous; HR, hazard ratio; RT, radiotherapy.  

a Recruitment to 5FU/FA/BV arm terminated at interim safety analysis after IFL/BV was determined to be safe.  
b Recruitment to BV arm terminated at interim efficacy analysis after survival determined to be inferior.
Appendix 2. Sequential randomized trials where bevacizumab has been added to all arms of the second cohort.

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Treatment allocation</th>
<th>Evaluable patients</th>
<th>Median survival (months)</th>
<th>Median time to progression (months)</th>
<th>Tumour response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunningham</td>
<td>Cetux + Irino</td>
<td>218</td>
<td>8.6</td>
<td>4.1</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Cetux</td>
<td>111</td>
<td>6.9</td>
<td>1.5</td>
<td>11</td>
</tr>
<tr>
<td>Saltz (20)</td>
<td>Cetux + Irino + BV</td>
<td>43</td>
<td>14.5</td>
<td>7.3</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Cetux + BV</td>
<td>40</td>
<td>11.4</td>
<td>4.9</td>
<td>20</td>
</tr>
<tr>
<td>Hochster</td>
<td>FOLFOX</td>
<td>49</td>
<td>19&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8.7</td>
<td>43</td>
</tr>
<tr>
<td>TREE-1 (21)</td>
<td>bFOL</td>
<td>50</td>
<td>18</td>
<td>6.9</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>CapeOx</td>
<td>48</td>
<td>17</td>
<td>5.9</td>
<td>35</td>
</tr>
<tr>
<td>Hochster</td>
<td>FOLFOX + BV</td>
<td>71</td>
<td>26&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9.9</td>
<td>53</td>
</tr>
<tr>
<td>TREE-2 (21)</td>
<td>bFOL + BV</td>
<td>70</td>
<td>21</td>
<td>8.3</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>CapeOx + BV</td>
<td>72</td>
<td>27</td>
<td>10.3</td>
<td>48</td>
</tr>
<tr>
<td>Fuchs</td>
<td>FOLFIRI</td>
<td>144</td>
<td>23.1</td>
<td>7.6</td>
<td>47</td>
</tr>
<tr>
<td>BICC-C P1 (22)</td>
<td>mIFL</td>
<td>141</td>
<td>17.6</td>
<td>5.9</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>CapeIri</td>
<td>145</td>
<td>18.9</td>
<td>5.8</td>
<td>39</td>
</tr>
<tr>
<td>Fuchs</td>
<td>FOLFIRI + BV</td>
<td>57</td>
<td>28.0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>11.2</td>
<td>58</td>
</tr>
<tr>
<td>BICC-C P2 (22)</td>
<td>mIFL + BV</td>
<td>60</td>
<td>19.2</td>
<td>8.3</td>
<td>53</td>
</tr>
</tbody>
</table>

Notes: Cetux, cetuximab; Irino, irinotecan; BV, bevacizumab; FOLFOX, infusional 5FU + oxaliplatin; bFOL, bolus5FU + oxaliplatin; CapeOx, capecitabine + oxaliplatin; FOLFIRI, infusional 5FU + irinotecan; mIFL, modified bolus 5FU + irinotecan; CapeIri, capecitabine + irinotecan; NR, not reported (not yet reached).

<sup>a</sup> Median overall survival for all three arms combined was 18.2 months in TREE-1 and 24.4 months in TREE-2.
<sup>b</sup> Median survival for FOLFIRI plus bevacizumab arm reported in updated results published in a letter to the editor (32).
Appendix 3. Ongoing trials.

