

Off-Label Uses of Bevacizumab: Breast and Lung Cancer Indications



Assessment
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Executive Summary

Background

Bevacizumab (Avastin[®]) is a humanized recombinant antibody to vascular endothelial growth factor-A (VEGF-A). VEGF-A bound to bevacizumab cannot bind to or activate VEGF receptors (VEGF-R) on vascular endothelial and other cells. Biological consequences include inhibition of angiogenesis (growth of new blood vessels) in tumors.

Bevacizumab combined with intravenous fluorouracil-based chemotherapy is indicated as first- or second-line therapy for advanced or metastatic colon or rectal cancers. Ongoing studies investigate use of bevacizumab in adjuvant therapy regimens following surgery for operable stages of colon and rectal cancers.

Objective

This Assessment summarizes and evaluates evidence on outcomes of bevacizumab for breast cancer and non-small cell lung cancer (NSCLC). For both cancers, evidence on bevacizumab is assessed separately as second- or subsequent-line therapy for advanced or metastatic disease, as first-line therapy for advanced or metastatic disease, or as adjuvant therapy for early stage disease. Another Assessment (Vol. 21, No. 9) summarizes and evaluates evidence on health outcomes of bevacizumab for clear cell renal carcinoma and other malignancies besides colorectal cancers.

Search Strategy

MEDLINE[®] was searched through July 2006 using the terms “Avastin” or “bevacizumab,” cross-indexed with breast or lung neoplasms, or indexed as a clinical trial NOT colon cancer. Hand-searching of reference lists and online searches of recent meeting presentations in the U.S. supplemented the search, which was limited to English-language articles on human subjects.

Selection Criteria

The Assessment includes full-length, peer-reviewed articles reporting on 10 or more patients. Also summarized are meeting presentations with slides available online showing results of phase III randomized comparative trials (RCTs).



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Part I: Breast Cancer

A. Second- or Subsequent-Line Therapy for Advanced or Metastatic Disease

Main Results

One of 2 available studies was a dose-escalation trial of bevacizumab monotherapy (5–20 mg/kg; total n=75) that lacked controls managed without bevacizumab, and did not demonstrate a dose-response relationship for the clinical outcomes reported. The second was an RCT (total n=462) of capecitabine with versus without bevacizumab as second- or third-line therapy for metastatic disease that relapsed after doxorubicin and a taxane (used separately as adjuvant therapy or for relapse). The RCT reported no significant difference between arms for duration of response, progression-free survival (PFS), or overall survival (OS), and an absolute increase of 17.5% in grade 3 (treatable) hypertension.

Author's Conclusions and Comments

Neither study showed improved OS or PFS. However, ongoing trials are testing bevacizumab combined with drugs other than capecitabine. Also, results of the currently available studies may not be generalizable to patients whose disease has not separately failed regimens that used doxorubicin and a taxane.

B. First-Line Therapy for Advanced or Metastatic Disease

Main Results

An Eastern Cooperative Oncology Group (ECOG) multicenter RCT (E2100) on paclitaxel with (n=341) versus without (n=339) bevacizumab as first-line therapy for inoperable metastatic disease was presented at two national meetings but has not been published. The first interim analysis reported statistically significant improvement in overall response rate (ORR), PFS, and OS. The second interim analysis also found statistically significant improvement in ORR (30% versus 14%, $p<0.0001$) and PFS (11.4 versus 6.1 months; $p<0.0001$), but effects on OS were no longer statistically significant (28.4 versus 25.2 months; $p=0.12$). The only other study, a published pilot trial on inoperable locally advanced or inflammatory disease, lacked controls.

Author's Conclusions and Comments

Although the first interim analysis of E2100 found a statistically significant increase in median duration of OS for the bevacizumab arm compared with the control arm, the between-arm difference was not statistically significant in the second interim analysis. Definitive conclusions await results from the final analysis. Between-arm differences in PFS significantly favored bevacizumab in each interim analysis, but evaluation of response and progression was unblinded and without central review. Furthermore, evidence is presently unavailable to determine whether longer time to progression translated to improved health status of the patients randomized to bevacizumab. For these reasons, the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) deferred conclusions on outcomes of first-line bevacizumab for advanced or metastatic breast cancer, pending availability of final results from the unpublished E2100 phase III RCT.

C. Adjuvant Therapy after Resection

Main Result

No evidence was found on outcomes of bevacizumab for adjuvant therapy of resected breast cancer.

Part II: Non-Small Cell Lung Cancer:

A. Second- or Subsequent-Line Therapy for Advanced or Metastatic Disease

Main Results

The literature search identified one uncontrolled dose-finding study on second-line therapy (n=34) that combined bevacizumab with erlotinib. The report did not include concurrent or historical controls managed with erlotinib alone.

B. First-Line Therapy for Advanced or Metastatic Disease

Main Results

Two RCTs investigated carboplatin plus paclitaxel, one of several regimens used as initial therapy for inoperable NSCLC, with versus without bevacizumab. One was a small, 3-arm phase II RCT that compared 2 dose levels of bevacizumab versus controls (n=32–34 per arm). Between-arm differences in PFS or OS were not statistically significant. The second, an ECOG multicenter RCT (E4599), was presented at a national meeting but has not been published. Interim analysis found that adding bevacizumab (n=424) to carboplatin plus paclitaxel (n=431 controls) significantly improved ORR (27% versus 10%; p<0.0001), median PFS (6.4 versus 4.5 months; p<0.0001), and median OS (12.5 versus 10.2 months; p=0.007).

Author's Conclusions and Comments

The published phase II RCT lacked sufficient statistical power to detect between-arm differences in survival outcomes, as the goal was to select a dose for and judge whether a phase III trial was warranted. Although the E4599 interim analysis found statistically significant improvement in OS and PFS, the independent data and safety monitoring board continued the trial after reviewing these interim results, and did not recommend crossing over control patients to bevacizumab. Therefore, the MAP deferred conclusions on bevacizumab for first-line therapy of advanced, metastatic, or recurrent NSCLC, pending availability of final results from the unpublished E4599 phase III RCT.

C. Adjuvant Therapy after Resection

Main Result

No evidence was found on outcomes of bevacizumab for adjuvant therapy of resected NSCLC.

For reasons detailed above, the MAP deferred decisions on outcomes of bevacizumab as first-line therapy for advanced or metastatic breast or lung cancers, pending availability of final results from the completed ECOG E2100 (breast cancer) and E4599 (lung cancer) phase III RCTs.

For the remaining indications, the MAP made the following judgments, based on the available evidence, about whether bevacizumab meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria as therapy for breast or lung cancers. Three indications were evaluated separately for both malignancies:

- second- or subsequent-line therapy for advanced or metastatic disease;
- first-line therapy for advanced or metastatic disease; and
- adjuvant therapy for operable, early stage disease.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

The U.S. Food and Drug Administration (FDA) approved bevacizumab (Avastin®) in February 2004 as first-line therapy for metastatic carcinoma of the colon or rectum, when used in combination with intravenous fluorouracil-based chemotherapy. In June 2006, the FDA added second-line therapy for metastatic colorectal cancer as a second approved indication for bevacizumab, when used in combination with intravenous fluorouracil-based chemotherapy. Use of bevacizumab to

treat patients with breast, lung, renal cell, or other non-colorectal cancers is an off-label indication, whether it is given as second- or subsequent-line therapy for advanced or metastatic disease, first-line therapy for advanced or metastatic disease, or as adjuvant therapy for an earlier disease stage.

The company's Web site (<http://www.gene.com/gene/pipeline/status/oncology/avastin/index.jsp>) notes that a supplemental biologics licensing application (sBLA) submitted to FDA in April 2006 was granted priority review status, which requires a final decision by 6 months from submission (i.e., by October 2006). This sBLA seeks approval for a third bevacizumab indication: first-line treatment of non-small cell lung cancer (in combination with platinum-based chemotherapy) in patients with histology other than predominantly squamous cell. In May 2006, the manufacturer submitted a sBLA for a fourth indication: first-line treatment of metastatic breast cancer. The manufacturer requested and FDA granted priority review status for this sBLA also (i.e., final decision by November 2006). However, FDA also requested more documentation from the pivotal trial supporting the sBLA on metastatic breast cancer, and the manufacturer predicts this will delay FDA's final action.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

Available evidence does not permit conclusions on outcomes of bevacizumab as second- or subsequent-line therapy of advanced or metastatic breast or lung cancers, or on outcomes of bevacizumab as a component of adjuvant therapy for either malignancy.

3. The technology must improve the net health outcome; and

4. The technology must be as beneficial as any established alternatives.

Since available evidence is insufficient to permit conclusions, it cannot be determined whether bevacizumab improves net health outcome as second-line therapy of patients with breast or lung cancers. Consequently, it also cannot be determined whether the improvement from use of bevacizumab for either of these indications is as beneficial as any established alternatives.

5. The improvement must be attainable outside the investigational settings.

For all indications considered here, whether bevacizumab improves health outcomes, and whether the improvement from use of bevacizumab is as beneficial as any established alternatives, has not yet been determined in the investigational setting.

Based on these findings, bevacizumab does not meet the TEC criteria as second-line therapy for advanced or metastatic breast or lung cancers or as a component of adjuvant therapy for either of these malignancies. Decisions are deferred on whether bevacizumab meets TEC criteria for first-line therapy of advanced or metastatic breast or lung cancers.

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Assessment Objective

Bevacizumab (Avastin®) is a humanized recombinant antibody to vascular endothelial growth factor-A (VEGF-A). VEGF-A bound to bevacizumab cannot bind to or activate VEGF receptors (VEGF-R) on vascular endothelial and other cells. Biological consequences of preventing VEGF-A from binding to and activating VEGF-R include inhibition of angiogenesis (growth of new blood vessels) in tumors.

Bevacizumab combined with intravenous fluorouracil-based chemotherapy is indicated as first- or second-line therapy for advanced or metastatic colon or rectal cancers. Ongoing studies investigate use of bevacizumab in adjuvant therapy regimens following surgery for operable stages of colon and rectal cancers.

