



cancer care
ontario

program in
evidence-based care

action cancer
ontario

programme de soins
fondé sur des preuves

CED-CCO Special Advice Report 12 EDUCATION AND INFORMATION 2012

The Use of Bevacizumab in Metastatic Breast Cancer

R. Dent, A.E. Haynes, K. Enright, C. Hamm, M. Trudeau, and A. Eisen

Report Date: April 17, 2009

This CED-CCO Special Advice Report was put in the Education and Information section in 2012. The PEBC has a formal and standardized process to ensure the currency of each document ([PEBC Assessment & Review Protocol](#)).

The report, which consists of consists of a Summary and a Full Report, is available on the CCO web site (<http://www.cancercare.on.ca>).

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

Report Citation (Vancouver Style): Dent R, Haynes AE, Enright K, Hamm C, Trudeau M, Eisen A. The use of bevacizumab in metastatic breast cancer. Toronto (ON): Cancer Care Ontario; 2009 Apr 17 [Education and Information 2012]. Program in Evidence-based Care CED-CCO Special Advice Report No.: 12 Education and Information.



CED-CCO Special Advice Report 12 EDUCATION AND INFORMATION 2012

The Use of Bevacizumab in Metastatic Breast Cancer

R. Dent, A.E. Haynes, K. Enright, C. Hamm, M. Trudeau, and A. Eisen

Report Date: April 17, 2009

*The 2009 guideline recommendations were put in the
Education and Information section*

*This means that the recommendation will no longer be
maintained but may still be useful for academic or other
information purposes.*

SUMMARY

QUESTION

Does bevacizumab (alone or in combination with other systemic therapies) improve outcomes in women with locally advanced or metastatic breast cancer compared to the same therapy without bevacizumab? Outcomes of interest include overall survival, progression-free survival, objective response rate, quality of life, and adverse events.

TARGET POPULATION

This evidence-based series applies to adult women with locally advanced (stage IIIb) or metastatic (stage IV) breast cancer.

RECOMMENDATIONS

The following recommendations reflect the opinions of the authors of this special advice report.

- For women with metastatic or locally advanced breast cancer receiving taxane-based chemotherapy as first-line therapy, the addition of bevacizumab could be offered to improve progression-free survival.
- The addition of bevacizumab to chemotherapy is not recommended for patients with metastatic breast cancer receiving second-line therapy or greater.

QUALIFYING STATEMENTS

- Bevacizumab should not be administered to patients with cerebral metastases, uncontrolled hypertension, severe proteinuria, advanced atherosclerotic disease, bleeding diatheses, or with non-healing wounds, recent surgery, or trauma (i.e., within the previous 28 days), as those patients were excluded from enrolment in clinical trials using bevacizumab.
- The addition of bevacizumab to paclitaxel chemotherapy is associated with significant but manageable toxicity, specifically hypertension, proteinuria, neuropathy, fatigue, and infection. In the most recent randomized study of bevacizumab and docetaxel chemotherapy, the toxicities were much less frequent than in the study of bevacizumab and paclitaxel.

KEY EVIDENCE

Three phase III randomized controlled trials (RCTs) (1-3) comparing a chemotherapy regimen to the same regimen plus bevacizumab were included in this report. Two of the clinical trials studied bevacizumab in combination with a taxane-based chemotherapy in the first-line treatment of metastatic breast cancer (1,2). The remaining trial studied bevacizumab in combination with capecitabine for second-line or greater treatment (3).

First-line Treatment of Metastatic Breast Cancer

Bevacizumab with Weekly Paclitaxel Chemotherapy

Miller et al (1) randomized patients to receive weekly paclitaxel and 10 mg/kg of bevacizumab every two weeks or to weekly paclitaxel alone. Patients receiving weekly paclitaxel with bevacizumab did not have a statistically significant improvement in overall survival (26.7 versus [vs.] 25.2 months; hazard ratio [HR]=0.88, p=0.16) compared to weekly paclitaxel alone. There was a statistically significant increase in median progression-free survival (11.8 vs. 5.9 months; HR=0.60, p<0.001) and overall response rate (36.9% vs. 21.2%; p<0.001) in the cohort receiving bevacizumab with paclitaxel versus paclitaxel alone. The predominant grade 3/4 toxicities observed in the combination arm versus standard arm included hypertension (14.8% vs. 0%, p <0.001), proteinuria (3.6% vs. 0%, p<0.001), headache (2.2% vs 0.0%, p=0.008), and cerebrovascular ischemia (1.9 vs. 0.0%, p=0.02).

Bevacizumab with Docetaxel Chemotherapy

A phase III RCT by Miles et al (2) randomized patients to one of three arms of docetaxel combined with either bevacizumab 15 mg/kg or 7.5 mg/kg, or placebo given every three weeks. The median overall survival has not yet been reached in any arm. Patients receiving docetaxel in combination with bevacizumab 15 mg/kg and 7.5 mg/kg had a small but statistically significant increase in median progression-free survival compared to docetaxel alone (8.8 vs. 8.0 months; HR=0.72, p=0.0099) and (8.7 vs. 8.0 months; HR 0.79, p=0.0318). There was a significant increase in overall response rate in patients receiving bevacizumab 15 mg/kg (63.1% vs. 44.4%, p=0.0001) and 7.5 mg/kg (55.2% vs. 44.4%, p=0.0295) compared to docetaxel alone. Grade 3/4 toxicities seen in earlier studies were observed less frequently than in previous studies. For example, there did not appear to be a significant increase in the rate of grade 3/4 hypertension in patients receiving bevacizumab 15 mg/kg (3.2% vs. 1.3%, p=not reported) and 7.5 mg/kg (0.4 vs. 1.3%, p=not reported). Further details of toxicity are expected in the final publication of the study.

Meta-Analysis

A meta-analysis of reported hazard ratios for progression-free survival from the two RCTs with first-line taxane-based therapy was performed. This indicated a significant benefit

in progression-free survival for the addition of bevacizumab to taxane-based chemotherapy compared to taxane-based therapy alone (HR=0.64; 95% confidence interval, 0.54 to 0.77, $p<0.00001$).

Second-line or Greater Treatment of Metastatic Breast Cancer ***Bevacizumab with Capecitabine Chemotherapy***

Miller et al (3) randomized patients who had received previously treatment for metastatic breast cancer to bevacizumab 15 mg/kg combined with capecitabine every three weeks or to capecitabine alone. No significant differences in overall survival or progression-free survival were detected between the two arms.

FUTURE RESEARCH

The RIBBON-1 study is a double-blind, placebo-controlled phase III study in first-line metastatic HER2-negative breast cancer investigating bevacizumab in combination with either taxane-based, anthracycline-based, or Xeloda (capecitabine) chemotherapies compared to the same therapy with placebo. The RIBBON-2 study is a placebo-controlled phase III trial enrolling patients who have received only one prior chemotherapy regimen. Patients are randomized to receive either bevacizumab or placebo in combination with taxane-based, gemcitabine, vinorelbine, or Xeloda (capecitabine) chemotherapy. The data will likely be presented at the American Society of Clinical Oncology meeting in June 2009. Randomized phase III trials evaluating the benefit of adding bevacizumab to chemotherapy in high-risk individuals in adjuvant setting are currently underway.