<table>
<thead>
<tr>
<th>Description</th>
<th>Protocol ID</th>
<th>Last date modified</th>
<th>Trial type</th>
<th>Accrual</th>
<th>Primary outcome</th>
<th>Sponsorship</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III randomized study of cetuximab and/or bevacizumab in combination</td>
<td>CALGB/SWOG C80405, NCT00265850</td>
<td>May 28, 2008</td>
<td>Phase III, randomized, open-label,</td>
<td>Expected enrolment 2,300</td>
<td>Overall survival</td>
<td>NCI</td>
<td>Accruing</td>
</tr>
<tr>
<td>with either oxaliplatin, fluorouracil, and leucovorin calcium (FOLFOX) or</td>
<td></td>
<td></td>
<td>multicentre</td>
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<tr>
<td>irinotecan hydrochloride, fluorouracil, and leucovorin calcium (FOLFIRI)</td>
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<td>in patients with previously untreated metastatic adenocarcinoma of the colon</td>
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<tr>
<td>or rectum.</td>
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</tr>
<tr>
<td>Phase III randomized study of irinotecan hydrochloride-based chemotherapy</td>
<td>SWOG/CALGB/ECOG/CAN-NCIC/NCCTG/</td>
<td>May 28, 2008</td>
<td>Phase III, randomized, multicentre</td>
<td>Expected enrolment 1,260</td>
<td>Overall survival</td>
<td>NCI</td>
<td>Accruing</td>
</tr>
<tr>
<td>and cetuximab with versus without bevacizumab in patients with metastatic</td>
<td>S-0600, NCT00499369</td>
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<tr>
<td>colorectal cancer that progressed on first-line therapy.</td>
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<tr>
<td>Maintenance treatment versus observation after induction in advanced</td>
<td>NCT00442637, CAIRO3</td>
<td>February 28, 2007</td>
<td>Phase III, randomized, open-label</td>
<td>Expected enrolment 635</td>
<td>Progression-free survival after re-introduction of MTD chemotherapy and bevacizumab</td>
<td>Dutch Colorectal Cancer Group, Koningin Wilhelmina Fonds (Dutch Cancer Fund), Sanofi-Aventis, Hoffmann-La Roche</td>
<td>Accruing</td>
</tr>
<tr>
<td>colorectal carcinoma.</td>
<td></td>
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<tr>
<td>Randomized, multicentre, phase III study, to evaluate the efficacy and</td>
<td>TTD-05-02, MACRO, NCT00335595</td>
<td>May 4, 2007</td>
<td>Phase III, randomized, multicentre,</td>
<td>Expected enrolment 470</td>
<td>Free time to disease progression</td>
<td>Spanish Cooperative Group for Gastrointestinal Tumour Therapy, Sanofi-Aventis, Hoffmann-La Roche</td>
<td>Accruing</td>
</tr>
<tr>
<td>safety of bevacizumab alone or combined with capecitabine and oxaliplatin</td>
<td></td>
<td></td>
<td>open-label</td>
<td></td>
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<tr>
<td>as support therapy after initial chemotherapy treatment with capecitabine,</td>
<td></td>
<td></td>
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<tr>
<td>oxaliplatin, and bevacizumab in metastatic colorectal cancer patients.</td>
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<tr>
<td>Phase III study of capecitabine with versus without bevacizumab in elderly patients with metastatic colorectal cancer.</td>
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<tr>
<td><strong>Protocol ID:</strong></td>
<td>MO19286, NCT00484939</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Last date modified:</strong></td>
<td>May 16, 2008</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Trial type:</strong></td>
<td>Phase III, randomized, open-label, multicentre</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Accrual:</strong></td>
<td>Expected enrolment not reported</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Primary outcome:</strong></td>
<td>Progression-free survival</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Sponsorship:</strong></td>
<td>Hoffman-La Roche</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Status:</strong></td>
<td>Accruing</td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase II randomized study of neoadjuvant and adjuvant cetuximab, leucovorin calcium, oxaliplatin, and fluorouracil with versus without bevacizumab in patients with resectable liver metastases secondary to colorectal cancer.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protocol ID:</strong></td>
</tr>
<tr>
<td><strong>Last date modified:</strong></td>
</tr>
<tr>
<td><strong>Trial type:</strong></td>
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<tr>
<td><strong>Accrual:</strong></td>
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<tr>
<td><strong>Primary outcome:</strong></td>
</tr>
<tr>
<td><strong>Sponsorship:</strong></td>
</tr>
<tr>
<td><strong>Status:</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q2W FOLFIRI regimen plus panitumumab or a Q2W FOLFIRI regimen plus bevacizumab for 2nd-line mCRC.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protocol ID:</strong></td>
</tr>
<tr>
<td><strong>Last date modified:</strong></td>
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<tr>
<td><strong>Trial type:</strong></td>
</tr>
<tr>
<td><strong>Accrual:</strong></td>
</tr>
<tr>
<td><strong>Primary outcome:</strong></td>
</tr>
<tr>
<td><strong>Sponsorship:</strong></td>
</tr>
<tr>
<td><strong>Status:</strong></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>FOLFIRI plus cetuximab versus bevacizumab in first line treatment CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Protocol ID:</strong></td>
</tr>
<tr>
<td><strong>Last date modified:</strong></td>
</tr>
<tr>
<td><strong>Trial type:</strong></td>
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<tr>
<td><strong>Accrual:</strong></td>
</tr>
<tr>
<td><strong>Primary outcome:</strong></td>
</tr>
<tr>
<td><strong>Sponsorship:</strong></td>
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<tr>
<td><strong>Status:</strong></td>
</tr>
</tbody>
</table>
The Role of Bevacizumab (Avastin®) Combined With Chemotherapy in the Treatment of Patients With Advanced Colorectal Cancer: EBS Development Methods and External Review Process

S. Welch, W. Kocha, R.B. Rumble, K. Spithoff, J. Maroun, and the Gastrointestinal Cancer Disease Site Group

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Developed by the Gastrointestinal Cancer Disease Site Group

Original Report Date: December 12, 2005
Current Report Date: May 28, 2008

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based clinical practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our Groups and Panels, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic
review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.
The Evidence-based Series:
Each Evidence-based Series is comprised of three sections.

- **Section 1: Guideline Recommendations.** Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.

- **Section 2: Evidentiary Base.** Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.

- **Section 3: EBS Development Methods and External Review Process.** Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review
This evidence-based series was developed by the Gastrointestinal Cancer DSG of CCO’s PEBC. The series is a convenient and up-to-date source of the best available evidence on the role of bevacizumab (Avastin®) combined with chemotherapy in the treatment of adult patients with advanced colorectal cancer, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Evidence was selected and reviewed by members of the PEBC’s Gastrointestinal Cancer DSG and methodologists. This evidence-based series has been reviewed and approved by the Gastrointestinal Cancer DSG, which is comprised of medical, radiation, and surgical oncologists, a gastroenterologist, and two patient representatives.