The Assessment's 2 sections summarize and evaluate evidence on health outcomes of bevacizumab for breast cancer and non-small cell lung cancer. For both malignancies, available evidence is assessed separately on bevacizumab for first-line, or second- and subsequent-line therapy of metastatic or advanced disease, or as adjuvant therapy for earlier-stage (operable) disease. Another Assessment (Vol. 21, No. 9) summarizes and evaluates evidence on health outcomes of bevacizumab for clear cell renal carcinoma and other malignancies besides colorectal cancers.

Introduction

Vascular Endothelial Growth Factors and Angiogenesis

Vascular endothelial growth factors (VEGFs) and their receptors (VEGF-Rs) contribute to tumor growth and metastasis by promoting angiogenesis, the growth of new vasculature (for reviews, see Folkman 2006; Cebe-Suarez et al. 2006; Bouis et al. 2006; Hicklin and Ellis 2005; Verheul and Pinedo 2005; Rhee and Hoff 2005; Schneider and Miller 2005; Fidler et al. 2005). Without angiogenesis, nutrients, oxygen and other essential molecules reach malignant cells only by passive diffusion from pre-existing blood vessels, which would limit most tumors to diameters of several millimeters. Certain normal physiologic processes (e.g., embryonic development, menstruation, ovulation, wound healing) require angiogenesis, and some non-cancer pathologic processes are linked

to angiogenesis (e.g., macular degeneration, atherosclerosis, rheumatic diseases, psoriasis).

As depicted in Figure 1, the VEGF network includes 6 secreted glycoprotein ligands (VEGF-A through VEGF-E and placental growth factor or PlGF), three receptors (VEGF-R1 through VEGF-R3), and two co-receptors, neuropilin-1 and -2 (Hicklin and Ellis 2005). Each VEGF-R includes an intracellular tyrosine kinase domain activated by extracellular ligand binding. Endothelial cells increase their survival, proliferation, migration, and differentiation; bone marrow endothelial progenitors are mobilized into the peripheral circulation; and venules and small veins become more permeable to macromolecules after VEGF/VEGF-R signaling through tyrosine kinase activation. These responses help promote growth of new blood vessels and lymphatics (Folkman 2006; Cebe-Suarez et al. 2006; Bouis et al. 2006; Hicklin and Ellis 2005; Verheul and Pinedo 2005; Rhee and Hoff 2005; Fidler et al. 2005).

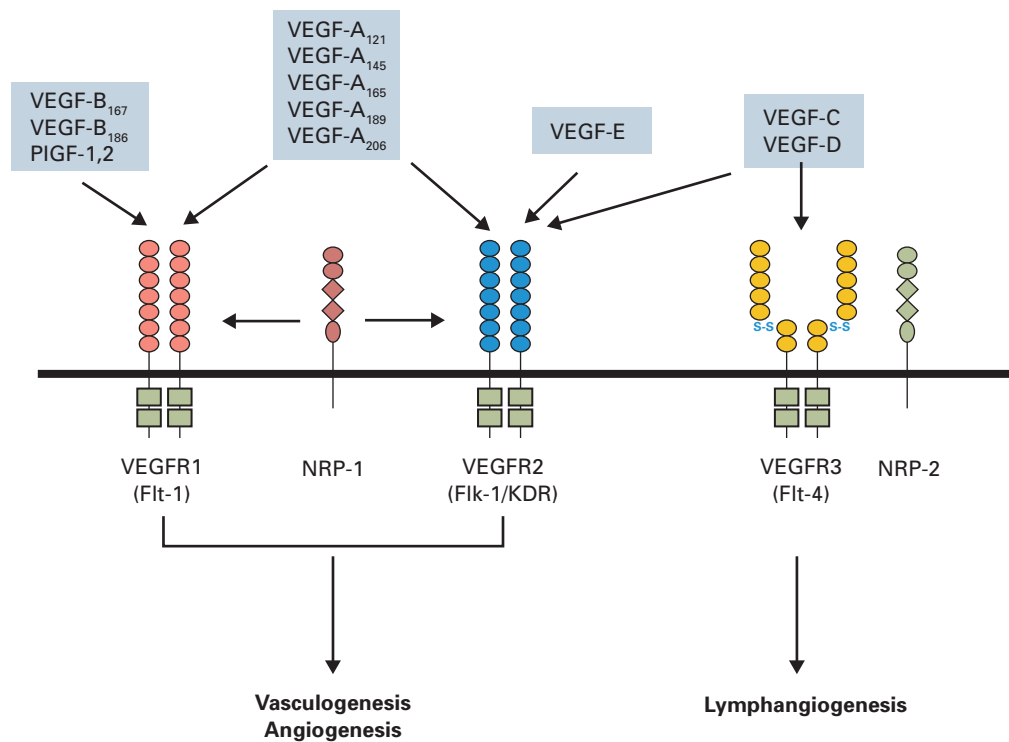
Besides the VEGF glycoproteins and their receptors, multiple other factors stimulate or inhibit angiogenesis (Folkman 2006; Cebe-Suarez et al. 2006; Bouis et al. 2006; Hicklin and Ellis 2005; Verheul and Pinedo 2005; Rhee and Hoff 2005; Fidler et al. 2005; Folkman 2005). Basic fibroblast growth factor, epidermal growth factor, angiopoietins, and matrix metalloproteases are examples of pro-angiogenic factors. Endostatin, angiostatin, tumstatin, and thrombospondins-1 and -2 are examples of endogenous anti-angiogenic factors. The local balance between pro- and anti-angiogenic factors controls normal and pathologic angiogenesis.

The ability to inhibit tumor angiogenesis by blocking one target may be difficult to predict, given the complex network of multiple pathways that regulate and influence this process. Furthermore, different malignancies, or stages of a specific malignancy, may differ in effects of inhibiting angiogenesis on tumor growth, disease progression and clinical outcomes of treatment. Hence, empirical evidence is needed from well-designed and rigorously conducted clinical trials (that are disease- and stage-specific) to assess outcomes of an anti-angiogenic therapy.

Bevacizumab for Colon or Rectal Cancer

Bevacizumab is a humanized monoclonal antibody directed against VEGF-A (Hicklin and

Figure 1. Binding Specificity of Various Vascular Endothelial Growth Factor (VEGF) Family Members and Their Receptors



The VEGF family consists of seven ligands derived from distinct genes (VEGF-A, -B, -C, -D and -E, placenta growth factor [PlGF] -1 and -2). In addition, specific family members, such as VEGF-A, may be expressed as isoforms due to mRNA alternative splicing. VEGF family members and isoforms have specific binding affinities to VEGF receptor (VEGFR) -1, VEGFR-2 and VEGFR-3 tyrosine kinase receptors as shown. In addition, neuropilin (NRP) -1 and NRP-2 are co-receptors for specific isoforms of VEGF family members and increase binding affinity of these ligands to their respective receptors.

From: Hicklin and Ellis. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol*, 2005; 23(5):1011-27. Reprinted with permission from the American Society of Clinical Oncology.

Ellis 2005; Verheul and Pinedo 2005; Rhee and Hoff 2005; Schneider and Miller 2005; Folkman 2005; Culy 2005; Midgley and Kerr 2005). It binds to all isoforms of VEGF-A, and prevents its binding to VEGF-R1 or VEGF-R2 (see Figure 1). In animal model systems (e.g., human tumor xenotransplants in athymic mice), bevacizumab decreases growth of tumor microvasculature and inhibits progression of metastatic disease. Initial clinical trials on bevacizumab focused on first-line therapy for metastatic colon or rectal cancer.

Efficacy Outcomes. Regulatory approval of bevacizumab was supported by 2 randomized controlled clinical trials (Genentech Biooncology 2006). The first was a 3-arm

phase II randomized controlled trial (RCT) in patients with colon or rectal cancer not previously treated for metastatic disease, comparing controls given placebo plus fluorouracil/leucovorin (FU/LV, weeks 1–6 of each 8-week cycle) versus FU/LV plus bevacizumab at either 5 or 10 mg/kg every 2 weeks (Kabbinnavar et al. 2003). Treatment in each arm continued until disease progressed. Results (Table 1) showed that median duration of progression-free survival (PFS) in the low-dose bevacizumab arm, but not the high-dose arm, was significantly longer than for controls. The package insert summary states that overall survival (OS) and overall (complete plus partial) response rates (ORR) in each bevacizumab dose arm was not significantly different from control ORR.

Although Kabbinavar et al. (2003) published identical point estimates for ORR in each arm, they reported a statistically significant increase in the 5-mg/kg arm compared with controls ($p=0.029$). Subsequent trials of bevacizumab for first-line therapy of metastatic colon cancer used this lower dose.

The second, a phase III RCT, began as a 3-arm comparison of FU/LV plus irinotecan (IFL) and placebo, versus IFL plus bevacizumab, and versus FU/LV plus bevacizumab (Hurwitz et al. 2004, 2005). The third arm was discontinued (after randomizing $n=110$ to FU/LV plus bevacizumab) when a planned interim analysis confirmed the adverse event rate in the IFL plus bevacizumab arm did not exceed acceptable limits. Table 2 shows that compared with IFL alone, bevacizumab significantly increased ORR and the median durations of OS, PFS, and response.

A later report compared patients randomized to arm 3 (FU/LV + bevacizumab; $n=110$) versus control patients ($n=100$) randomized to IFL plus placebo before arm 3 was closed (Hurwitz et al. 2005). Additionally, a randomized phase II trial compared FU/LV ± bevacizumab in patients ($n=209$) undergoing first-line therapy for colon or rectal cancer judged by investigators to be non-optimal candidates for the irinotecan component of IFL (Kabbinavar et al. 2005a). Finally, a combined analysis pooled individual patient data from all 3 trials comparing FU/LV + bevacizumab ($n=249$) versus controls (IFL or FU/LV; $n=241$) managed without bevacizumab (Kabbinavar et al. 2005b). Results from the 3 trials and pooled analysis are summarized in Table 3. In the pooled analysis, bevacizumab significantly improved OS, PFS and response rate. However, none of the individual trials reported a significant effect on OS, and only 2 of 3 (Kabbinavar et al. 2003, 2005a) reported significant effects on PFS.