IMPLICATIONS FOR POLICY

In February 2008, the Food and Drug Administration (FDA) in the United States approved the use of bevacizumab in conjunction with paclitaxel for the treatment of patients who have not received chemotherapy for their metastatic breast cancer. In February 2009, Health Canada approved the use of bevacizumab in combination with paclitaxel for the treatment of patients with HER2 negative metastatic breast cancer.

In Ontario, it is estimated that 8500 new cases of breast cancer were diagnosed in 2008 (4). Each year, about 25% of breast cancer patients, or 2000 women, die of metastatic disease. Over two thirds of these women have HER2-negative disease, and a significant proportion of those patients would be expected to be eligible to receive chemotherapy treatment, including the option of treatment in combination with bevacizumab.

RELATED PROGRAM IN EVIDENCE-BASED CARE GUIDELINES

Evidence-based Series

- #1-12: *The Role of Gemcitabine in the Management of Metastatic Breast Cancer.*
Available at: <http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34178>.

Practice Guideline Reports

- #1-3 Version 2.2003: *The Role of the Taxanes in the Management of Metastatic Breast Cancer.*
Available at: <http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34140>.
- #1-6: *Epirubicin, as a Single Agent or in Combination, for Metastatic Breast Cancer.*
Available at: <http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34174>.
- #1-11 Version 2.2002: *Use of Bisphosphonates in Women with Breast Cancer.*
Available at: <http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34182>.

- #1-16 Version 2.2003: *Capecitabine in Stage IV Breast Cancer*.
Available at: <http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=13874>.

Evidence Summary Reports

- #1-4: *Vinorelbine in Stage IV Breast Cancer*.
Available at: <http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=34144>.

Funding

The PEBC is a provincial initiative of Cancer Care Ontario 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.

Copyright

This report is copyrighted by Cancer Care Ontario; the report and the illustrations herein may not be reproduced without the express written permission of Cancer Care Ontario. Cancer Care Ontario reserves the right at any time, and at its sole discretion, to change or revoke this authorization.

Disclaimer

Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the 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.

For information about the PEBC and the most current version of all reports, please visit the CCO web site 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—SUMMARY

1. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med*. 2007;357(26):2666-76.
2. Miles D, Chan A, Romieu G, Dirix LY, Cortes J, Pivot X, et al. Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBc): AVADO [abstract and slide presentation on the Internet]. *J Clin Oncol* (ASCO Annual Meeting Proceedings). 2008;26(15 Suppl):Abstract LBA1011. [Cited 2009 Mar 10]. Slides available at: http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=34482.
3. Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. *J Clin Oncol*. 2005;23(4):792-9.
4. Canadian Cancer Statistics 2008. Toronto, Canada: Canadian Cancer Society/National Cancer Institute of Canada; 2008 Apr [cited 2009 Mar 24]. Available from: <http://www.cancer.ca/statistics>.

FULL REPORT

QUESTION

Does bevacizumab (alone or in combination with chemotherapy) improve outcomes in women with locally advanced or metastatic breast cancer compared to chemotherapy alone? Outcomes of interest include overall survival, progression-free survival, objective response rate, quality of life, and adverse events.

INTRODUCTION

Breast cancer is the most common cancer site in women, representing 28.3% of all new cancer cases in Canada in 2008 (1). Breast cancer is the second leading cause of cancer death, representing 15.2% of all cancer deaths. Thus, 1 in 9 women in Canada will develop breast cancer and 1 in 28 will die of the disease. For that reason, there is great interest in improving the treatment results for this group of patients.

Although a number of hormonal therapy and chemotherapy options have been developed for the palliation of metastatic breast cancer, virtually all patients ultimately develop resistance to those treatments. Furthermore, second-line or greater chemotherapy regimens may be associated with significant adverse effects that diminish a patient's quality of life. Thus, the development of effective and safe therapies for use in breast cancer remains a priority.

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.

A range of studies has examined the relationship between VEGF expression and clinical outcome in breast cancer. In general, they have concluded that VEGF leads to worse disease-free and overall survival rates in patients with early breast cancer. The largest of those trials showed that VEGF was an independent prognostic marker in both node-positive and node-negative breast cancer (2)

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 (3,4). Phase II clinical trials have suggested activity in breast, lung, renal, and colorectal cancers in the metastatic setting (5,6). The Committee to Evaluate Drugs Cancer Care Ontario (CED-CCO) subcommittee requested advice on the role of bevacizumab in locally advanced or metastatic breast cancer on the basis of published and emerging phase III trials involving bevacizumab in the treatment of metastatic breast cancer.

METHODS

This advice report, produced by the Program in Evidence-based Care (PEBC) of CCO, is a convenient and up-to-date source of the best available evidence on the role of bevacizumab in the treatment of adult women with locally advanced or metastatic breast cancer, developed through a systematic review of the available evidence. Contributing authors disclosed any potential conflicts of interest. The PEBC is editorially independent of the Ontario Ministry of Health and Long-Term Care.

The PEBC has a formal standardized process to ensure the currency of each clinical guidance report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original clinical guidance report information.

Literature Search Strategy

MEDLINE (Ovid) (2001 through February Week 3 [February 26] 2009), EMBASE (Ovid) (2001 through Week 08 [February 26] 2009), and the Cochrane Library (2009, Issue 1) databases were searched. The search strategies for MEDLINE and EMBASE are shown in Appendix 1. Search strategies in other databases were similar.

In addition, conference proceedings of the American Society of Clinical Oncology (ASCO) 2001 to 2008 and the San Antonio Breast Cancer Symposium (SABCS) 2001 to 2008 were searched for abstracts of relevant trials. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>), the National Guidelines Clearinghouse (<http://www.guideline.gov/index.asp>), and the National Institute for Clinical Excellence (<http://www.nice.org.uk/>) were also searched for existing evidence-based practice guidelines.

Relevant articles and abstracts were selected and reviewed by two reviewers, and the reference lists from these sources were searched for additional trials. Personal files were also searched.

Study Selection Criteria

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were published full report articles or published meeting abstracts of:

1. Randomized trials that compared systemic therapy with bevacizumab to the same therapy without bevacizumab in adult women with locally advanced or metastatic breast cancer.
2. Randomized trials including adult women with locally advanced or metastatic breast cancer evaluating bevacizumab alone or in combination with other systemic therapies.
3. Systematic reviews, meta-analyses, or clinical practice guidelines of bevacizumab in adult women with locally advanced or metastatic breast cancer.
4. Publications of randomized trials, systematic reviews, or meta-analyses must have reported comparative data on one or more of the following outcomes: overall survival, progression-free survival, objective response rate, quality of life, or adverse events.

Exclusion Criteria

Studies were excluded if they were:

1. Letters, comments, books, notes, or editorial publication types.
2. Articles published in a language other than English, due to financial considerations for translation.

Synthesizing the Evidence

An aggregate data meta-analysis was performed by pooling results of published studies using Review Manager 5.0 (7) statistical software, available through the Cochrane Collaboration. Outcomes considered for pooling included overall survival, progression-free survival, and adverse events. A random effects model was used for all pooling.

As hazard ratios (HR), rather than the number of events at a certain time point, are the preferred statistic for pooling time-to-event outcomes (8), those were extracted directly from the most recently reported trial results. The variances of the HR estimates were calculated from the reported confidence intervals (CI), using the methods described by Parmar et al (8).