Disease Site Group Consensus Process
The role for bevacizumab in the management of advanced colorectal cancer was considered by the Gastrointestinal Cancer DSG. Data from randomized clinical trials involving patients with advanced colorectal cancer have consistently shown a survival advantage to the addition of bevacizumab to standard 5FU based chemotherapy. For many centres in Canada, the combination of infusional 5FU with irinotecan (FOLFIRI) represents the standard first-line therapy. A clinical trial of FOLFIRI with or without bevacizumab has not been performed to date. The consensus of the DSG members was that the available data supports a recommendation to extrapolate the benefit of bevacizumab when added to any 5FU-based chemotherapy. This recommendation did not extend to capecitabine, as there are no published or presented trials to provide information regarding the optimal dose of this agent when combined with bevacizumab.

None of the patients included in these randomized clinical trials had received treatment with bevacizumab prior to study entry. The DSG members agreed that a recommendation could not be made regarding the continuation of bevacizumab in second-line therapy after progression on first-line therapy containing bevacizumab. The Gastrointestinal DSG will continue to update this guideline in the future, as necessary, should results of ongoing clinical trials involving bevacizumab in the treatment of advanced colorectal cancer yield new information.

External Review by Ontario Clinicians
Following the review and discussion of Sections 1 and 2 of this evidence-based series, the Gastrointestinal Cancer DSG circulated the clinical practice guideline and systematic review
to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

<table>
<thead>
<tr>
<th>BOX 1: DRAFT RECOMMENDATIONS (approved for external review September 23, 2005)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target Population</strong></td>
</tr>
<tr>
<td>These recommendations apply to adult patients with advanced colorectal cancer who are considered candidates for systemic therapy.</td>
</tr>
<tr>
<td><strong>Recommendation</strong></td>
</tr>
<tr>
<td>• Patients with advanced colorectal cancer receiving 5-fluorouracil (5FU)-based chemotherapy as either first- or second-line therapy should be offered bevacizumab, at a dose of 5mg/kg every two weeks, to improve overall survival.</td>
</tr>
<tr>
<td><strong>Qualifying Statements</strong></td>
</tr>
<tr>
<td>• Data from available randomized clinical trials have suggested a survival benefit with the addition of bevacizumab to several 5FU-based regimens, including regimens of 5FU / folinic acid, 5FU with irinotecan (IFL), and 5FU with oxaliplatin (FOLFOX4). These studies have included regimens using 5FU given by bolus and by infusional means. Survival benefit has been shown with the addition of bevacizumab to both first- and second-line chemotherapy. A reasonable conclusion is that bevacizumab in combination with all 5FU-based chemotherapy is more effective than all 5FU-based chemotherapy alone.</td>
</tr>
<tr>
<td>• Given the data supporting the addition of bevacizumab to IFL and to FOLFOX, the DSG finds the addition of bevacizumab to FOLFIRI reasonable, despite the fact that this combination has not been formally evaluated in the clinical trial setting. This guideline reflects previous recommendations supporting the use of FOLFIRI over IFL.</td>
</tr>
<tr>
<td>• As there are no reported trials demonstrating the efficacy or safety of bevacizumab with oral 5FU treatments, such as capecitabine, that combination is currently not recommended outside of clinical trials.</td>
</tr>
<tr>
<td>• The weight of evidence supports the use of bevacizumab with 1st-line chemotherapy for patients with advanced colorectal cancer. Although the evidence is less compelling for its use with 2nd-line chemotherapy, this treatment is recommended if bevacizumab is not included in the initial treatment regimen.</td>
</tr>
<tr>
<td>• FOLFOX plus bevacizumab has only been evaluated in the second-line setting. Should oxaliplatin be available, and administered, to patients in the first-line setting, the DSG finds it reasonable to include bevacizumab in order to improve survival.</td>
</tr>
<tr>
<td>• The role of continuing bevacizumab after disease progression on a bevacizumab-containing regimen is not clear due to the absence of evidence. Therefore, the continuation of bevacizumab in patients who have progressed on this therapy cannot currently be recommended outside of clinical trials.</td>
</tr>
<tr>
<td>• Contraindications to the use of bevacizumab include cerebral metastases, uncontrollable hypertension, and severe proteinuria. Bevacizumab should not be administered to patients with advanced atherosclerotic disease, bleeding diatheses, or those with non-healing wounds, recent surgery or trauma (i.e., within the previous 28 days), since those patients were excluded from enrolment in clinical trials using bevacizumab.</td>
</tr>
</tbody>
</table>
The decision to include bevacizumab in 5FU-based regimens requires discussion with the patient regarding risks of added toxicity and potential benefit.

Methods

Feedback was obtained through a mailed survey of medical oncologists in Ontario. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on September 27, 2005. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The DSG reviewed the results of the survey.

Results

Fifteen responses were received out of the 27 surveys sent (55.6% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 12 indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 4.

Table 4. Responses to eight items on the practitioner feedback survey.