Table 1. Results of Phase II RCT from Package Insert (PI) and Kabbinavar et al. (2003)

	FU/LV + placebo		FU/LV + BEV 5 mg/kg		FU/LV + BEV 10 mg/kg	
	data in PI	published	data in PI	published	data in PI	published
n	36		35		33	
Median OS (months)	13.6	13.8 (9.1–23.0) ^c	17.7	21.5 (17.3–NYR ^d) ^c	15.2	16.1 (11.0–20.7) ^c
Median PFS (months)	5.2	5.2 (3.5–5.6) ^c	9.0 ^a	9.0 ^a (5.8–10.9) ^c	7.2	7.2 (3.8–9.2) ^c
Overall response rate (ORR; %)	17	17 (7–34%) ^c	40 ^b	40 ^b (24–58%) ^c	24	24 (12–43%) ^c

^a $p<0.005$ by logrank test versus control arm

^b $p=0.029$ by χ^2 test versus control arm reported in Kabbinavar et al. (2003), while package insert states the difference is not significant

^c 95% confidence interval

^d not yet reached

Table 2. Results of Hurwitz et al. 2004

	IFL + placebo	IFL + BEV
n	411	402
Median OS (months)	15.6	20.3 ^a HR=0.66
Median PFS (months)	6.2	10.6 ^a HR=0.54
Overall responses (%)	35%	45% ^b
Median response duration (months)	7.1	10.4 ^c

^a $p<0.001$ versus control arm, by stratified logrank test

^b $p<0.01$ versus control arm, by χ^2 test

^c HR=0.62 for relapse, $p=0.001$

As of this writing, no trials that randomized patients undergoing first-line therapy for advanced or metastatic colon or rectal cancer have published final data on effects of adding bevacizumab to regimens other than FU/LV or IFL. A search of the NCI clinical trials Web site (cancernet.nci.nih.gov) identified 3 closed, but as-yet unpublished, trials that investigated combinations of bevacizumab with oxaliplatin plus FU/LV or capecitabine (a fluoropyrimidine prodrug converted to fluorouracil in vivo) for this indication (NCT numbers 00062426, 00070122, 00069095). Additional ongoing phase III trials are studying regimens that combine bevacizumab with: capecitabine and mitomycin (NCT 00294359); capecitabine and oxaliplatin with versus without cetuximab (NCT00208546); oxaliplatin plus (FU/LV or capecitabine) with versus without erlotinib (NCT00265824); (oxaliplatin or irinotecan) plus FU/LV and bevacizumab, cetuximab or both (NCT00265850); and oxaliplatin plus FU/LV versus FU/LV plus cetuximab (NCT00252564). Of the 5 ongoing trials, only 2 (NCT numbers 00294359 and 00265850) do not include bevacizumab in each arm.

Adverse Effects. When combined with IFL, bevacizumab did not significantly increase the proportion of patients discontinuing therapy

due to adverse events (7.1% versus 8.4%) but did significantly increase the incidence of any grade 3 or 4 adverse event (from 74% to 84.9%; $p<0.01$) (Hurwitz et al. 2004). This was largely attributable to grade 3 hypertension (2.3% versus 11%), and grade 3 or 4 diarrhea (25% versus 32%). Bevacizumab did not significantly increase hemorrhage, proteinuria, or thromboembolism in this RCT, although earlier phase II studies had identified these as potential adverse effects. Six patients (1.5%; one fatality) given bevacizumab, but no controls, experienced gastrointestinal perforation.

The package insert includes black-boxed warnings of possible gastrointestinal perforations or wound-healing complications in patients given bevacizumab. It also warns that some patients treated with chemotherapy plus bevacizumab have experienced serious, sometimes fatal, hemoptysis. However, reports of hemoptysis are from trials on patients with non-small cell lung cancer (Sanborn and Sandler 2006; see Section II of this Assessment).

The pooled analysis of individual patient data from 3 trials comparing FU/LV plus bevacizumab (n=244) versus controls given FU/LV or IFL (n=237) also compared adverse events

Table 3. Results Comparing FU/LV + Bevacizumab versus Controls

	Kabbinavar 2003		Hurwitz 2005		Kabbinavar 2005a		Kabbinavar 2005b	
	FU/LV + placebo	FU/LV + BEV	IFL + placebo	FU/LV + BEV	FU/LV + placebo	FU/LV + BEV	either control	FU/LV + BEV
n	36	35	100	110	105	104	241	249
Median OS (months)	13.6	17.7	15.1	18.3*	12.9	16.6*	14.6	17.9 ^d HR=0.74 (0.59–0.93)
Median PFS (months)	5.2	9.0	6.8	8.8*	5.5	9.2 ^a HR=0.50 (0.34–0.73)	5.6	8.8 ^a HR=0.63 (0.50–0.78)
overall responses (%)	17	40	37	40*	15.2	26.0* ^b	24.5	34.1 ^e
Median response duration (months)	NR	NR	7.2	8.5*	6.8	9.2* ^c	NR	NR

* difference from controls not statistically significant
^a $p<0.0002$ versus controls
^b $p=0.055$
^c $p=0.088$
^d $p=0.0081$ by logrank test
^e $p=0.0190$

(Kabbinavar et al. 2005b). Those given bevacizumab had higher proportions with any grade 3 or 4 event (81% versus 73%), grade 3 or 4 diarrhea (37% versus 34%), grade 3 hypertension (16% versus 3%), and grade 3 or 4 bleeding (5% versus 2%). However, study authors did not report test results for statistical significance of these differences. Similar proportions of patients in each group discontinued treatment (10% versus 8%) due to adverse events. Gastrointestinal perforation occurred in 1% of those given bevacizumab plus FU/LV, but not in any controls.

Second- or Subsequent-line Therapy for Advanced or Metastatic Disease. On June 20, 2006, the FDA added a second indication for bevacizumab, approving its combined use with fluorouracil-based chemotherapy as second-line treatment of advanced (inoperable) or metastatic colon or rectal cancers (<http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=9827>). The evidence reviewed by FDA was an unblinded 3-arm RCT (the ECOG E3200 trial) that compared bevacizumab alone versus bevacizumab plus FU/LV and oxaliplatin (the FOLFOX4 regimen) and versus controls given FOLFOX4 only. This study was presented at a national meeting (Giantonio et al. 2005), but has not yet been published. The trial enrolled patients with previously treated metastatic colorectal cancer that failed prior therapy with a fluoropyrimidine and irinotecan. The data and safety monitoring board closed the bevacizumab-alone arm 2 months before accrual targets were met for the other 2 arms (February versus April 2003), based on an interim analysis that showed decreased survival compared with FOLFOX4 alone (Genentech Biooncology 2006). Results of the E3200 trial

at a median follow-up of 28 months are summarized in Table 4 (Giantonio et al. 2005).

Presently, other data are unavailable from peer-reviewed publications on outcomes of bevacizumab for second- or subsequent-line therapy of colorectal cancer. The Avastin® package insert (Genentech Biooncology 2006) reports on an uncontrolled trial (Study 4; total n=339) of FU/LV plus bevacizumab in patients with metastatic colorectal cancer that progressed after irinotecan- and oxaliplatin-containing regimens (i.e., third-line therapy for refractory disease). Only one of the first 100 patients enrolled in this study experienced a partial response, and none had a complete response.

The NCI clinical trials web site (cancernet.nci.nih.gov) lists one closed (NCT00025337) and 3 open trials (NCT numbers 00278889, 00100841, and 00177307) on bevacizumab plus chemotherapy as second-line therapy for unresectable (advanced or metastatic) colon or rectal cancers.

Adjuvant Therapy for Early Stage Disease. Presently, data are unavailable from peer-reviewed publications on outcomes of bevacizumab as a component of adjuvant therapy for resected colon or rectal cancer. Two phase III RCTs are investigating bevacizumab as part of adjuvant chemotherapy for early stage (resected) colon cancer. One of these, the international 3-arm AVANT trial, is comparing FU/LV plus oxaliplatin (controls; arm A) versus the same regimen plus bevacizumab (arm B) and versus capecitabine and oxaliplatin plus bevacizumab (arm C). The AVANT trial Data Safety Monitoring Board (DSMB) suspended accrual of new patients in February 2006 because of

Table 4. Results of ECOG Trial E3200 on Bevacizumab for Second-Line Therapy of Colorectal Cancer

	FOLFOX4 Alone	FOLFOX4 + Bevacizumab	Bevacizumab Alone
n	290	289	243
Median OS (months)	10.8	12.9 ^a	10.2 ^b
Median PFS (months)	4.8	7.2 ^c	2.7 ^d
Overall responses (%)	9.2	21.8 ^e	3.0
CR/PR rates (%)	0.7/8.5	1.9/19.9	0/3.0

^a HR=0.76 versus FOLFOX4 alone, p=0.0018

^b not significantly different from FOLFOX4 alone

^c HR=0.64 versus FOLFOX4 alone, p<0.0001

^d p<0.0001 versus FOLFOX4 alone

^e p<0.0001 versus FOLFOX4 alone

an unexpected number of non-cancer-related deaths in one arm (Tuma 2006; <http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=9367>).

On May 23, 2006, the manufacturer announced that the DSMB recommended resuming accrual (<http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=9687>). DSMB analysis showed all-cause mortality (excluding recurrent colon cancer) was 0.8%, 0.5%, and 1.05% in arms A, B, and C, respectively. However, additional review and clearance by relevant Institutional Review Boards and European Health Authorities are necessary before accrual can resume. This trial began in December 2004 and enrolled approximately two-thirds of the targeted 3,450 patients before accrual was suspended. Patients already enrolled have continued on study treatment, despite the accrual halt.

The second study of bevacizumab in adjuvant therapy for colorectal cancer, NSABP C-08, compares the same regimens as arms A and B of the AVANT trial (Tuma 2006). It also opened in 2004 and has enrolled more than 2,000 of its accrual target: 2,714 patients. Since the suspected excess deaths in AVANT were in arm C, a regimen not included in NSABP C-08, the DSMB for the C-08 trial did not suspend accrual.

A recently opened phase III RCT, ECOG-E5204, is investigating adjuvant therapy for stage II or III rectal cancer, following resection and neoadjuvant chemoradiotherapy (<http://cancer.net.ncl.nih.gov/search/ViewClinicalTrials.aspx?cdrid=467561&version=HealthProfessional&protocolsearchid=2346010>). All patients on this trial are given adjuvant therapy with FU/LV plus oxaliplatin, and are randomized to either bevacizumab or no biological therapy. The accrual target is 2,100 patients, and the number of patients enrolled since opening in the past several months is unknown.