Statistical heterogeneity was calculated using the χ^2 test for heterogeneity and the I^2 percentage. A probability level for the χ^2 statistic less than or equal to 10% ($p \leq 0.10$) indicates significant statistical heterogeneity. An I^2 value of 25%, 50%, or 75% was considered low, moderate, or high heterogeneity, respectively (9). The measures of treatment effect were

expressed as HRs for overall survival and progression-free survival, with 95% CI. An $HR > 1.0$ indicates that patients receiving bevacizumab had a higher probability of experiencing death or progression (PFS) or death (OS); conversely, an $HR < 1.0$ suggests that patients receiving the control experienced a higher probability of an event.

An a priori decision was made to split the trials of first-line therapy and second-line or greater therapy into different subgroups in the meta-analysis as bevacizumab may have a greater effect when given earlier in the disease course. In addition, the trials of first-line therapy both gave patients bevacizumab in combination with a taxane, whereas the second-line trial gave bevacizumab in combination with capecitabine.

Literature Search Results

A total of 420 citations of studies that included women with locally advanced or metastatic breast cancer were identified from the MEDLINE, EMBASE, and Cochrane Library databases. From those citations, a total of two full publications (10,11) met eligibility criteria and were included (Figure 1). Eight abstracts met the eligibility criteria and were included (12-20). In total three unique trials were identified (Table 1). Only the most recent publication (abstract or full report) or abstracts reporting additional data were referenced.

Figure 1. Selection of studies investigating bevacizumab (BVZ) in metastatic breast cancer from the search results of MEDLINE, EMBASE, and the Cochrane Library databases, and the conference proceedings of ASCO and SABCS.

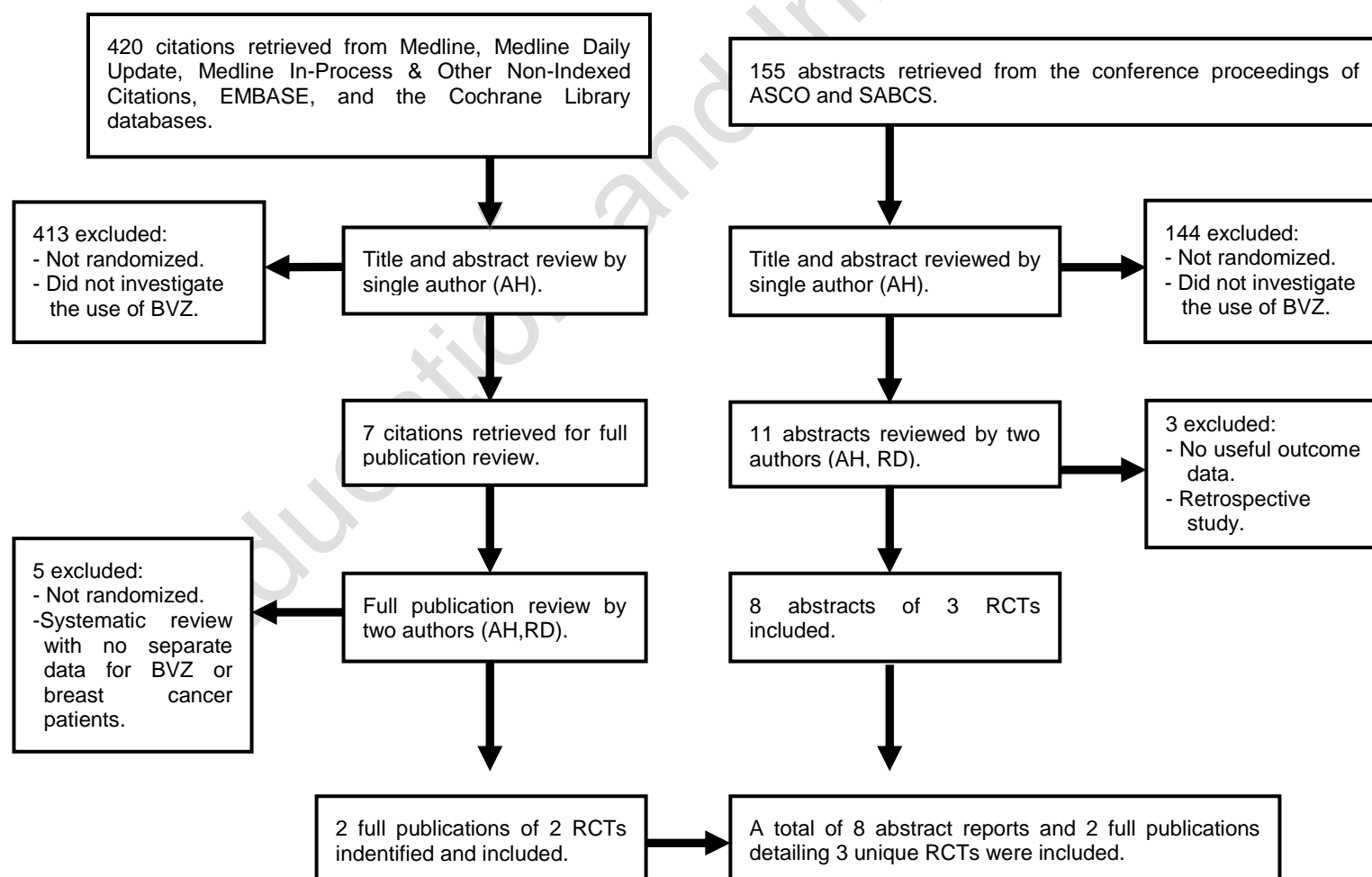


Table 1. Identified publications of RCTs of bevacizumab for metastatic breast cancer.

Trial	Primary publication	Additional publications	Purpose of additional publication
Miller, 2005	Miller et al, 2005 (10)	Miller et al, 2002 abs (16)	Ongoing trial report
E2100	Miller et al, 2007 (11)	Miller et al, 2005 abs (17)	Interim analysis
		Miller et al, 2005 abs (18)	Interim analysis
		Wagner et al, 2006 abs (19)	QOL analysis
		Klencke et al, 2008 abs (20)	Independent review of efficacy outcomes
AVADO	Miles et al, 2008 (12)	Fumoleau et al, 2008 abs (13)	Analysis of time to PD or death from last DCT
		Dirix et al, 2008 abs (14)	Retrospective analysis of brain metastases
		Wardley et al, 2008 abs (15)	Analysis of anticoagulation therapy

Notes: abs=abstract; DCT=docetaxel; PD=progressive disease; QOL=quality of life.

Trial Quality

As shown in Table 2, two of the RCTs were available as fully published reports (10,11). The primary endpoint for all three RCTs was PFS, and all three reported a sample size calculation (Table 2). All of the trials enrolled the required number of patients. The two fully published trials reported final analyses that were based on the intent-to-treat (ITT) population. Miles et al (12) reported, in abstract form, a final ITT analysis of the AVADO trial for the primary outcome (PFS) and response. Overall survival data, a secondary outcome, were still being collected at the time of publication. Both fully published trials were open-label studies; however, Miller et al (10) reported that all patients were centrally assessed by independent reviewers (radiologists and oncologists) who were blinded to both treatment assignment and investigator assessment. Miles et al (12) reported that the AVADO trial was double-blind and placebo-controlled; however, the authors did not specify to what the term double-blind referred. Both fully published trials assessed response, QOL, and adverse events using the same instruments: Response Evaluation Criteria in Solid Tumours (RECIST), Functional Assessment of Cancer Therapy-Breast (FACT-B), and National Cancer Institute - Common Toxicity Criteria (NCI-CTC) Version 2.0, respectively. Miles et al (12) did not report on the criteria or instrument used to assess patients. The method of randomization was reported for only one trial (11). All three trials stratified patients during randomization (Table 2). None of the RCTs reported on allocation concealment. Miller et al (11) reported that 1% of patients were lost to follow-up. The remaining two trials did not report if any patients were lost to follow-up (10,12).