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)</th>
</tr>
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<tbody>
<tr>
<td>The rationale for developing a guideline, as stated in the “Introduction” section of the report, is clear.</td>
<td>12(100) 0(0) 0(0)</td>
</tr>
<tr>
<td>There is a need for a guideline on this topic.</td>
<td>12(100) 0(0) 0(0)</td>
</tr>
<tr>
<td>The literature search is relevant and complete.</td>
<td>12(100) 0(0) 0(0)</td>
</tr>
<tr>
<td>The results of the trials described in the report are interpreted according to my understanding of the data.</td>
<td>12(100) 0(0) 0(0)</td>
</tr>
<tr>
<td>The draft recommendations in the report are clear.</td>
<td>12(100) 0(0) 0(0)</td>
</tr>
<tr>
<td>I agree with the draft recommendations as stated.</td>
<td>12(100) 0(0) 0(0)</td>
</tr>
<tr>
<td>This report should be approved as a practice guideline.</td>
<td>12(100) 0(0) 0(0)</td>
</tr>
<tr>
<td>If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?</td>
<td>Very likely or likely 9(75) Unsure 1(8) Not at all likely or unlikely 2(17)</td>
</tr>
</tbody>
</table>

Summary of Written Comments

Four respondents (33%) provided written comments. The main points contained in the written comments were:

- A practice guideline without funding for the drug is not useful. The guideline recommendations cannot be used in practice because there is currently no access to bevacizumab.
- While the efficacy of bevacizumab is convincing, the financial impact makes it unlikely it will be funded.

Modifications/Actions in Response to Practitioner Feedback

No substantial changes were made to the practice guideline or systematic review based on the practitioner feedback survey. Although bevacizumab is not currently funded or available in Ontario, the DSG felt that an evidence-based series on the subject was warranted due to emerging evidence of the efficacy of bevacizumab and the knowledge that the drug would be
considered for funding in the future. The financial impact of bevacizumab was beyond the scope of this guideline.

Report Approval Panel
The final evidence-based series report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Panel included:

- The DSG included comparisons between treatment groups from randomized phase II trials. As the intent of phase II trials is generally not to compare treatment arms, the DSG needs to provide a greater level of appraisal by commenting on the study design and associated limitations and be certain that comparisons between randomized groups are legitimate.
- A summary of key trial quality characteristics should be included.
- The justification for not pooling the data and conducting a meta-analysis is weak.
- The DSG cautiously used the word “offered” in their sole recommendation. The reason for this qualification is unclear given the consistent results in the two major studies demonstrating superior overall survival. The DSG should expand the discussions about trade-offs/preferences, expand on what they perceive to be the limitations of the data, or, if more appropriate, state that the therapy is recommended.
- It is unclear why the DSG uses qualifying type words such as “suggested” or “reasonable” in the first Qualifying Statement.
- It is not clear why the single arm phase II studies were included, unless they better elucidate toxicities. The wording of the first sentence under Literature Search Results should be rephrased, as these two studies do not contribute to “comparisons”.

Modifications/Actions in Response to RAP Feedback
- The authors agreed that it should be made clearer in the guideline that the randomized phase II trials were not sufficiently powered for a survival endpoint. Statistical comparisons between groups were considered legitimate as both trials were designed for this purpose. A section on Study Quality was added with a discussion of the limitations of randomized phase II trials. Further comments on trial design and statistical comparisons were added to the text of the Results section.
- The authors reconsidered the original decision not to perform a meta-analysis as additional survival data became available after this decision was made. One-year overall survival was pooled and the meta-analysis was added to Section 2 of this evidence-based series.
- The words “should be offered” were changed to “is recommended” as the DSG felt this was appropriate. A Qualifying Statement urging clinicians to discuss the trade-off between increased toxicity and potential benefits was moved to the Recommendation section for clarity.
- In the first Qualifying Statement, the words “suggested a survival benefit” were replaced with the words “demonstrated a significant advantage”.
- The authors decided to retain the single-arm phase II trials as they provide useful information on toxicity. Wording in the Literature Results section was changed to reflect that these trials are not comparisons.
Policy Review
A draft of this evidence-based series was sent for review by the Drug Quality and Therapeutics Committee -Special Oncology Subcommittee (DQTC-SOS) of Ontario for funding consideration in 2005.

ONGOING DEVELOPMENT AND MAINTENANCE
This report reflects the integration of feedback obtained from the Report Approval Panel of the PEBC and through the external review process, with final approval given by the Gastrointestinal Cancer DSG. This report was updated in November 2007 and May 2008 to incorporate new evidence. The following key changes were made:

November 2007
- The literature search was updated to August 2007. The full publication of the trial by Giantonio et al (3) and the abstract report of the trial by Saltz et al (4) were added to the Results section of the Systematic Review.
- Non-randomized trials and sequential randomized trials where the first cohort compared two or more chemotherapy regimens without bevacizumab and the second cohort evaluated the same regimens with bevacizumab were removed from the Results section of the Systematic Review.
- A meta-analysis of one-year survival data was replaced by a meta-analysis of published mortality hazard ratios.
- The statement indicating that there was no evidence for the safety of bevacizumab with oral fluoropyrimidines was removed.
- The recommendations were changed to state that the addition of bevacizumab to fluoropyrimidine-based, instead of 5FU-based, chemotherapy is recommended, given the available evidence on the safety and efficacy of bevacizumab with capecitabine.

May 2008
- The literature search was updated to April 2008. The full publication of the trial by Saltz et al (5) was added to the Results section of the Evidentiary Base.
- Additional details were added to the tables in Section 2 (Table 1 and Appendix 1).
- The meta-analysis was revised to exclude the Kabbinavar 2003 phase II randomized trial (6). Insufficient details were available in the trial report to determine the variance estimate for the mortality hazard ratio.

Further updates will be conducted as new evidence informing the question of interest emerges.