FDA Status. The U.S. Food and Drug Administration (FDA) approved bevacizumab (Avastin®) in February 2004 as first-line therapy for metastatic carcinoma of the colon or rectum, when used in combination with intravenous fluorouracil-based chemotherapy. In June 2006, the FDA added second-line therapy for metastatic colorectal cancer as a

second approved indication for bevacizumab, when used in combination with intravenous fluorouracil-based chemotherapy. Use of bevacizumab to treat patients with breast, lung, renal cell, or other non-colorectal cancers is an off-label indication, whether it is given as second- or subsequent-line therapy for advanced or metastatic disease, first-line therapy for advanced or metastatic disease, or as adjuvant therapy for an earlier disease stage.

The company's Web site (<http://www.gene.com/gene/pipeline/status/oncology/avastin/index.jsp>) notes that a supplemental biologics licensing application (sBLA) submitted to FDA in April 2006, was granted priority review status, which requires a final decision by 6 months from submission (i.e., by October 2006). This sBLA seeks approval for a third bevacizumab indication: first-line treatment of non-small cell lung cancer (in combination with platinum-based chemotherapy) in patients with histology other than predominantly squamous cell. In May 2006, the manufacturer submitted a sBLA for a fourth indication: first-line treatment of metastatic breast cancer. The manufacturer requested and FDA granted priority review status for this sBLA also (i.e., final decision by November 2006). However, FDA also requested more documentation from the pivotal trial supporting the sBLA on metastatic breast cancer, and the manufacturer predicts this will delay FDA's final action.

Methods

Search Methods

MEDLINE® was searched via PubMed using the terms "Avastin" or "bevacizumab" (as a text word or MeSH® substance name), cross-indexed with breast neoplasms, lung neoplasms, renal neoplasms, or ovarian neoplasms (as a text words or MeSH® headings), or indexed as a clinical trial NOT colon cancer. Search was performed through July 2006, limited to English-language articles on human subjects. Electronic search was supplemented with a hand-search of bibliographies from recent review articles and clinical studies, and with online searches of abstracts presented at the 2005 meetings of the American Society of Clinical Oncology (ASCO) and the San Antonio Breast Cancer Symposium (SABCS).

Study Selection

Studies were selected for inclusion in the Assessment if they were:

- full-length, peer-reviewed articles published in an English-language journal; and
- treated patients with breast or lung cancer; and
- reported on at least one relevant clinical outcome (response rate; overall, progression-free, or disease-free survival; adverse effects attributable to bevacizumab; or treatment-related mortality).

To provide more complete information, data from interim analyses of phase III trial presented at ASCO or SABCS were also abstracted and included in evidence tables, if slides were available online. However, since such data have not yet undergone peer review, they were not used to determine whether bevacizumab met TEC criteria for any off-label indications.

Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association's Medical Advisory Panel (MAP) on June 22, 2006. To maintain the timeliness of the scientific information in this Assessment, literature search updates were performed subsequent to the Panel's review (see "Search Methods"). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the text and tables where appropriate. There were no studies that would change the conclusions of the Assessment.

Part I: Bevacizumab for Breast Cancer

Background

The American Cancer Society estimates nearly 213,000 new cases and nearly 41,000 deaths from breast cancer in 2006 (PDQ 2006a; American Cancer Society 2006). It is the most common malignancy in U.S. women, and the second most common cause of death from cancer (after lung cancer). While the incidence of breast cancer has increased over the past several decades, mortality apparently is decreasing, which likely is attributable to the combination of earlier detection through increased use of mammography screening

and improved effectiveness of multi-modality therapy (Wood et al. 2005; NCCN 2006a).

Breast Cancer Staging

Invasive breast cancer is staged using the American Joint Cancer Committee (AJCC) Tumor-Node-Metastasis (TNM) system (for details, see Wood et al. 2005; PDQ 2006a; NCCN 2006a). TNM stages with similar prognoses and treatment options are grouped into stage I (T1N0M0); stage IIA (T0-1N1M0 or T2N0M0); stage IIB (T2N1M0 or T3N0M0); stage IIIA (T0-2N2M0 or T3N1-2M0); stage IIIB (T4N0-2M0); stage IIIC (T1-4N3M0); or stage IV (T1-4N0-3M1). Patients with stages I, IIA-B, or IIIA, and some with stage IIIC, have early stage or operable breast cancer. Patients with advanced disease (stage IIIB and some stage IIIC) or with distant metastases (stage IV) have inoperable breast cancer. Presently, most invasive breast cancers in the U.S. are initially diagnosed at an operable stage.

Breast Cancer Treatment

Operable Breast Cancer. Initial management for most cases of operable breast cancer begins with surgery, either by mastectomy or by lumpectomy (Wood et al. 2005; PDQ 2006a; NCCN 2006a). Postoperative radiation therapy is recommended for lumpectomy patients, and for mastectomy patients at elevated risk of locoregional recurrence. Subsequent therapy depends on multiple patient and tumor characteristics including: age at diagnosis (pre- versus postmenopausal), performance status and comorbidity, tumor size and grade, number of involved nodes, presence of hormone receptors, adequacy of surgical margins, and overexpression of HER2/*neu* (for details, see Wood et al. 2005; PDQ 2006a; NCCN 2006a; Carlson et al. 2006).

Adjuvant Therapy. Endocrine therapy using tamoxifen, an aromatase inhibitor, or (less commonly) ovarian ablation is used for patients whose tumors test positive for estrogen and/or progesterone receptors (Wood et al. 2005; PDQ 2006a; NCCN 2006a; Carlson et al. 2006; Goldhirsch et al. 2005). Most node-negative patients at intermediate or high risk of relapse (see PDQ 2006a, NCCN 2006a, or Goldhirsch et al. 2005 for risk category definitions), and nearly all node-positive patients, are offered adjuvant chemotherapy to reduce the risk. Postoperative radiation therapy often is delayed until after adjuvant chemotherapy, although they may be used concurrently with certain regimens (NCCN 2006a). Patients older than 70

years with hormone receptor-positive tumors may be given tamoxifen alone.

The most recent overview analysis from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) estimated that use of a combination regimen for adjuvant chemotherapy decreased the annual odds of recurrence by 23% ($p=0.02$) and the annual odds of death by 17% ($p=0.02$), relative to no adjuvant chemotherapy (EBCTCG 2005; Wood et al. 2005). Combination regimens are superior to monotherapy, and various regimens are used (Wood et al. 2005; PDQ 2006a; NCCN 2006a; Goldhirsch et al. 2005). Examples include: cyclophosphamide and doxorubicin without (AC) or with fluorouracil (CAF or FAC); cyclophosphamide and epirubicin without (EC) or with fluorouracil (CEF or FEC); docetaxel, doxorubicin and cyclophosphamide (TAC); and (less frequently) cyclophosphamide, methotrexate, and fluorouracil (CMF). An earlier EBCTCG overview estimated that combinations with an anthracycline (epirubicin or doxorubicin) decreased the annual odds of recurrence by 12% ($p=0.006$) and the annual odds of death by 11% ($p=0.02$), when compared with CMF (EBCTCG 1998). Patients now given CMF may also receive up to 4 cycles of doxorubicin or epirubicin as monotherapy. Some given FEC may also be given paclitaxel. Patients with HER2/*neu* positive tumors may be given an adjuvant regimen that includes trastuzumab (Herceptin[®]) (Romond et al. 2005; Piccart-Gebhart et al. 2005).

Advanced and Metastatic Disease. A minority of patients with inoperable stage IIIB or IIIC may achieve disease-free survival for 10 years or more with multi-modality therapy (Wood et al. 2005; PDQ 2006a; NCCN 2006a). Initial responses to chemotherapy may convert some patients to eligibility for surgery. Treatment for metastatic or recurrent breast cancer rarely is curative, but does extend survival duration for many patients (Wood et al. 2005; PDQ 2006a; NCCN 2006a). Additional surgery and radiation may be useful for some local recurrences, but systemic therapy is the mainstay of treatment for recurrent and metastatic disease. Endocrine therapy is used initially for newly diagnosed inoperable disease (hormone receptor positive or unknown), and for recurrent disease that remains responsive to hormonal therapy. Bisphosphonates are used to reduce fractures and other morbidity in patients with skeletal metastases.

Cytotoxic drugs are recommended for patients with advanced or metastatic disease that is hormone-receptor negative or refractory to endocrine therapy, and who are without contraindications, significant comorbidity, or poor performance status (Wood et al. 2005; PDQ 2006a; NCCN 2006a; O'Shaughnessy 2005). Median survival for these patients ranges from 18 to 24 months (Wood et al. 2005). Treatment may be monotherapy or a regimen combining drugs the patients was not given for adjuvant therapy. Those who progress or relapse after first-line therapy for advanced or metastatic disease may be offered additional single drugs or combination regimens (second- or third-line therapy).

Examples of single agents with demonstrated activity in advanced, recurrent or metastatic breast cancer include: paclitaxel, docetaxel, capecitabine, vinorelbine, gemcitabine, and pegylated liposomal doxorubicin (Wood et al. 2005; PDQ 2006a; NCCN 2006a; O'Shaughnessy 2005). Combination regimens include those listed above for adjuvant therapy (if not used already in the adjuvant setting), docetaxel plus capecitabine, gemcitabine plus paclitaxel, and vinorelbine plus epirubicin. Patients with HER2/*neu* positive recurrent or metastatic tumors who did not receive it in the adjuvant setting are likely to be given a regimen of trastuzumab plus chemotherapy: either paclitaxel or docetaxel with or without carboplatin, or vinorelbine.

Formulation of the Assessment

Patient Indications

Bevacizumab may be used alone or in combination to treat three different groups of breast cancer patients. Each of the following is considered a separate indication:

- A. Patients undergoing second- or subsequent-line therapy for recurrent, advanced or metastatic disease.
- B. Patients undergoing first-line therapy for advanced or metastatic disease.
- C. Patients undergoing adjuvant therapy for early stage disease.

Technologies to be Compared

For each indication, outcomes of bevacizumab will be compared with outcomes of one or more treatment regimens presently recommended for the same disease stage in the National Comprehensive Cancer Network (NCCN)

guidelines or the National Cancer Institute's PDQ summary of treatment options.