Table 2. Quality characteristics of identified RCTs.

Author, year (ref)	Primary outcome	Required sample size	Secondary outcomes	Randomization method	Allocation concealment	Blinding	ITT analysis	Final analysis	Early termination	Losses to follow-up	Ethical Approval
Fully published trials											
Miller, 2007 (11)	PFS	685 pts req'd to provide 546 events to give 85% power at $\alpha=0.05$ to detect a 33% improvement in mdn PFS (6 mos to 8 mos).	ORR, OS, QOL, Tox	Permuted blocks within strata ^A	NR	Open-label	Yes	Yes	No	1%	Yes
Miller, 2005 (10)	PFS, Tox	400 pts req'd to provide 265 events to give 90% power at $\alpha=0.05$ to detect an improvement in mdn PFS from 4 mos to 6 mos.	ORR, DoR, OS, QOL	NR - stratified ^B	NR	Outcome assessors	Yes	Yes	No	NR	Yes
Abstracts											
Miles, 2008 abs (12)	PFS	705 pts req'd to give 80% power at $\alpha=0.05$ to detect an improvement in mdn PFS from 6.0 mos to 8.6 mos for each BVZ arm compared to placebo.	ORR, DoR, TTF, OS, Tox, QOL	NR - stratified ^C	NR	Double-blind ^D	Yes	Yes	No	NR	NR

Notes: abs=abstract; DoR=duration of response; ITT=intention-to-treat; mdn=median; mos=months; NR=not reported; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; pts=patients; QOL=quality of life; ref=reference; req'd=required; TTF=time-to-treatment failure; Tox=toxicity.

^AStratified by disease-free interval (≤ 24 mos or > 24 mos); number of metastatic sites (< 3 or ≥ 3); previous adjuvant chemotherapy (yes or no); estrogen-receptor status (positive or negative or unknown).

^BStratified by ECOG performance status (0 or 1); number of prior chemotherapy regimens for metastatic disease (0 or ≥ 1); and study site.

^CStratified by region; prior taxane therapy; time to relapse since adjuvant chemotherapy; measurable disease; hormone receptor status.

^DTrial was described as double-blind; however, none of the available abstracts report the aspects of the trial that were blinded.

Trial and Patient Characteristics

Trial and patients characteristics of the included RCTs can be found in Table 3. Two RCTs examined the use of bevacizumab as part of first-line therapy in patients with metastatic breast cancer. Both trials combined bevacizumab with a taxane regimen. Miles et al (12) randomized patients to one of three arms of docetaxel combined with either bevacizumab 15 mg/kg or 7.5 mg/kg, or placebo. All three arms were well balanced with respect to baseline characteristics. Miller et al (11) randomized patients to receive paclitaxel and bevacizumab or to paclitaxel alone. The authors reported that more patients assigned to the paclitaxel-alone arm had measurable disease and visceral disease. The authors performed a multivariate analysis, which included a number of variables, including measurable disease and number of metastatic sites in the model.

Table 3. Patient and intervention details for RCTs of bevacizumab in metastatic breast cancer.

Author, year (ref)	Patient characteristics	Treatment	Differences between treatment groups at baseline
First-line therapy			
Miles, 2008 (12)	MBC (or locally recurrent); HER2 negative, no prior chemo for locally recurrent or MBC. Prior adjuvant chemo allowed if relapse ≥ 6 months since last dose (≥ 12 months if taxane-based).	DCT 100 mg/m ² + BVZ 15 mg/kg, q3w until PD or tox. ^A DCT 100 mg/m ² + BVZ 7.5 mg/kg, q3w until PD or tox. ^A DCT 100 mg/m ² + placebo, q3w for 9 cycles max.	NR
Miller, 2007 (11)	MBC not previously treated with chemo for metastatic disease; previous hormonal therapy or adjuvant chemo allowed. HER2 positive included only if they had previously received trastuzumab.	PAC 90 mg/m ² d1,8,15 + BVZ 10 mg/kg iv d1,15, q28d until PD. PAC 90 mg/m ² d1,8,15, q28d until PD.	More patients assigned to PAC-alone arm had measurable disease and visceral disease.
Second-line or greater therapy			
Miller, 2005 (10)	MBC previously treated with both anthracycline and taxane and at least one but no more than two prior chemo regimens for metastatic disease. HER2 positive included only if they had previously received trastuzumab.	CAP 2500 mg/m ² /d orally twice daily for 14d then 7d rest period + BVZ 15 mg/kg iv d1, q21d until PD or 35 cycles max. CAP 2500 mg/m ² /d orally twice daily for 14d then 7d rest period, q21d until PD or 35 cycles max.	Balanced.

Notes: abs=abstract; ATZ=anastrozole; BVZ=bevacizumab; CAP=capecitabine; chemo=chemotherapy; CYCLO=cyclophosphamide; d=day(s); DCT=Docetaxel; ER=estrogen receptor; iv=intravenous; max=maximum; MBC=metastatic breast cancer; NR=not reported; PAC=paclitaxel; PD=progressive disease; PR=progesterone receptor; q=every; ref=reference; RT=radiation therapy; TAM=tamoxifen; tox=toxicity; w=week(s).

^ADocetaxel was given for a maximum of 9 cycles; bevacizumab was given until disease progression or unacceptable toxicity.

^BPatients that were estrogen/progesterone receptor positive received ATZ.

It is important to note that although Miller et al (10) clearly outlined the eligibility criteria for patient enrolment, a large proportion of patients (20%) who were included in the final analysis did not meet the eligibility criteria for the trial. The most common violations were having received prior therapy within the past 21 days (n=21), having received more than two regimens for metastatic disease (n=19), and central nervous system metastasis (n=10).

Efficacy Outcomes

Data on efficacy outcomes for trials of bevacizumab in metastatic breast cancer can be found in Table 4.

Table 4. Efficacy outcomes for RCTs of bevacizumab in metastatic breast cancer.