Funding
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context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Contact Information
For further information about this report, please contact Dr. Jim Biagi, Co-Chair, Gastrointestinal Cancer Disease Site Group, Cancer Centre of Southeastern Ontario, Kingston General Hospital, 25 King St W, Kingston, ON, K7L 5P9; TEL 613-544-2630 ext. 4502; FAX 613-546-8209.

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822     Fax: 905-526-6775     E-mail: ccopgi@mcmaster.ca
REFERENCES


Evidence-based Series #2-25: Section 4-

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)
Developed by the Gastrointestinal Cancer Disease Site Group

The Role of Bevacizumab (Avastin®) Combined With Chemotherapy in the Treatment of Patients With Advanced Colorectal Cancer: Document Assessment and Review

Members of the Gastrointestinal Cancer Disease Site Group

Original Report Date: December 12, 2005
Current Report Date: May 28, 2008

REVIEW SUMMARY

The original version of this guidance document was released by Cancer Care Ontario’s Program in Evidence-based Care in 2005, and updated in 2008. In September 2011, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. A clinical expert (SW) reviewed and interpreted the new eligible evidence and proposed the existing recommendations should be delayed. The Gastrointestinal Cancer Disease Site Group (DSG) archived the recommendations found in Section 1 (Clinical Practice Guideline) in December 2013.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Questions Considered

1. Should adult patients with advanced (locally advanced non-resectable or metastatic) colorectal cancer who are considered candidates for systemic therapy receive bevacizumab (Avastin®) combined with cytotoxic chemotherapy?
Literature Search and New Evidence

The new search (May 2008-July 2013) yielded 13 new full text publications or abstracts of RCTs that compared bevacizumab combined with cytotoxic chemotherapy versus chemotherapy alone. An additional search for ongoing studies on Clinicaltrials.gov yielded 3 potentially relevant ongoing RCTs. Brief results of these searches are shown in the Document Review Tool.

Impact on Guidelines and Its Recommendations

The Gastrointestinal Cancer DSG ARCHIVED the 2008 recommendations on bevacizumab combined with chemotherapy in patients with advanced colorectal cancer.

Document Review Tool

<table>
<thead>
<tr>
<th>Number and title of document under review</th>
<th>2-25 The Role of Bevacizumab (Avastin®) Combined with Chemotherapy in the Treatment of patients with Advances Colorectal Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Report Date</td>
<td>May 2008</td>
</tr>
<tr>
<td>Clinical Expert</td>
<td>Dr. Stephen Welch</td>
</tr>
<tr>
<td>Research Coordinators</td>
<td>Norma P. Varela, Samantha Craigie</td>
</tr>
<tr>
<td>Date Assessed</td>
<td>September 2011</td>
</tr>
<tr>
<td>Approval Date and Review Outcome (once completed)</td>
<td>ARCHIVED- December 17, 2013</td>
</tr>
</tbody>
</table>

Original Question(s):

Should adult patients with advanced (locally advanced non-resectable or metastatic) colorectal cancer who are considered candidates for systemic therapy receive bevacizumab (Avastin®) combined with cytotoxic chemotherapy?

Target Population:

These recommendations apply to adult patients with advanced colorectal cancer who are considered candidates for systemic therapy.

Study Section Criteria:

**Inclusion Criteria:**

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts of:

1. Randomized controlled trials (RCTs) comparing chemotherapy plus bevacizumab with chemotherapy alone in the treatment of adult patients with advanced colorectal cancer. Overall survival, progression-free survival, and/or response rate had to be reported.

2. Syntheses of evidence in the form of meta-analyses of RCTs meeting the above criteria.

**Exclusion Criteria:**

The following were not considered for inclusion in this report:
1. Phase I and single-arm phase II studies.
2. Abstract reports of RCTs presenting preliminary or interim data only.
3. Results of RCTs reported in letters or editorials.
4. Papers published in a language other than English, as translation services were not available.

Search Details:
- Jan 2008 to 2013 (Medline week 1 and Embase week 1), search updated July 30, 2013
- Jan 2008 to July 2013 (ASCO Annual Meeting)
- May 2008 to July 2013 (Clinicaltrial.gov)

Brief Summary/Discussion of New Evidence:
Of 466 total hits from Medline + Embase and 658 total hits from ASCO conference abstract searches, 13 references representing 8 RCTs were found evaluating chemotherapy with and without bevacizumab in the treatment of advanced colorectal cancer, of which 1 RCT was already included in the existing guideline (rows highlighted in grey in the Table). 7 RCTs are potentially new studies, of which 5 had full text publications and 2 were in abstract form.