Health Outcomes

Primary health outcomes of interest include overall, progression-free, or disease-free survival; adverse effects attributable to bevacizumab; and treatment-related mortality. Response rates (overall responses, as the sum of complete and partial responses) are a secondary outcome.

Specific Assessment Question(s)

In patients with breast cancer, does treatment with bevacizumab improve health outcomes, as compared to standard treatment regimens for:

- A. second- or subsequent-line therapy of locally advanced or metastatic disease;
- B. first-line therapy of locally advanced or metastatic disease; or
- C. adjuvant therapy of early stage disease?

Review of Evidence

A. Second- or Subsequent-Line Therapy for Advanced, Recurrent, or Metastatic Breast Cancer

The literature search identified 2 published studies on bevacizumab for second- or subsequent-line therapy of advanced or metastatic breast cancer (Table 5). Cobleigh et al. (2003) reported a nonrandomized dose escalation trial on bevacizumab alone for previously treated metastatic disease without evidence of central nervous system (CNS) involvement. The study compared intravenous doses of 3 mg/kg (n=18), 10 mg/kg (n=41) and 20 mg/kg (n=16) every other week, but lacked controls managed without bevacizumab. Although overall response rate (ORR) and response duration appeared least favorable at the lowest bevacizumab dose (3 mg/kg), results were not reported from tests for statistical significance of observed differences. Severe hypertension (grades 3 or 4) occurred in 17% to 22% of patients in each dose group, but there was no evidence for a dose-response relationship. Other severe adverse events (grades 3 or 4) were reported for all treated patients regardless of dose, and included proteinuria (8.3%) and thrombotic events (4%).

Miller et al. (2005a) reported a randomized phase III trial of oral capecitabine (2.5 g/m² per day; days 1–14 of each 21-day cycle) alone

(n=230) versus combined with bevacizumab (n=232; 15 mg/kg on day 1 of each cycle). Eligibility required prior treatment with an anthracycline and a taxane; either 1 or 2 prior chemotherapy regimens for metastatic disease; and no CNS metastases. Patients with HER-2 positive tumors were included only if they had previously progressed while on trastuzumab therapy. Although ORR was significantly greater in the arm given bevacizumab (19.8% versus 9.1%; p=0.001), study arms did not differ significantly in durations of response, progression-free survival (PFS) or overall survival (OS) (Table 5). Hypertension was the only severe adverse event (grades 3 or 4) reported more frequently in the arm given capecitabine plus bevacizumab (17.9% versus 0.5%; all grade 3).

A small, uncontrolled, phase II trial combined bevacizumab with docetaxel in a mixed population (n=27) undergoing first-line (78%) or second-line (22%) therapy for metastatic disease (Ramaswamy et al. 2006). Response rate was 52% (all PRs) and median PFS was 7.5 months. This study is not included in Table 5 since outcomes were not reported separately by indication.

B. First-Line Therapy for Advanced or Metastatic Breast Cancer

Miller et al. have presented first (2005b; ASCO, 06/2005) and second (2005c; SABCs, 12/2005) interim analyses from the E2100 randomized phase III trial of paclitaxel alone (n=346 treated, 339 eligible patients evaluated; 90 mg/m² paclitaxel days 1, 8, and 15 every 4 weeks) versus the same dose and schedule of paclitaxel plus bevacizumab (n=365 treated, 341 eligible patients evaluated; 10 mg/kg bevacizumab days 1 and 15 every 4 weeks) (Miller 2003; Tyagi and Tripathy 2005). As of this writing, final results are unavailable from the E2100 trial; however, slides and video are available on-line from presentations of each interim analysis (Miller et al. 2005b, 2005c).

Patients were eligible for E2100 if they had locally recurrent or metastatic breast cancer not previously treated with chemotherapy. Prior adjuvant therapy was permitted, but those given an adjuvant or neoadjuvant taxane within the previous year were ineligible. Patients with CNS metastasis were excluded, and a head CT was required at study entry. Patients with HER-2 over-expressing tumors must have failed prior trastuzumab therapy. Assessment of response or progression was not blinded to assigned treat-

Table 5. Outcomes of Bevacizumab for Breast Cancer

Study/ Design	Disease Stage	Regimens Compared	n	ORR (CR/PR)	Median Response Duration	PFS at 1 year	Median PFS	OS at 1 year	Median OS	Hyper- tension Grd 3/4	Bleeding Grd 3/4	Thrombotic Events Grd 3/4	Proteinuria Grd 3/4	Tx-related Deaths	
Cobleigh et al. 2003; published phase I/II dose escalation trial	metastatic disease; no CNS mets.; ≥2nd-line Tx	bevacizumab 3 mg/kg (every 2wk)	18	5.6%	3.1 mos	not reported	not reported	not reported	14.0 mos	22%	0	4%	8.3%	none reported	
		10mg/kg (≤13 doses)	41	7.3	5.6 mos				12.8 mos	17%					
		20 mg/kg	16	6.3%	8.0 mos				7.6 mos	19%					
Miller et al. 2005a; published RCT	metastatic disease; no CNS mets.; 2nd-line Tx	capecitabine + bevacizumab	232	19.8% (NR)	5.0 mos	~15%	4.9 mos	~57%	15.1 mos	17.9%	0.4%	5.6%	0	none reported	
		capecitabine alone	230	9.1% (NR)	7.6 mos	~10%	4.2 mos	~57%	14.5 mos	0.5%	0.5%	3.7%	0	none reported	
				p=0.001	NS	NS		NS		all grade 3	all grade 3				
Miller et al. 06/2005b; E2100 RCT; ASCO slides	local recurrence or metastatic disease; no brain mets.; 1st-line Tx	paclitaxel + bevacizumab	365	28.2% (NR)	not reported	~45%	10.97 mos	~82%	~29 mos	13.3%	0.9%	1.2%	2.4%	none reported	
		paclitaxel alone	346	14.2% (NR)	not reported	~25%	6.11 mos	~70%	~23 mos	0	0	1.2%	0	none reported	
				p<0.0001		HR=0.50 (0.40–0.62) log rank p<0.001		HR=0.67 (0.50–0.92) log rank p=0.01		p<0.0001			p=0.0004		
Miller et al. 12/2005c; E2100 RCT; SABCS slides	local recurrence or metastatic disease; no brain mets.; 1st-line Tx	paclitaxel + bevacizumab	341	29.9% (NR)	not reported	~47%	11.4 mos	~82%	28.4 mos	15–16%	2–3%	2%	2%	none reported	
		paclitaxel alone	339	13.8% (NR)	not reported	~25%	6.11 mos	~75%	25.2 mos	2%	0	4%	0	none reported	
				p<0.0001		HR=0.51 (0.43–0.62) log rank p<0.0001		HR=0.84 (0.64–1.05) log rank p=0.12		p<0.0001	p=0.02		p=0.002		
Wedam et al. 2006; published pilot study (27 mos median F/U)	stage III/IV inflammatory or locally advanced disease; 1st-line Tx	bevacizumab alone, 1 cycle; bevacizumab + doxorubicin + paclitaxel, 6 cycles; loco- regional Tx; bevacizumab alone, 8 cycles	21	67% (0/67%)	not reported	77.5% (53.3% at 2 years)	25.3 mos	90.5% (80% at 2 years)	not yet reached	38%	0	5%	0	none reported	
											(24% post- surgical wound- healing complica- tions)				

ment. The first interim analysis was conducted before final eligibility review and includes all treated patients in each arm; the second interim analysis includes all eligible patients in each arm, regardless of treatment (K. Miller, personal communication, May 12, 2006).

Interim results (Table 5) suggest that bevacizumab added to paclitaxel significantly increased ORR (second analysis: 29.9% versus 13.8%; $p < 0.0001$) and median PFS (11.4 versus 6.1 months; $p < 0.0001$). Data were not shown on the proportion of complete versus partial responses. Although the first interim analysis reported a statistically significant effect of bevacizumab on median OS (approximately 29 versus 23 months; $p = 0.01$), the difference was not significant in the second interim analysis (28.4 versus 25.2 months; $p = 0.12$). Bevacizumab apparently increased grades 3 or 4 hypertension by approximately 13% ($p < 0.0001$), and also increased grades 3 or 4 bleeding ($p = 0.02$) and proteinuria ($p = 0.002$) by approximately 2% each.

Most recently, Wedam et al. (2006) reported results from an uncontrolled single-arm pilot study of bevacizumab for first-line therapy in patients ($n = 21$) with previously untreated stage III or IV inflammatory or locally advanced breast cancer. Patients received a single cycle of bevacizumab monotherapy (15 mg/kg on day 1), followed 3 weeks later by 6 cycles of the same dose of bevacizumab plus doxorubicin (50 mg/m²) and docetaxel (75 mg/m²), all on day 1 of each 3-week cycle. Patients had local therapy (surgery followed by radiation therapy to the chest wall and supraclavicular area) at least 4 weeks after the last cycle of chemotherapy plus bevacizumab, and an additional 8 cycles of bevacizumab monotherapy (15 mg/kg on day 1, every 3 weeks) after radiation therapy was completed. All responses were partial (67%), median PFS was 25.3 months, and median OS had not been reached at the time of analysis (80% alive at 2 years). Serious (grade 3 or 4) hypertension occurred in 38% of patients, and 24% had wound-healing complications after surgery. While no instances of grade 3 or 4 hemorrhage were reported, 5% experienced serious thrombotic events.

C. Adjuvant Therapy for Early Stage Breast Cancer

The literature search did not identify any studies reporting outcomes of bevacizumab as a component of adjuvant therapy for operable breast cancer.

Discussion

Part A: Second- or Third-line Therapy, Inoperable or Recurrent Disease. The studies complete thus far do not demonstrate that bevacizumab improves outcomes as second- or subsequent-line therapy of advanced or metastatic breast cancer. Of the 2 studies available, one was a dose escalation trial of bevacizumab monotherapy (5–20 mg/kg; total $n = 75$) that lacked controls managed without bevacizumab, and failed to demonstrate a dose-response relationship for the clinical outcomes reported (Cobleigh et al. 2003). The second was an RCT (total $n = 462$) of capecitabine with versus without bevacizumab as second- or third-line therapy (Miller et al. 2005a). However, the RCT reported no significant difference between arms for duration of response, progression-free or overall survival, and an absolute increase of 17.5% in grade 3 (treatable) hypertension.