Author, year (ref)	Treatment	N	OR (%)	Comp	OS			PFS			Follow- up, mdn (mos)
					Mdn (mos)	Comp	HR (95% CI)	Mdn (mos)	Comp	HR (95% CI)	
First-line therapy											
Miles, 2008 abs (12)	DCT/BVZ 15 mg/kg	247	63.1 ^{A,B}	p=0.0001 ^A	NYR	p=NR	0.68 ^A (0.45-1.04)	8.8	p=0.0099	0.72 ^A (0.57-0.90)	10.2
	DCT/BVZ 7.5 mg/kg	248	55.2 ^{A,B}	p=0.0295 ^A	NYR	p=NR	0.92 ^A (0.62-1.37)	8.7	p=0.0318	0.79 ^A (0.63-0.98)	
	DCT/placebo	241	44.4 ^B	-	NYR	-	-	8.0	-	-	
Miller, 2007 (11)	PAC/BVZ 10 mg/kg	347	36.9	p<0.001	26.7	p=0.16	0.88	11.8	p<0.001	0.60 (0.51-0.70)	NR
	PAC	326	21.2		25.2			5.9			
Second-line or greater therapy											
Miller, 2005 (10)	CAP/BVZ 15 mg/kg	232	19.8	p=0.001	15.1	p=NS	NR	4.86	p=0.857	0.98 (0.77-1.25)	NR
	CAP	230	9.1		14.5			4.17			

Notes: abs=abstract; BVZ=bevacizumab; CAP=capecitabine; CI=confidence interval; comp=comparison; DCT=docetaxel; HR=hazard ratio; mdn=median; mos=months; N=number of patients; NR=not reported; NS=not significant; NYR=not yet reached; OR=objective response rate; OS=overall survival; PAC=paclitaxel; PFS=progression-free survival; ref=reference.

^ACompared to DCT/placebo arm.

^BObjective response rate for patients with measurable disease: BVZ 15 mg/kg, N=206; BVZ 7.5 mg/kg, N=201; placebo, N=207.

Survival

Both of the RCTs by Miller et al (10,11) reported no significant difference in OS (Table 4); however, neither trial was powered to detect differences in that outcome. Miles et al (12) reported that median OS was not yet reached in any arm at 10.2 months of follow-up. The authors reported that follow-up is continuing and that OS data will be forthcoming. Of note, that trial is also not powered to detect differences in OS.

Pooling of OS data was considered; however only one trial reported sufficient OS data for meta-analysis.

Disease control

Miller et al (10) reported that median PFS was not significantly different between the arm receiving capecitabine and bevacizumab compared to capecitabine alone (HR=0.98; 95% CI, 0.77 to 1.25). All patients had previously received treatment for metastatic disease.

Both of the RCTs of bevacizumab as part of first-line therapy reported statistically significant differences in PFS (Table 4). Miles et al (12) reported two different analyses of PFS. The first, reported above and in Table 4, was an unstratified analysis. The other was a stratified analysis that censored patients who received non-protocol antineoplastic therapy given prior to disease progression. For the bevacizumab 15 mg/kg arm compared to the control, the HR was 0.61 (95% CI, 0.48 to 0.78). For the bevacizumab 7.5 mg/kg arm

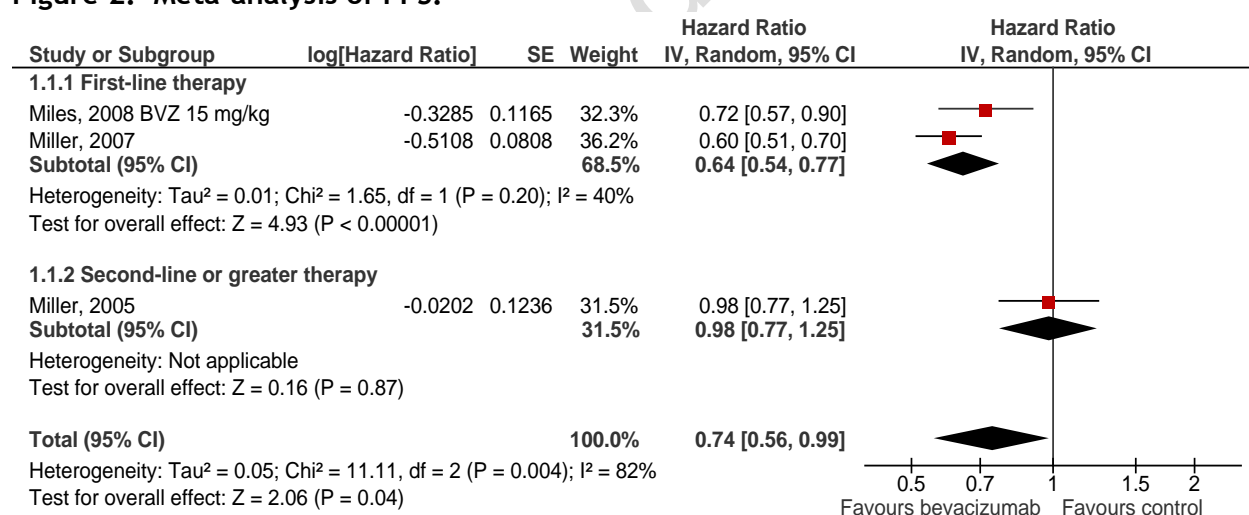
compared to control, the HR was 0.69 (95% CI 0.54 to 0.89). Miles et al did not report any further details regarding the analysis.

A meta-analysis of PFS data from all three trials was performed (Figure 2). Due to the design of the AVADO trial (12)—two treatment arms and only one control arm—and the fact that the authors reported PFS for each treatment arm compared to the control separately, both treatment arm comparisons could not be included in the PFS meta-analysis. An a priori decision was made to include the comparison of bevacizumab 15 mg/kg given every three weeks versus control over the bevacizumab 7.5 mg/kg every three weeks comparison as the 15 mg/kg dose more closely matched the dose of 10mg/kg every two weeks, given in the other first-line trial reported by Miller et al (11) (i.e., equivalent to 5mg/kg per week).

The overall HR for bevacizumab-containing regimens compared to the same regimen without bevacizumab was 0.74 (95% CI, 0.56 to 0.99). Statistical heterogeneity was significant ($p=0.004$) and the I^2 statistic indicated a high amount of heterogeneity (82%). The HR for first-line bevacizumab-containing therapy was 0.64 (95% CI, 0.54 to 0.77). Statistical heterogeneity was not statistically significant ($p=0.20$); however, the I^2 statistic indicated a moderate amount of heterogeneity (40%).

A sensitivity analysis was conducted to determine if the choice of treatment arm from the AVADO trial would have an effect on the overall or subgroup HRs. When the 7.5 mg/kg arm comparison was used instead of the 15 mg/kg comparison, the overall HR was 0.77 (95% CI, 0.57 to 1.02), with a significant and high amount of statistical heterogeneity ($p=0.002$, $I^2=83\%$). For the trials of first-line therapy, the pooled HR was 0.68 (95% CI, 0.52 to 0.89). Statistical heterogeneity was still significant ($p=0.05$), and the I^2 statistic indicated a high amount of heterogeneity (75%).

Figure 2. Meta-analysis of PFS.



Response

As shown in Table 4, all three RCTs reported statistically significant improvements in objective response rates in favour of bevacizumab.

Quality of life

All three trials indicated that QOL was a secondary outcome of interest; however, only the two fully published RCTs reported data on QOL (10,11). In the second-line bevacizumab trial (10), 194 and 176 patients in the bevacizumab arm and control arm, respectively,

completed a baseline QOL assessment and at least one additional QOL assessment using the FACT-B questionnaire. Time to deterioration in QOL was not significantly different between the bevacizumab and the control arms (2.86 months versus [vs.] 2.92 months; $p=0.633$). In the first-line bevacizumab trial (11), 631 patients completed the FACT-B questionnaire at baseline and 488 and 368 patients completed subsequent questionnaires at 17 weeks and 33 weeks, respectively. No significant difference in the mean change in score from baseline for the FACT-B was reported.