### Randomized Controlled Trials

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Population</th>
<th>Median follow up</th>
<th>Outcomes</th>
<th>Brief Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A: Capecitabine 1000 mg/m² bid days 1-14 (n=140) + bevacizumab 7.5 mg/kg q3w (n=140)</td>
<td>Patients ≥70y with previously untreated mCRC</td>
<td>NR</td>
<td>PFS, OS, ORR</td>
<td>BEV + cape significantly prolonged PFS: med 9.1 vs 5.1 mo, HR=0.53, CI 0.41-0.69, p&lt;0.001; OS: HR=0.79, CI 0.57-1.09, p=0.182</td>
<td>Saunders 2013 (abstract)</td>
</tr>
<tr>
<td>Arm A: BEV (5 mg/kg) plus mIFL (irinotecan 125 mg/m², leucovorin 20 mg/m² bolus, 5-FU 500 mg/m²) (n=139) + mIFL (irinotecan 125 mg/m², leucovorin 20 mg/m² bolus, 5-FU 500 mg/m²) (n=64) (2:1 randomization)</td>
<td>Previously untreated, measurable mCRC, Chinese patients</td>
<td>NR</td>
<td>PFS, OS, ORR</td>
<td>PFS: Arm A vs Arm B: 6-mo 62.6% (54.5-70.6) vs 25.0 (14.4-35.6), p&lt;0.001; Median PFS: 8.3 (7.4-8.9) vs 4.2 (3.7-4.9), p&lt;0.001, HR=0.44 (0.31-0.63); Median OS (m0), arm A vs B: 18.7 (15.8-19.6) vs 13.4 (9.7-17.2), p=0.014, HR=0.62 (0.41-0.95); ORR, %, arm A vs B: 35.3 (27.5-43.5) vs 17.2 (8.4-27.7), p=0.013</td>
<td>Guan 2010, Guan 2010 (2) (abstracts)</td>
</tr>
<tr>
<td>Arm A: mFOLFOX6 or FOLFIRI with BEV (n=92) + mFOLFOX6 or FOLFIRI without BEV (n=92)</td>
<td>Patients with measurable mCRC</td>
<td>22 mo</td>
<td>PFS, OS, response</td>
<td>Study accrual stopped prematurely (at 185 of 262 target patients); PFS: med 6.7 mo vs 5.2 mo for BEV vs chemo, HR=0.66, CI 0.49-0.90; OS: (immature) 16.5 mo vs 16 mo, HR=0.83, CI 0.57-1.22; Response: 21% vs 18%, p=0.0072</td>
<td>Masi 2013 (abstract)</td>
</tr>
</tbody>
</table>
### 2x2 design

| Arm A: XELOX (oxaliplatin 130 mg/m² followed by capecitabine 1000 mg/m² 2x/d) + placebo (n=350) | Patients aged ≥18 years, unresectable mCRC, no prior systemic therapy | 27.6 mo | PFS OS | Results presented as BEV (n=701) vs PLA (n=699) arms (XELOX and FOLFOX grouped) |
| Arm B: XELOX + BEV (7.5 mg/kg) (n=350) | | | | PFS: increased in BEV vs placebo: HR=0.83, 97.5% CI 0.72-0.95, p=0.0023; median PFS 9.4 mo vs 8.0 mo |
| Arm C: FOLFOX-4 + placebo (n=351) | | | | Median OS: 21.3 mo vs 19.9 mo, HR=0.89 (97.5% CI 0.76-1.03), p=0.0769 |
| Arm D: FOLFOX-4 + BEV (5 mg/kg) (n=349) | | | | Saltz 2008 |

### Patients with histologically confirmed stage IV cancer

| Arm A: Leucovorin 200 mg/m², 5-fluorouracil 500 mg/m², irinotecan 135 mg/m², plus BEV 7.5 mg/kg (n=114) | Patients ≥18 years, unresectable mCRC, no prior systemic therapy | 36 months (range 12-72) | Response rate, survival time | No complete responses. Partial response: 36.8% arm A vs 35.2% arm B |
| Arm B: same as arm A, no bevacizumab (n=108) | | | | Survival time, arm A vs B: 22 mo (CI 18.1-25.9) vs 25.0 mo (CI 18.1-31.9), p=0.1391 |
| Arm C: capecitabine, bevacizumab, mitomycin 7mg/m² q6wk (n=158) | | | | Stathopoulos 2010, Stathopoulos 2010 (2) (abstract) |

### Patients ≥18 years, mCRC, progression after first-line BEV treatment w/chemo

| Arm A: BEV+ chemotherapy (n=409) | Patients ≥18 years, mCRC, progression after first-line BEV treatment w/chemo | 9.6 mo (chemo alone), 11.1 mo (BEV+chemo) | ORR, TTP OS | Median OS: 9.8 mo (CI 8.9-10.7) chemo alone vs 11.2 (CI 10.4-12.2) mo BEV+chemo, HR 0.81, CI 0.69-0.94 |
| Arm B: chemotherapy alone (n=411) | | | | Median PFS: 4.1 mo (CI 3.7-4.4) chemo alone vs 5.7 mo (CI 5.2-6.2) BEV+chemo (HR 0.68, CI 0.59-0.78), p<0.0001 |

From the start of first-line treatment: Med OS: 22.5 mo (CI 21.4-24.5) chemo alone vs 23.9 (CI 22.2-25.7) BEV+chemo, HR 0.90, CI 0.77-1.05

**Note:** Results presented as BEV (n=701) vs PLA (n=699) arms (XELOX and FOLFOX grouped)

**Results:**
- **PFS:** Increased in BEV vs placebo: HR=0.83, 97.5% CI 0.72-0.95, p=0.0023; median PFS 9.4 mo vs 8.0 mo
- **Median OS:** 21.3 mo vs 19.9 mo, HR=0.89 (97.5% CI 0.76-1.03), p=0.0769

**References:**
- Saltz 2008
- Stathopoulos 2010, Stathopoulos 2010 (2) (abstract)
- Tebbutt 2010, Tebbutt 2009 (abstract), Price 2011 (abstract), Price 2012
- Bennouna 2013
- Dotan 2012
Arm A: IV day 1 every 21 days. (n=12)  
Arm B: Same as A, no bevacizumab (n=11)

Systematic Reviews and Meta-Analyses

5 meta-analyses were identified.