Given the many single drugs and combination regimens used for second- and subsequent-line therapy (see above, Background section of Part I), the limited available evidence on bevacizumab plus one other drug (capecitabine) cannot rule out the possibility of benefit from combining bevacizumab with other regimens for advanced, recurrent, or metastatic breast cancer. The NCI's clinical trials web site (canceret.nci.nih.gov) lists one open phase III trial in the second-line setting (NCT00281697) randomizing patients to bevacizumab or placebo added to one of several standard chemotherapy regimens. The Web site also lists an uncontrolled phase II trial (NCT00187694) that combines bevacizumab with letrozole for postmenopausal women with hormone-receptor-positive disease, unresectable breast cancer previously treated with up to 2 prior regimens. Four additional phase II trials on patients treated previously for inoperable disease have closed, including studies on bevacizumab plus erlotinib (NCT00054132), docetaxel (NCT00055861), low-dose cyclophosphamide and methotrexate (NCT00083031), and vinorelbine (NCT00017394).

Part B: First-line Therapy, Inoperable Disease. Conclusive evidence also is lacking on outcomes of bevacizumab for first-line therapy of advanced or metastatic breast cancer. As of this writing, only interim analyses presented at meetings are available from the one RCT completed to date (Miller et al. 2005b, 2005c). The first and second interim analyses disagree on

whether the longer duration of overall survival in the arm given bevacizumab was statistically significant. While effects on overall response rates and progression-free survival were statistically significant in both interim analyses, investigators assessing response and progression were not blinded to assigned treatment. Therefore, definitive conclusions must wait for the trial's final analysis. The only other study available, a published pilot trial on inoperable locally advanced or inflammatory disease (Wedam et al. 2006) lacked controls and thus also does not permit conclusions.

The NCI's clinical trials Web site (cancernet.nci.nih.gov) lists one open phase III randomized trial (NCT00262067) investigating multiple standard combination regimens that do or do not include an anthracycline, with versus without bevacizumab, as first-line therapy for advanced, recurrent or metastatic breast cancer. Additionally, at least 4 open and 3 completed (closed) phase II trials address this indication. The open phase II trials include combinations of bevacizumab plus: trastuzumab (NCT00935353; nonrandomized) for women with HER-2 over-expressing tumors; cyclophosphamide and methotrexate (NCT00121134; nonrandomized) for women with residual disease after neoadjuvant therapy surgery, and radiation therapy; docetaxel (NCT00217672; randomized) for HER-2-negative stage IV disease; and endocrine therapy (NCT00240071; nonrandomized) in women with acquired resistance to endocrine therapy (previously responsive metastatic disease). Closed phase II trials of first-line therapy for advanced, recurrent or metastatic breast cancer have studied bevacizumab combined with: capecitabine (NCT00121836), docetaxel plus capecitabine (NCT00088998), or docetaxel plus doxorubicin (NCT00016549). Additionally, two open randomized trials of first-line therapy for inoperable breast cancer are comparing paclitaxel plus bevacizumab with versus without gemcitabine (NCT00320541), or bevacizumab plus Abraxane™ (albumin particles with bound paclitaxel) given every 2 versus every 3 weeks (NCT00281528). However, patients in each arm of these 2 RCTs are treated with bevacizumab.

Part C: Adjuvant Therapy for Operable Disease. Evidence was unavailable on outcomes of bevacizumab as a component of adjuvant therapy for operable breast cancer. The NCI's clinical trials Web site (cancernet.nci.nih.gov) lists an open, nonrandomized

phase II trial (ECOG E2104; NCT00119262) of bevacizumab plus cyclophosphamide and doxorubicin, followed by bevacizumab plus paclitaxel as adjuvant therapy for resected, node-positive breast cancer. Additionally, 3 open trials and 1 closed trial are investigating the following neoadjuvant regimens (i.e., given prior to surgery) combined with bevacizumab: docetaxel, doxorubicin plus cyclophosphamide (NCT00128674); docetaxel and cyclophosphamide, followed by doxorubicin alone (NCT00203502); cyclophosphamide plus doxorubicin, followed by carboplatin and paclitaxel, followed by trastuzumab for HER-2-positive tumors or bevacizumab for HER-2-negative tumors (NCT00254592); and a randomized phase II trial (NCT00027885; closed after meeting its accrual target) comparing docetaxel with versus without bevacizumab followed by surgery, radiation therapy and adjuvant therapy with cyclophosphamide plus doxorubicin.

Summary of Application of the Technology Evaluation Criteria

For reasons discussed previously, the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) deferred decision on outcomes of bevacizumab as first-line therapy for metastatic breast cancer, pending availability of final results from the ECOG E2100 trial. Based on available evidence, the MAP made the following judgments about whether bevacizumab meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria as therapy for the remaining two breast cancer indications:

- A. second- or subsequent-line therapy for inoperable locally advanced, recurrent or metastatic disease; and
- C. adjuvant therapy for operable, early stage disease.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

The U.S. Food and Drug Administration (FDA) approved bevacizumab (Avastin®) in February, 2004 as first-line therapy, and in June 2006 as second-line therapy, when used in combination with intravenous fluorouracil-based chemotherapy for metastatic carcinoma of the colon or rectum. As of this writing, these are the only FDA-approved indications for bevacizumab.

Use of bevacizumab to treat breast cancer patients is an off-label indication, whether it is given as second- or subsequent-line therapy for advanced or metastatic disease, first-line therapy for advanced or metastatic disease, or as adjuvant therapy for an earlier disease stage.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

Available evidence did not permit conclusions for either indication: second- or subsequent-line therapy for advanced or metastatic disease; and adjuvant therapy for resected disease. One randomized trial (n=462) that reported no benefit from adding bevacizumab to capecitabine, and a smaller (n=75), uncontrolled dose escalation trial of bevacizumab monotherapy, were the only evidence found on outcomes of bevacizumab as second- or subsequent-line therapy of inoperable advanced, recurrent or metastatic breast cancer. No evidence was available on outcomes of bevacizumab as a component of adjuvant therapy for operable, early stage breast cancer.

**3. The technology must improve the net health outcome; and
4. The technology must be as beneficial as any established alternatives.**

Since available evidence is insufficient to permit conclusions, it cannot be determined whether bevacizumab improves health outcomes of patients with breast cancer, or whether the improvement from use of bevacizumab is as beneficial as any established alternatives.

5. The improvement must be attainable outside the investigational settings.

Whether bevacizumab improves health outcomes of patients with breast cancer, and whether the improvement from use of bevacizumab is as beneficial as any established alternatives, has not yet been determined in the investigational setting.

Based on the above, bevacizumab does not meet the TEC criteria as second- or subsequent line therapy of advanced, recurrent or metastatic breast cancer. Bevacizumab also does not meet the TEC criteria as adjuvant therapy for resectable, early stage breast cancer. The MAP deferred decision on whether bevacizumab

meets the TEC criteria as first-line therapy for metastatic breast cancer, pending availability of final results from the ECOG E2100 trial.

Part II: Bevacizumab for Non-small Cell Lung Cancer

Background

Lung cancer incidence has increased over the past three decades; it is the leading cause of cancer deaths in both men and women in the U.S. (Schrump et al. 2005; PDQ 2006b; NCCN 2006b). The American Cancer Society estimates 174,470 new cases and 162,460 deaths from lung cancer (small cell and non-small cell combined) are expected in 2006 (PDQ 2006b; American Cancer Society 2006). Survival at 5 years after lung cancer diagnosis is approximately 15%. All forms of lung cancer are associated with cigarette smoking, and approximately 85% of lung cancer deaths are attributable to smoking.

Presently, approximately 80–85% of new lung cancer cases have one of the histologies collectively termed non-small cell lung cancer (NSCLC) (Schrump et al. 2005; PDQ 2006b; NCCN 2006b). These include squamous cell, adeno-, large cell, adenosquamous, and pleomorphic or sarcomatoid carcinomas; carcinoid tumors; salivary-gland type carcinomas; and some unclassified carcinomas. The predominant histology has switched from squamous cell carcinoma in the 1960s to adenocarcinomas presently.

Non-Small Cell Lung Cancer Staging

NSCLC staging uses the American Joint Cancer Committee (AJCC) Tumor-Node-Metastasis (TNM) system (for details, see Schrump et al. 2005; PDQ 2006b; NCCN 2006b). TNM stages are grouped into stage IA (T1N0M0), stage IB (T2N0M0), stage IIA (T1N1M0), stage IIB (T2N1M0 or T3N0M0), stage IIIA (T1-2N2M0 or T3N1-2M0), stage IIIB (anyTN3M0 or T4anyNM0), and stage IV (anyTanyNM1). Stage groupings at diagnosis are combined further to indicate similar prognoses and treatment approaches. Those with surgically resectable disease include stages I, II, and selected stage III patients; survival at 5 years from diagnosis ranges from 70% (stage IA) to 30% (stage IIB). Locally and/or regionally advanced lung cancer (most patients with stages IIIA or IIIB) includes

T3 or T4 tumors (defined by the adjacent normal tissues and structures they have invaded, rather than by tumor size) and N2 or N3 nodal involvement (defined by location rather than number of involved nodes) in patients without distant metastasis. Survival at 5 years ranges from 10% to 30% for those with stage IIIA, but is less than 10% for stage IIIB. Less than 5% of those with metastatic lung cancer (stage IV) survive at 5 years after diagnosis.

Non-Small Cell Lung Cancer Treatment

Operable NSCLC. Surgery has the greatest potential to cure NSCLC confined to one hemithorax, but few patients are diagnosed at an operable stage and many of those are medically inoperable because of comorbidities (Schrump et al. 2005; PDQ 2006b; NCCN 2006b). Lobectomy is now the preferred surgical procedure for operable NSCLC; it has replaced pneumonectomy, unless complete en bloc resection of the tumor mass is clearly not possible with a lobectomy. Segmental or wedge resection is used for some patients with impaired pulmonary function and/or small tumors. Although recurrences are more frequent with wedge resections, data are lacking to show this reduces survival. Patients are often re-classified to a higher stage based on pathologic restaging after surgery. Repeat resection may be offered to some patients whose excised tissue shows positive margins.