Adverse Events

The rates of grade 3 or 4 adverse events in the RCTs of bevacizumab therapy in metastatic breast cancer can be found in Table 5. Only the first-line trial of bevacizumab therapy reported by Miller et al (11) reported whether significant differences in the number of adverse events existed between the treatment and control arms. The authors reported significantly higher rates of grade 3 or 4 hypertension (14.8% vs. 0%; $p<0.001$), proteinuria (3.5% vs. 0%; $p<0.001$), neuropathy (23.5% vs. 17.7%; $p=0.05$), fatigue (9.1% vs. 4.9%; $p=0.04$), infection (9.3% vs. 2.9%; $p<0.001$), headache (2.2% vs 0.0%, $p=0.008$), and cerebrovascular ischemia (1.9 vs. 0.0%, $p=0.02$) for patients receiving bevacizumab and paclitaxel compared to paclitaxel alone. Fatal adverse reactions occurred in 6/347 (1.7%) of patients who received paclitaxel plus bevacizumab. Causes of death were ruptured diverticulum (one patient), erosion in an area of bowel-wall involvement (one patient), and left ventricular dysfunction (one patient). Causes of death for the remaining three patients were not reported.

Pooling of the most common adverse events was considered. The two fully published trials reported that adverse events were rated using the NCI-CTC version 2.0 (10,11); however, Miles et al (12) did not report how adverse events were rated in the AVADO trial. In addition, none of the trial reports indicated the time points at which adverse events were recorded, thus making it difficult to ascertain whether it was appropriate or not to pool adverse event data. For example, grade 3 or 4 neutropenia occurred in 19.5% of 495 patients who received bevacizumab/docetaxel and in 17.2% of 233 patients who received docetaxel alone (12). When contrasted with the rate in the other first-line taxane-therapy trial (11) (bevacizumab/paclitaxel 0% of 365 patients and paclitaxel 0.3% of 346 patients), there is at least an order of magnitude difference in the rate of grade 3 or 4 neutropenia. The second-line capecitabine-based trial (10) also reported a rate of grade 3 or 4 neutropenia that was an order of magnitude lower than that reported for the AVADO trial. A similar case can be made for grade 3 or 4 hypertension, with the order of magnitude difference reversed for the AVADO trial (12) contrasted with the remaining two trials (10,11). Given the lack of information regarding adverse events, and the differences in the reported rates of adverse events, a meta-analysis of those outcomes was considered inappropriate.

Table 5. Grade 3 or 4 adverse events.

Author, year (ref)	Treatment	N	Hypertension (%)	Proteinuria (%)	Bleeding (%)	Thromboembolic (%)	Neuropathy (%)	Fatigue (%)	Neutropenia (%)	Infection (%)
First-line therapy										
Miles, 2008 abs (12)	DCT/BVZ 15 mg/kg	247	3.2	0.4	1.2	1.2	4.5	6.5	19.8	NR
	DCT/BVZ 7.5 mg/kg	250	0.4	0	1.2	1.2	3.2	8.4	19.2	NR
	DCT/placebo	233	1.3	0	0.9	3.4	1.7	5.2	17.2	NR
Miller, 2007 (11)	PAC/BVZ 10 mg/kg	365	14.8	3.5	NR	2.1	23.5	9.1	0	9.3
	PAC	346	0 p<0.001	0 p<0.001	NR	1.5	17.7 p=0.05	4.9 p=0.04	0.3	2.9 p<0.001
Second-line or greater therapy										
Miller 2005 (10)	CAP/BVZ 15 mg/kg	229	17.9	0.9	0.4	5.7	NR	NR	2.6 ^A	0.9
	CAP	215	0.5	0	0.5	3.7	NR	NR	2.8 ^A	0.5

Notes: abs=abstract; BVZ=bevacizumab; CAP=capecitabine; DCT=docetaxel; N=number of treated patients; PAC=paclitaxel; ref=reference.

^ALeukopenia.

DISCUSSION

The current evidence for bevacizumab in metastatic breast cancer consists of three RCTs. Two trials investigated the use of bevacizumab as part of first-line therapy with taxane-based regimens (11,12) while the remaining trial investigated its use as part of second-line or later therapy in combination with capecitabine (10). None of the RCTs reported a significant difference in OS; however, data are still being accumulated for OS in the AVADO first-line trial (12). There was a significant improvement in PFS in patients receiving bevacizumab and weekly paclitaxel, but the study was an open label trial, and the assessment of outcome was not blinded (11). There was, however, a retrospective independent review of blinded radiological and clinical data prior to FDA approval confirming the results (20). After controlling for an imbalance at baseline in presence of measurable disease and visceral metastatic sites between the control and bevacizumab groups, the results remained significant. The improvement in PFS with the combination of bevacizumab and docetaxel in the AVADO trial was much less impressive (12). These studies would likely be strengthened by the ability to identify patients most likely to benefit from VEGF-directed therapies, analogous to HER2 directed therapy with trastuzumab.

A meta-analysis of PFS produced conflicting results. There was no significant difference in PFS when the data from the AVADO 7.5 mg/kg arm compared to control were used (HR=0.77; 95% CI, 0.57 to 1.02). When the 15 mg/kg comparison was used instead, there was a significant difference in PFS (HR=0.74; 95% CI, 0.56 to 0.99). The two first-line taxane-based RCTs, through three comparisons of bevacizumab to control, independently and consistently demonstrated a significant improvement in PFS (Table 4), although the clinical significance of the improvement in the AVADO trial is minimal.

The second-line or greater RCT of bevacizumab in combination with capecitabine compared to capecitabine alone demonstrated no significant difference in PFS (HR=0.98; 95% CI, 0.77 to 1.25). These results may reflect the late-disease stage and poor prognostic factors of the patient population in the study, such as the inclusion of 23.4% of women with HER2-positive breast cancer. Patients in this trial had also received more chemotherapy than those in the RCT of paclitaxel and bevacizumab (11) that targeted first-line treatment of metastatic breast cancer. In comparison, more than 80% of patients in capecitabine trial (10) had received prior treatment for metastatic breast cancer, and 40% had received two or more prior regimens. As a result, patients in that trial likely had more chemotherapeutic resistance. It has also been suggested that as breast cancers progress the proportion and type of angiogenic mediators change.

Commonly observed adverse events in the RCTs of bevacizumab included grade 3 or 4 bleeding, thrombosis, hypertension, neutropenia, and proteinuria. Hypertension seen in clinical trials has been manageable with oral anti-hypertensive medications. Reported and ongoing phase III trials have excluded patients with cerebral metastases, proteinuria, or bleeding diathesis; thus, those conditions should be considered contraindications to the use of bevacizumab.

CONCLUSIONS

Thus far, there does not appear to be an increase in OS with the addition of bevacizumab to chemotherapy compared to chemotherapy alone. When weekly paclitaxel is added to bevacizumab compared to weekly paclitaxel alone, there is a clinically and statistically significant doubling of median PFS from 5.9 to 11.8 months with an HR of 0.6. Although the median PFS results from the trial combining docetaxel with bevacizumab are less impressive, the HRs are similar.