<table>
<thead>
<tr>
<th>Author</th>
<th>Intervention/ Criteria</th>
<th>Number</th>
<th>Outcomes</th>
<th>Brief results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cao et al 2009</td>
<td>RCTs comparing chemotherapy with or without BEV, in mCRC Jan 2003-Aug 2008</td>
<td>N=5 RCTs, Npatients= 3103</td>
<td>OS</td>
<td>PFS or TTP ORR</td>
</tr>
</tbody>
</table>
|                   |                                                                                                                                               |        |          | PFS: significant improvement when BEV added to chemo: HR=0.66, CI 0.56-0.77, p=0.00  
|                   |                                                                                                                                               |        |          | Median OS: HR=0.77, CI 0.67-0.89 (with BEV added to chemo)  
|                   |                                                                                                                                               |        |          | ORR: 40% in BEV+chemo vs 34.5% in chemo only, p=0.02, RR=1.50, CI 1.06-2.10 (increase in odds of response for addition of BEV)                         |
| Li and Chi 2011   | RCTs of standard first-line chemo with BEV for mCRC Up to and including end of 2009   | N= 3 RCTs, Npatients: 2317 | PFS OS   | Response rate                                                                                                                                                                                                   |
|                   |                                                                                                                                               |        |          | PFS: BEV vs chemo groups, PFS 9.8 mo vs 6.8 mo, HR=0.65, CI 0.42-0.88, z=5.52, p=0.000  
|                   |                                                                                                                                               |        |          | OS: BEV vs chemo, OS 20.7 mo vs 17.4 mo, HR=0.79, CI 0.61-0.97; z=8.63, p=0.000  
|                   |                                                                                                                                               |        |          | Response: BEV vs chemo, 40.0% vs 36.2%, OR 1.32, CI 0.89-1.98, z=1.37, p=0.17                                                                  |
| Loupakis et al 2010 | RCTs, phase 2 or 3, BEV+chemo vs chemo alone Up to March 2009                          | Primary: N= 4 RCTs, Npatients= 2624 | PFS OS   | Secondary: N=5 RCTs, Npatients =2728  
|                   |                                                                                                                                               |        |          | Comparing BEV+ chemo to chemo alone:  
|                   |                                                                                                                                               |        |          | PFS: BEV vs chemo groups, PFS 9.8 mo vs 6.8 mo, HR=0.65, CI 0.42-0.88, p=0.000  
|                   |                                                                                                                                               |        |          | OS: BEV vs chemo, OS 20.7 mo vs 17.4 mo, HR=0.79, CI 0.61-0.97; z=8.63, p=0.000  
|                   |                                                                                                                                               |        |          | Response: BEV vs chemo, 40.0% vs 36.2%, OR 1.32, CI 0.89-1.98, z=1.37, p=0.17                                                                  |
| Wagner 2009       | RCTs of chemotherapy with or without angiogenesis inhibitors (Cochrane review), 2000- Sept 2008 | BEV therapy: First line: N=4 RCTs, Npatients= 2526 | PFS OS   |  
|                   |                                                                                                                                               |        |          | First-line:  
|                   |                                                                                                                                               |        |          | PFS: HR=0.61 (CI 0.45-0.83) in favour of BEV  
|                   |                                                                                                                                               |        |          | OS: HR=0.81 (CI 0.73-0.90) in favour of BEV  
|                   |                                                                                                                                               |        |          | Second-line:  
|                   |                                                                                                                                               |        |          | PFS: HR=0.61 (CI 0.51-0.73) in favour of BEV  
|                   |                                                                                                                                               |        |          | OS: HR=0.75 (CI 0.63-0.89) in favour of BEV  
| Macedo 2012       | RCTs, chemo with or w/o BEV, mCRC, previously untreated patients, Aug 2002- March 2011 | N=6 RCTs, Npatients: 3060 | PFS OS   | ORR                                                                                                                                                                                                              |
|                   |                                                                                                                                               |        |          | PFS: HR=0.72, CI 0.66-0.78, in favour of BEV (advantage with 5-FU monotherapy or irinotecan-based chemo; oxaliplatin-based was beneficial but less)  
|                   |                                                                                                                                               |        |          | OS: HR=0.84, CI 0.77-0.91, in favour of BEV, only irinotecan regimen showed statistically significant data  
|                   |                                                                                                                                               |        |          | ORR: OR=1.12, CI 0.94-1.33, p=0.21. Fluorouracil monotherapy: OR=1.58, p=0.02 |

Ongoing Randomized Controlled Trials (RCTs)

Three phase III trials registered on or after May 1 2008, evaluating chemotherapy with or without bevacizumab were identified.