Patients with resectable tumors but who have medical contraindications to surgery are usually offered radiation therapy with curative intent (Schrump et al. 2005; PDQ 2006b; NCCN 2006b). Most often, this relies on external-beam radiation with 3-dimensional treatment planning. Emerging techniques for radiation therapy of NSCLC include image-guided and stereotactic body radiation therapies. However, data are presently unavailable to demonstrate better outcomes (longer survival or fewer adverse effects) from these newer approaches. Radiation therapy also may be used after resection to treat the margins, if pathology demonstrates there is tumor present.

Adjuvant Chemotherapy for Early Stage Disease. Although surgery and definitive radiation therapy often achieve adequate local control for operable disease, many of these patients relapse and die from distant metastases (Schrump et al. 2005; PDQ 2006b; NCCN 2006b). Patients with negative margins after resection of stage IA disease may be managed

with observation. Meta-analyses have shown that adjuvant cisplatin-based chemotherapy reduces recurrences (NSCLC Collaborative Group 1995) and improves long-term survival (Hotta et al. 2004a) for resected patients with stages IB through IIIA NSCLC. The most recent meta-analysis (11 trials; n=5716) estimated a hazard ratio (HR) of 0.872 (95% CI: 0.805-0.944; p=0.001) for improved survival with surgery plus adjuvant chemotherapy relative to surgery alone. Presently, the most commonly used regimens combine cisplatin with vinorelbine, etoposide, paclitaxel, or vinblastine (Schrump et al. 2005; PDQ 2006b; NCCN 2006b). However, some trials included in the Hotta et al. (2004a) meta-analyses used 3-drug regimens.

Data are presently unavailable to determine the optimal sequence of surgery and chemotherapy and the balance of risks and benefits from adding adjuvant radiation therapy (Schrump et al. 2005; PDQ 2006b; NCCN 2006b). Additional uncertainties include the optimal number of adjuvant chemotherapy cycles to be given, and whether carboplatin is equally effective and can replace cisplatin for adjuvant therapy.

Initial Treatment of Advanced Disease.

Locally advanced NSCLC is often treated with chemotherapy using a platinum-based two-drug combination plus radiation therapy (Schrump et al. 2005; Wakelee and Belani 2005; PDQ 2006b; NCCN 2006b). Concurrent chemotherapy plus radiation yields modestly improved outcomes compared with sequential therapy. Surgery may be added depending on the tumor's size and location and on the extent of nodal involvement. Patients with distant metastases are usually treated with chemotherapy alone.

First-line platinum-based chemotherapy improves symptom control and prolongs survival, compared with best supportive care (NCCN 2006b; Dooms et al. 2006; Pujol et al. 2006). Time to progression averages 4–6 months and median survival averages 8–10 months after first-line therapy begins, but outcomes vary depending on baseline prognostic variables including stage, weight loss, performance status and gender. Survival at 1 year ranges from 30% to 40% and from 10% to 15% at 2 years, in patients with good performance status and no significant comorbidities. Clinical guidelines (NCCN 2006b) agree with a meta-analysis of RCTs (Hotta et al. 2004b) that cisplatin and carboplatin have been proven similarly

effective in regimens used for first line therapy of advanced or metastatic disease. The NCCN guideline recommends combining either platinum drug with one of the following: paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, etoposide, or vinblastine.

Relapsed and Refractory Advanced Disease. Clinical guidelines (NCCN 2006b) recommend use of monotherapy with docetaxel, pemetrexed, or erlotinib as second-line therapy for advanced NSCLC patients whose disease has progressed during or after first-line chemotherapy. One RCT reported that docetaxel yields better outcomes than vinorelbine or ifosfamide (Fossella et al. 2000). Another RCT reported that pemetrexed achieves similar outcomes as docetaxel, but is more tolerable (Hanna et al. 2004). A placebo-controlled RCT reported that erlotinib extended the duration of survival in previously treated patients with advanced or metastatic NSCLC (Shepherd et al. 2005).

Formulation of the Assessment

Patient Indications

Bevacizumab may be used alone or in combination to treat 3 different groups of NSCLC patients. Each of the following is considered a separate indication:

- A. Patients undergoing second- or subsequent-line therapy for recurrent, locally or regionally advanced or metastatic disease.
- B. Patients undergoing first-line therapy for advanced or metastatic disease.
- C. Patients undergoing adjuvant therapy for early stage disease.

Technologies to be Compared

For each indication, outcomes of bevacizumab will be compared with outcomes of one or more treatment regimens presently recommended for the same disease stage in the National Comprehensive Cancer Network (NCCN) guidelines or the National Cancer Institute's PDQ summary of treatment options.

Health Outcomes

Primary health outcomes of interest include overall, progression-free, or disease-free survival; adverse effects attributable to bevacizumab; and treatment-related mortality. Response rates (overall responses, as the sum of complete and partial responses) are a secondary outcome.

Specific Assessment Question(s)

In patients with NSCLC, does treatment with bevacizumab improve health outcomes, as compared to standard treatment regimens for:

- A. second- or subsequent-line therapy of locally or regionally advanced, recurrent or metastatic disease;
- B. first-line therapy of locally or regionally advanced or metastatic disease; or
- C. adjuvant therapy of early stage disease?

Review of Evidence

A. Second- or Subsequent-Line Therapy for Advanced, Recurrent, or Metastatic NSCLC

The literature search identified only one published report on bevacizumab (combined with erlotinib) as second-line therapy for advanced, recurrent or metastatic NSCLC free from CNS metastasis (Table 6; Herbst et al. 2005). The trial began with a phase I dose-finding study using cohorts of 3 patients each as the bevacizumab dose escalated from 7.5 to 15 mg/kg and the erlotinib dose escalated from 100 to 150 mg/day. Bevacizumab was given intravenously on day 1 of each 21-day cycle, and erlotinib was given orally each day. The trial's phase I portion established 15 mg/kg bevacizumab and 150 mg/day erlotinib as the phase II doses. Outcomes for the 5 patients given these doses in phase I were combined with outcomes for an additional 28 patients treated in the uncontrolled phase II portion of the study (total n=34).

By RECIST criteria, there were no complete responses and 18% partial responses among patients given this regimen for second-line therapy of advanced or metastatic NSCLC (Table 6). The median duration of response was not reached at the time of analysis, but exceeded 25 weeks.

Median PFS was 6.2 months and median OS was 12.6 months for those treated at the phase II dose. Hypertension was the only reported grade 3 or 4 toxicity attributable to bevacizumab. The trial did not include controls treated with erlotinib alone. For comparison, an RCT of erlotinib monotherapy versus placebo as second-line therapy for advanced or metastatic NSCLC reported median PFS of 2.2 months and OS of 6.7 months (Shepherd et al. 2005).

Table 6. Outcomes of Bevacizumab for Non-Small Cell Lung Cancer

Study/ Design	Disease Stage	Regimens Compared	n	ORR (CR/PR)	Median Response Duration	PFS at 1 year	Median PFS	OS at 1 year	Median OS	Hyper- tension Grd 3/4	Bleeding Grd 3/4	Thrombotic Events Grd 3/4	Proteinuria Grd 3/4	Tx- Related Deaths
Herbst et al. 2005; published phase I/II study	recurrent or stages IIIB or IV; non-squamous; no CNS mets.; 2nd-line Tx (≥1 prior chemo)	bevacizumab + erlotinib	6	33% (0/33%)	>25 weeks	38% (24.3%– 59.6%; n=40)	7 mos (n=40)	54.2% (40.0%– 73.4%; n=40)	12.6 mos (n=40)		0	0	0	0
		phase I: dose finding	34 (6+ 28)	18% (0/18%)			6.2 mos (n=34 at phase II dose)	12.6 mos (n=34 at phase II dose)	6.9% (2 of 34)					
Johnson et al. 2004; published randomized phase II study	recurrent or stages IIIB or IV; no CNS mets.; 1st-line Tx (no prior chemo)	15 mg/kg bev + carbo/taxol	34	40% ¹	not reported	~20% ¹	7.0 mos ¹	~63%	17.7 mos	5.9%	0 ²	14.7%	41% (any grade)	4 (11.8%)
		7.5 mg/kg bev + carbo/taxol	32	21.9% ¹	not reported	~10% ¹	4.1 mos ¹	~40%	11.6 mos	0	6.3% ²	6.3%	21.9% (any grade)	4 (12.5%)
		carbo/taxol only (crossover at progression)	32	31.3% ¹	not reported	~10% ¹	5.9 mos ¹	~58%	14.9 mos	3.1%	0	9.4%	not reported	1 (3.1%)
						15 mg/kg: 33% HR progress., p=0.185		p=0.63, 15 mg/kg bevacic vs. control						
Sandler et al., 06/2005 E4599 RCT ASCO slides	recurrent or stages IIIB or IV; non- squamous; no CNS mets.; 1st-line Tx (no prior chemo)	15 mg/kg bev + carbo/taxol	424	27% (1.4%/ 25.8%)	not reported	14.6%	6.4 mos	51.9% (22.1% at 2 years)	12.5 mos	6.0%	4.5%	3.8% (venous) 1.9% (arterial)	not reported	8 (1.9% of n=420)
		carbo/taxol only (crossover not allowed)	431	10.0% (0/10.0%)	not reported	6.4%	4.5 mos	43.7% (16.9% at 2 years)	10.2 mos	0.7%	0.7%	3.0% (venous) 1.0% (arterial)	not reported	2 (0.5% of n=427)
				p<0.0001		HR=0.62 (0.53–0.72) p<0.0001	HR=0.77 (0.65–0.93) p=0.007	p<0.001	p<0.001	NS				

¹ Johnson et al. 2004 reported freedom from progression and median time to progression, rather than progression-free survival. Abstracted data on response rates and time to progression are from blinded assessments by Independent Review Facility; published article reported these alongside data from unblinded investigators.

² In subsequent update by Sandler (ASCO presentation, 06/2005), overall incidence of life-threatening hemorrhage across the two bevacizumab arms was 9% (6 of 66). Risk factors included baseline hemoptysis and squamous histology (4 of 13 (31%) compared with 2 of 53 (4%) for non-squamous histology).