Women with metastatic or locally advanced breast cancer receiving taxane-based chemotherapy as first-line therapy could be offered bevacizumab to improve PFS. In this

setting, the addition of bevacizumab would be analogous to the efficacy seen with the combination of docetaxel and capecitabine. The addition of bevacizumab to chemotherapy is not currently recommended for patients with metastatic breast cancer receiving second-line therapy or greater outside of a clinical trial.

ONGOING TRIALS

The National Cancer Institute's clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) and the National Institutes of Health Clinical Trials database (<http://clinicaltrials.gov/>) were searched for reports of new or ongoing randomized trials investigating the use of bevacizumab in patients with locally advanced or metastatic breast cancer that met our eligibility criteria. Appendix 2 provides details of the identified ongoing trials.

CONFLICT OF INTEREST

The authors of this special advice report disclosed potential conflicts of interest relating to the topic of this special advice report. One author (RD) received honoraria from the manufacturer of bevacizumab for conducting presentations and as an advisory board participant. One author has received research support from the manufacturer of bevacizumab (MT). The remaining authors (AEH, CH, AE) reported no conflicts of interest.

ACKNOWLEDGEMENTS

The PEBC would like to thank Dr. Rebecca Dent, Dr. Katherine Enright, Dr. Caroline Hamm, Dr. Andrea Eisen, Dr. Maureen Trudeau, and Mr. Adam Haynes for taking the lead in drafting this special advice report.

REFERENCES

1. Canadian Cancer Statistics 2008. Toronto, Canada: Canadian Cancer Society/National Cancer Institute of Canada; 2008 Apr [cited 2009 Mar 24]. Available from: <http://www.cancer.ca/statistics>.
2. Linderholm BK, Lindh B, Beckham L, Tavelin B, Grankvist K, Bergh J, et al. The prognostic value of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) and associations to first metastasis site in 1307 patients with primary breast cancer [abstract]. Proc Am Soc Clin Oncol 2001;20:Abstract 13.
3. Gordon MS, Margolin K, Talpaz M, Sledge GW Jr, Holmgren E, Benjamin R, et al. Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. J Clin Oncol. 2001;19(3):843-50.
4. Margolin K, Gordon MS, Holmgren E, Gaudreault J, Novotny W, Fyfe G, et al. Phase Ib trial of intravenous recombinant humanized monoclonal antibody to vascular endothelial growth factor in combination with chemotherapy in patients with advanced cancer: pharmacologic and long-term safety data. J Clin Oncol. 2001;19(3):851-6.
5. Langmuir VK, Cobleigh MA, Herbst RS, Holmgren E, Hurwitz H, Kabbinavar F, et al. Successful long-term therapy with bevacizumab (Avastin) in solid tumours [abstract]. Proc Am Soc Clin Oncol. 2002;21:Abstract 32.
6. Ramaswamy B, Elias AD, Kelbick NT, Dodley A, Morrow M, Hauger M, et al. Phase II trial of bevacizumab in combination with weekly docetaxel in metastatic breast cancer patients. Clin Cancer Res. 2006;12(10):3124-9.
7. Review Manager (RevMan) [Computer Program]. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2008.
8. Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med. 1998;17:2815-34.
9. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.
10. Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol. 2005;23(4):792-9.
11. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 2007;357(26):2666-76.
12. Miles D, Chan A, Romieu G, Dirix LY, Cortes J, Pivot X, et al. Randomized, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBc): AVADO [abstract and slide presentation on the Internet]. J Clin Oncol (ASCO Annual Meeting Proceedings). 2008;26(15 Suppl):Abstract LBA1011. [Cited 2009 Mar 10]. Slides available at: http://www.asco.org/ASCO/Abstracts+%26+Virtual+Meeting/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=34482.
13. Fumoleau P, Greil R, Rayson D, Müller V, Barni S, Aleknavicius E, et al. Bevacizumab (BV) maintenance therapy significantly delays disease progression (PD) or death compared with placebo (PL) in the AVADO trial (BV + docetaxel [D] vs D + PL in 1st-line HER2-negative locally recurrent [LR] or metastatic breast cancer [mBC]) [abstract on the Internet]. 31st Annual San Antonio Breast Cancer Symposium. 2008 [cited 2009 Mar 10]:Abstract 903. Available at: <http://www.sabcs.org/EnduringMaterials/Index.asp#abstracts>.

14. Dirix LY, Romieu G, Provencher L, Grimes D, de Souza Viana L, Paterson A, et al. Safety of bevacizumab (BV) plus docetaxel (D) in patients (pts) with locally recurrent (LR) or metastatic breast cancer (mBC) who developed brain metastases during the AVADO phase III study [abstract on the Internet]. 31st Annual San Antonio Breast Cancer Symposium. 2008 [cited 2009 Mar 10]:Abstract 4116. Available at: <http://www.sabcs.org/EnduringMaterials/Index.asp#abstracts>.
15. Wardley A, Lohrisch C, Joy AA, Young S, Yi FF, Marme A, et al. Effect of anticoagulation therapy on bleeding and thromboembolic events (TEs) in the AVADO phase III study of docetaxel (D) ± bevacizumab (BV) in inoperable locally recurrent (LR) or metastatic breast cancer (mBC) [abstract on the Internet]. 31st Annual San Antonio Breast Cancer Symposium. 2008 [cited 2009 Mar 10]:Abstract 1035. Available at: <http://www.sabcs.org/EnduringMaterials/Index.asp#abstracts>.
16. Miller KD, Rugo HS, Cobleigh MA, Marcom PK, Chap LI, Holmes FA, et al. Phase III trial of capecitabine (Xeloda®) plus (Avastin™) versus capecitabine alone in women with metastatic breast cancer (MBC) previously treated with an anthracycline and a taxane [abstract]. Breast Cancer Res Treat (25th Annual San Antonio Breast Cancer Symposium). 2002;76(Suppl 1):Abstract 36.
17. Miller KD, Wang M, Gralow J, Dickler M, Cobleigh MA, Perez EA, et al. A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: a trial coordinated by the Eastern Cooperative Oncology Group (E2100) [abstract]. Breast Cancer Res Treat (28th Annual San Antonio Breast Cancer Symposium). 2005;94(Suppl 1):Abstract 3.
18. Miller K, Wang M, Gralow J, Dickler M, Cobleigh MA, Perez EA, et al. First-line bevacizumab and paclitaxel in patients with locally recurrent or metastatic breast cancer: a randomized, phase III trial coordinated by the Eastern Cooperative Oncology Group (E2100) [abstract]. Eur J Cancer. 2005;3(2):77-8.
19. Wagner LI, Wang M, Miller K, Davidson NE, Gralow J, Dickler M, et al. Health-related quality of life among patients with metastatic breast cancer receiving paclitaxel versus paclitaxel plus bevacizumab: results from the Eastern Cooperative Oncology Group (ECOG) study E2100 [abstract]. Breast Cancer Res Treat (29th Annual San Antonio Breast Cancer Symposium). 2006;100(Suppl 1):Abstract 5078.
20. Klencke BJ, Bhattacharya S, Samant MK, Gralow JR, Dickler MN, Cobleigh MA, et al. Independent review of E2100 progression-free survival (PFS) with the addition of bevacizumab (B) to paclitaxel (P) as initial chemotherapy for metastatic breast cancer (MBC) [abstract]. J Clin Oncol (ASCO Annual Meeting Proceedings). 2008;26(15 Suppl):Abstract 1036.