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Official Title</th>
<th>Status</th>
<th>Protocol ID</th>
<th>Last Updated</th>
<th>Estimated Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients will be randomized to one of 2 chemotherapy strata. Those in stratum 1 will receive chemotherapy (AIO-IRI, FOLFIRI, CAPEIRI or XELOIRI) alone, or in combination with Avastin (5mg/kg iv on days 1 and 14 of each 4 week cycle or 7.5mg/kg on days 1 and 22 of each 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A Randomized, Open-label Phase III Intergroup Study: Effect of Adding Bevacizumab toCross Over Fluoropyrimidine Based Chemotherapy (CTX) in Patients With Metastatic Colorectal</td>
<td>Ongoing but not recruiting</td>
<td>NCT007001 02</td>
<td>May 30 2013</td>
<td>May 2013</td>
<td></td>
</tr>
</tbody>
</table>
week cycle) and those in stratum 2 will receive chemotherapy (FUFOX, FOLFOX, CAPOX or XELOX) alone, or in combination with Avastin (5mg/kg on days 1 and 14 of each 4 week cycle or 7.5mg/kg on days 1 and 22 of each 6 week cycle)

| Active Comparator: Arm I | Patients receive either irinotecan hydrochloride over 1 hour or oxaliplatin over 1 hour on day 1. Patients also receive leucovorin calcium IV over 2 hours and fluorouracil IV over 46 hours continuously beginning on day 1. Treatment repeats every 2 weeks for up to 12 courses in the absence of disease progression or unacceptable toxicity. Experimental: Arm II | Patients receive combination chemotherapy as in arm I and bevacizumab IV on day 1. Treatment repeats every 2 weeks for up to 12 courses in the absence of disease progression or unacceptable toxicity. | An open-label, multicenter, randomized phase III study of second-line chemotherapy with or without bevacizumab in metastatic colorectal cancer patients who have received first-line chemotherapy plus bevacizumab. | Ongoing but not recruiting | NCT007205 12 | October 12, 2012 | March 2014 |

| Drug: FOLFOX OR FOLFIRI + BEVACIZUMAB | Drug: FOLFOX or FOLFIRI | Drug: FOLFOX or FOLFIRI + CETUXIMAB | Drug: FOLFOX or FOLFIRI + BEVACIZUMAB + CETUXIMAB | Sequential treatment strategy for metastatic colorectal cancer: a phase III prospective randomized multicenter study of chemotherapy (ct) with or without bevacizumab as first-line therapy followed by two phase III randomized studies of ct alone or ct plus bevacizumab with or without cetuximab as second-line therapy | Currently recruiting patients | NCT018784 22 | June 12, 2013 | March 2014 |

Nr: not reported; mCRC: metastatic colorectal cancer; PFS: progression-free survival; OS: overall survival; BEV: bevacizumab; med: median; HR: hazard ratio; CI: 95% confidence interval; mo: months; RR: relative risk; OR: odds ratio; ORR: objective response rate;

**Clinical Expert Interest Declaration:**

Instructions. Instructions. For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.
1. Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? | NO

2. On initial review,  
   a. Does the newly identified evidence support the existing recommendations?  
   b. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? | a. YES  
   b. YES.

3. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary: | YES.

4. Do the PEBC and the DSG/GDG responsible for this document have the resources available to write a full update of this document within the next year? | n/a

<table>
<thead>
<tr>
<th>Review Outcome</th>
<th>ARCHIVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSG/GDG Approval Date</td>
<td>December 17, 2013</td>
</tr>
<tr>
<td>DSG/GDG Commentary</td>
<td>No comments</td>
</tr>
</tbody>
</table>
New References Identified


**Literature Search Strategy**

**Cochrane Library**

“Bevacizumab” (title/abstract/keywords) AND “colorectal cancer” (all text)

**Medline**

1. meta-Analysis as topic.mp.
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview).tw.
5. (systematic adj (review$ or overview$)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinic$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? or random allocation or random allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. Animal/
38. Human/
39. 37 not 38
40. 36 not 39
41. bevacizumab.mp.
42. avastin.mp.
43. 41 or 42
44. (drug therapy or chemotherapy or systematic therapy).mp.
45. 43 and 44
46. exp colorectal neoplasms/
47. 45 and 46
48. 40 and 47
49. (2008: or 2009: or 2010: or 2011: or "2012" or "2013").ed.
50. 48 and 49

**Embase**
1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or matematical sumar$ or quantitative synthesis$ or quantitative overview).tw.
4. (systematic adj (review$ or overview?)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or science citation index or scisearch or bids or single or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and random.tw.
18. (clinic$ and trial$1).tw.
19. ((singl$ or doubl$ or tre$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
20. placebo/
21. (placebo? or random allocation or random allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. Animal/
33. Human/
34. 32 not 33
35. 31 not 34
36. bevacizumab.mp.
37. avastin.mp.
38. 36 or 37
39. chemotherapy/
40. 38 and 39
41. (locally adj advanced).tw.
42. (advanced or metastatic or non-resectable).tw.
43. or/41-42
44. colorectal neoplasms/ or exp colonic neoplasms/ or exp rectal neoplasms/
45. 43 and 44
46. 40 and 45
47. (2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$).ew.
48. 46 and 47
49. 35 and 48
ASCO Annual Meeting - [http://www.ascopubs.org/search](http://www.ascopubs.org/search)
“Bevacizumab” AND “colorectal cancer”, 2008-2013

Search terms: “bevacizumab”
Conditions: “colorectal cancer”
Phase 3
Age: adult (18+), senior (66+)
First received: From May 1 2008 to July 29, 2013
OUTCOMES DEFINITION

1. **ARCHIVED** - An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website, each page is watermarked with the word “ARCHIVED”.

2. **ENDORSED** - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DELAY** - A delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. **UPDATE** - An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.