Appendix 1. Literature search strategies.

Ovid MEDLINE

1. exp breast neoplasms/
2. ((breast or mammary or mammarian) and (cancer\$ or carcinoma\$ or neoplasm\$ or tumor\$ or malignan\$)).tw.
3. 1 or 2
4. bevacizumab.tw.
5. avastin.tw.
6. 4 or 5
7. 3 and 6
8. meta-analysis as topic/
9. meta analysis.pt.
10. meta analy\$.tw.
11. metaanaly\$.tw.
12. (systematic adj (review\$1 or overview\$1)).tw.
13. or/8-9
14. cochrane.ab.
15. embase.ab.
16. (cinahl or cinhal).ab.
17. science citation index.ab.
18. bids.ab.
19. cancerlit.ab.
20. or/14-19
21. reference list\$.ab.
22. bibliograph\$.ab.
23. hand-search\$.ab.
24. relevant journals.ab.
25. manual search\$.ab.
26. or/21-25
27. selection criteria.ab.
28. data extraction.ab.
29. 27 or 28
30. review.pt.
31. review literature as topic/
32. 30 or 31
33. 29 and 32
34. comment.pt.
35. letter.pt.
36. editorial.pt.
37. or/34-36
38. 13 or 20 or 26 or 33
39. 38 not 37
40. randomized controlled trials as topic/
41. randomized controlled trial.pt.
42. random allocation/
43. double blind method/
44. single blind method/
45. Clinical Trials, Phase III as Topic/
46. clinical trial, phase III.pt.
47. Clinical Trials, Phase II as Topic/

48. clinical trial, phase II.pt.
49. (clinic\$ adj trial\$1).tw.
50. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.
51. placebos/
52. placebo\$.tw.
53. (allocated adj2 random\$).tw.
54. random allocation.tw.
55. randomly allocated.tw.
56. or/40-55
57. case report.tw.
58. letter.pt.
59. historical article.pt.
60. or/57-59
61. 56 not 6053
62. 39 or 6154
63. practice guideline/
64. practice guideline\$.mp.
65. 63 or 64
66. 62 or 65
67. 7 and 66
68. limit 67 to (English language and humans)

EMBASE

1. exp Breast Cancer/
2. ((breast or mammary or mammarian) and (cancer\$ or carcinoma\$ or neoplasm\$ or tumo?r\$ or malignan\$)).tw.
3. 1 or 2
4. Bevacizumab/
5. bevacizumab.tw.
6. avastin.tw.
7. or/4-6
8. 3 and 7
9. exp meta-analysis/
10. ((meta adj analy\$) or metaanaly\$).tw.
11. (systematic adj (review\$1 or overview\$1)).tw.
12. or/9-11
13. cancerlit.ab.
14. cochrane.ab.
15. embase.ab.
16. (cinahl or cinhal).ab.
17. science citation index.ab.
18. bids.ab.
19. or/13-18
20. reference list\$.ab.
21. bibliograph\$.ab.
22. hand-search\$.ab.
23. manual search\$.ab.
24. relevant journals.ab.
25. or/20-24
26. data extraction.ab.

27. selection criteria.ab.
28. 26 or 27
29. review.pt.
30. 28 and 29
31. letter.pt.
32. editorial.pt.
33. 311 or 3224
34. 12 or 19 or 25 or 30
35. 34 not 33
36. randomized controlled trial/
37. randomization/
38. single blind procedure/
39. double blind procedure/
40. placebo/
41. randomi?ed control\$ trial\$.tw.
42. rct.tw.
43. random allocation.tw.
44. randomly allocated.tw.
45. allocated randomly.tw.
46. (allocated adj2 random\$).tw.
47. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw.
48. placebo\$.tw.
49. or/36-48
50. case study/
51. case report.tw.
52. abstract report/
53. letter/
54. or/50-53
55. 49 not 54
56. exp practice guideline/
57. practice guideline\$.tw.
58. 56 or 57
59. 35 or 55 or 58
60. 8 and 59
61. limit 60 to (human and English language)

Appendix 2. Ongoing trials.

A Multicenter, Phase III, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination With Chemotherapy Regimens in Subjects With Previously Untreated Metastatic Breast Cancer

Protocol ID:	NCT00262067, RIBBON 1
Last date modified:	September 29, 2008
Trial type:	Randomized, placebo-controlled
Accrual:	1200
Primary outcome:	Progression-free survival
Sponsorship:	Genentech; Hoffmann-La Roche
Status:	Ongoing, not accruing

A Phase III, Multicenter, Randomized, Placebo-Controlled Trial Evaluating the Efficacy and Safety of Bevacizumab in Combination With Chemotherapy Regimens in Subjects With Previously Treated Metastatic Breast Cancer

Protocol ID:	NCT00281697, RIBBON 2
Last date modified:	September 22, 2008
Accrual:	650
Trial type:	Randomized, placebo-controlled
Primary outcome:	Progression-free survival
Sponsorship:	Genentech
Status:	Ongoing, not accruing

A Randomized Phase III Double-Blind Placebo-Controlled Trial of First-Line Chemotherapy and Trastuzumab With or Without Bevacizumab for Patients With HER-2/NEU Over-Expressing Metastatic Breast Cancer

Protocol ID:	NCT00520975
Last date modified:	April 4, 2009
Trial type:	Randomized, double-blind, placebo-controlled
Accrual:	489
Primary outcome:	Progression-free survival
Sponsorship:	Eastern Cooperative Oncology Group; National Cancer Institute (NCI); North Central Cancer Treatment Group; Cancer and Leukemia Group B; Southwest Oncology Group
Status:	Accruing

A Randomized, Open-Label Study to Compare the Effect of First-Line Treatment With Avastin in Combination With Herceptin/Docetaxel and Herceptin/Docetaxel Alone on Progression-Free Survival in Patients With HER2 Positive Locally Recurrent or Metastatic Breast Cancer

Protocol ID:	NCT00391092
Last date modified:	March 16, 2009
Accrual:	410
Trial type:	Randomized, open-label, active control
Primary outcome:	Progression-free survival
Sponsorship:	Hoffmann-La Roche
Status:	Accruing

Appendix 2 (Continued). Ongoing trials

Multicenter, Randomized Study to Evaluate the Efficacy and Safety of Bevacizumab in Combination with Letrozole Compared to Letrozole Alone, in Postmenopausal Women with Advanced or Metastatic Cancer with Indication of Hormonotherapy as First-line Treatment

Protocol ID:	NCT00545077
Last date modified:	November 11, 2008
Trial type:	Randomized, open-label, active control
Accrual:	378
Primary outcome:	Progression-free survival
Sponsorship:	Spanish Breast Cancer Research Group; Hoffmann-La Roche
Status:	Accruing

Endocrine Therapy in Combination With Anti-VEGF Therapy: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Endocrine Therapy Alone or Endocrine Therapy Plus Bevacizumab (NSC 704865; IND 7921) for Women With Hormone Receptor-Positive Advanced Breast Cancer

Protocol ID:	NCT00601900
Last date modified:	April 4, 2009
Accrual:	502
Trial type:	Randomized, double-blind, placebo-controlled
Primary outcome:	Progression-free survival and adverse events
Sponsorship:	Cancer and Leukemia Group B; National Cancer Institute (NCI)
Status:	Accruing