B. First-Line Therapy for Advanced or Metastatic NSCLC

The literature search identified only one published trial of bevacizumab as first-line therapy for patients with advanced or metastatic NSCLC free from CNS metastasis (Table 6; Johnson et al. 2004). This was a 3-arm randomized trial comparing carboplatin plus paclitaxel alone (n=32) versus the same combination plus bevacizumab at doses of 7.5 mg/kg (n=32) or 15 mg/kg (n=34). Controls in the arm given carboplatin plus paclitaxel alone were permitted to cross over to bevacizumab if their disease progressed. Responses and progression were initially assessed by investigators not blinded to assigned treatment, then by blinded assessors at an Independent Review Facility. While the publication reports results from both assessments, the data abstracted in Table 6 are from the blinded assessment.

Although more patients responded, and the median time to progression and duration of survival were longer, in the arm given 15 mg/kg bevacizumab, the differences were not statistically significant. However, the trial lacked sufficient statistical power to detect differences in these outcomes, as the objective was to select a dose for and judge whether a phase III trial was warranted. Hypertension, thrombotic events, and proteinuria were the most common adverse events attributable to bevacizumab. Nine treatment-related deaths occurred, with 4 in each of the bevacizumab arms and only 1 in the control arm.

There also were 6 cases of life-threatening (n=2) or fatal (n=4) hemoptysis or hematemesis, of which 5 were in the 7.5 mg/kg bevacizumab arm and one was in the 15 mg/kg arm. All 6 patients had centrally located tumors near major blood vessels, 4 of the 6 had squamous cell carcinoma histology, and 5 had cavitation or necrosis of tumors either at baseline or while on bevacizumab. Based on this report, the FDA added a black box warning to the package insert on possible life-threatening or fatal hemoptysis while on bevacizumab. Additionally, subsequent trials of bevacizumab for NSCLC excluded those with a history of hemoptysis or predominantly squamous cell histology.

Sandler et al. (2005) presented results from a planned second interim analysis of the E4599 RCT, comparing 200 mg/m² paclitaxel plus

carboplatin dosed to achieve an area under the curve of 6 mg/mL × min (n=431) versus the same regimen of carboplatin and paclitaxel plus 15 mg/kg bevacizumab once every 3 weeks (n=424). Chemotherapy drugs and bevacizumab were administered on day 1 in each of six 21-day cycles, with additional bevacizumab on the same schedule and dose for the experimental arm until patients progressed. Patients in the control arm were not permitted to cross over at the time of progression. As of this writing, final results are unavailable from the E4599 trial; however, slides and video are available online from a presentation of the second interim analysis (Sandler et al. 2005).

Patients were eligible for the E4599 trial if they had chemotherapy naive stage IIIB or stage IV non-squamous NSCLC with good performance status (ECOG 0–1) and without history of hemoptysis, thrombotic or hemorrhagic disorders, or CNS metastasis. Patients were stratified before randomization by whether they: had previously received radiation therapy; had recurrent versus stages IIIB or IV disease; had lost <5% or ≥5% of body weight; and had or did not have a measurable site of disease.

Interim results suggest statistically significant improvement of overall response rate (27% versus 10%; p<0.0001), median progression-free survival (6.4 versus 4.5 months; p<0.0001) and overall survival (12.5 versus 10.2 months; p=0.007) in the arm randomized to bevacizumab (Table 6). After reviewing these interim results, the trial's data and safety monitoring board continued follow-up without crossover of control patients to bevacizumab. Five patients (1.4%) in the bevacizumab arm and none in the control arm achieved complete responses; however, information was unavailable on response duration. There were 8 treatment-related deaths in the bevacizumab arm, including 5 from hemoptysis, 2 from gastrointestinal bleeding, and one from neutropenic fever. The 2 deaths in the control arm included one each from gastrointestinal bleeding and neutropenic fever. Hypertension and bleeding of grades 3 or 4 also occurred more frequently in the bevacizumab arm.

C. Adjuvant Therapy for Early Stage NSCLC

The literature search did not identify any studies reporting outcomes of bevacizumab as a component of adjuvant therapy for operable NSCLC.

Discussion

Part A: Second- or Third-line Therapy, Inoperable or Recurrent Disease. Available evidence does not demonstrate that bevacizumab improves health outcomes as second- or subsequent-line therapy of advanced, recurrent or metastatic NSCLC. Only one uncontrolled study (n=34; Herbst et al. 2005) reported outcomes of bevacizumab plus erlotinib as second-line therapy for these patients. Since the study lacked concurrent or historical controls managed with erlotinib alone, no conclusions are possible on benefits and harms of adding bevacizumab. Furthermore, this study tested the effects of adding bevacizumab to only one of at least 3 alternative drugs with demonstrated efficacy as second-line therapy for inoperable or recurrent NSCLC.

The NCI's clinical trials web site (cancernet.nci.nih.gov) lists one open, placebo-controlled, double-blind phase III RCT (NCT00130728) comparing erlotinib alone versus erlotinib plus bevacizumab as second-line therapy for advanced, recurrent or metastatic NSCLC. It also lists a closed, randomized phase II trial (NCT00095225) that compared bevacizumab plus either docetaxel, pemetrexed, or erlotinib versus docetaxel or pemetrexed alone as second-line therapy for recurrent or refractory NSCLC. Additionally, 2 uncontrolled phase II trials of second-line therapy are studying bevacizumab plus pemetrexed for stable brain metastases (NCT00227019) or for stage IIIB or IV NSCLC (NCT00268489). Finally, patients undergoing either second-line or first-line therapy are eligible for a randomized phase II trial (NCT00250978) comparing bevacizumab plus docetaxel versus docetaxel alone as therapy for malignant pleural effusion from advanced NSCLC, and for two uncontrolled phase II trials investigating bevacizumab combined with docetaxel plus carboplatin (NCT00271505), or with (unspecified) first- or second-line therapy in subjects with brain metastases from non-squamous NSCLC (NCT00312728).

Part B: First-line Therapy, Inoperable Disease. Current evidence does not establish conclusively whether bevacizumab improves health outcomes as first-line therapy of advanced or metastatic NSCLC. The evidence includes one published 3-arm trial (n=98; Johnson et al. 2004) and an unpublished 2-arm

trial (n=855; Sandler et al. 2005) with interim results reported at a national meeting. Both trials compared paclitaxel plus carboplatin alone versus the same two drugs plus bevacizumab. The published 3-arm trial (n=32–34 per arm) tested 2 doses of bevacizumab (7.5 or 15 mg/kg once every 3 weeks) versus controls, permitted crossover to bevacizumab if controls had progressive disease, and reported no statistically significant differences between arms in progression-free or overall survival. However, the trial's objective was to select a dose for and evaluate whether a phase III trial was warranted, leaving it with inadequate statistical power to detect difference in the outcomes reported.

Investigators from the unpublished trial (n=424 and 431 per arm) presented results of a planned second interim analysis at a national meeting in June 2005 and reported that bevacizumab significantly increased the duration of progression-free (6.4 versus 4.5 months; $p < 0.0001$) and overall survival (12.5 versus 10.2 months; $p = 0.007$). However, after reviewing results of the interim analysis, the trial's data and safety monitoring board did not terminate the trial or recommend crossover of those in the control arm to bevacizumab. Thus, definitive conclusions await final analysis of this unpublished trial.

Both RCTs reported severe and sometimes fatal hemoptysis among patients receiving bevacizumab combined with carboplatin and paclitaxel. Five of 6 cases in the 3-arm trial (9% of 66 treated patients; includes 4 fatalities) occurred at the lower dose of bevacizumab (7.5 mg/kg once every 3 weeks). Risk factors suggested after analysis of patient and tumor characteristics include prior history of hemoptysis, centrally located tumors adjacent to major blood vessels, squamous cell histology, and cavitation or necrosis of tumors at baseline or during therapy. The FDA added a black-box warning noting the risk of hemoptysis from bevacizumab therapy to the drug's package insert. Subsequent trials in NSCLC patients excluded those with a history of hemoptysis and those with squamous cell histology. Nevertheless, the E4599 trial reported fatal hemoptysis in 5 of 420 patients (1.2%) in the bevacizumab arm, and nonfatal hemoptysis of grade ≥ 3 in an additional 3 patients (0.7%). Only one of 427 control patients (0.2%) had grade ≥ 3 nonfatal hemoptysis.

As of this writing, results on outcomes of bevacizumab in first-line therapy of inoperable advanced or metastatic NSCLC are available only for the combination with carboplatin plus paclitaxel. This is only one of many regimens currently used for this indication (see above, Background section of Part II). The clinical trials web site (cancernet.nci.nih.gov) lists one placebo-controlled phase III RCT (NCT00257608) testing bevacizumab with versus without erlotinib for first-line therapy of non-squamous NSCLC, and a randomized phase II trial (NCT00313768) that tests the paclitaxel/carboplatin/bevacizumab regimen with versus without an investigational drug (PF-5512676). Additionally, the NCI web site lists 10 separate nonrandomized phase II studies of bevacizumab for first-line therapy of advanced or metastatic NSCLC. Bevacizumab combinations being tested include: erlotinib, carboplatin, paclitaxel and radiation therapy (NCT00280150); cisplatin, etoposide and radiotherapy with versus without bevacizumab followed by docetaxel and bevacizumab (SWOG-S0535); carboplatin and paclitaxel in newly diagnosed squamous cell NSCLC (NCT00318136); radiation therapy followed by paclitaxel, carboplatin, and bevacizumab (NU-05L1); gemcitabine plus carboplatin in non-squamous NSCLC (NCT00323869 and NCT00150657); vinorelbine for stage IIB, IV or recurrent (after radiation therapy) non-squamous NSCLC (NCT00234052); oxaliplatin and gemcitabine (NCT00217282); and oxaliplatin and pemetrexed (NCT00251524 and NCT00254319). Except for the E4599 trial, no closed phase II or III studies of first-line therapy with bevacizumab are listed.

Part C: Adjuvant Therapy for Operable NSCLC. Evidence was unavailable to permit conclusions on outcomes of bevacizumab as a component of adjuvant or neoadjuvant (preoperative) therapy for operable NSCLC. The NCI clinical trials web site (cancernet.nci.nih.gov) lists one open phase III RCT of adjuvant chemotherapy with versus without bevacizumab (ECOG-E1505) for completely resected patients with stages IB to IIIA NSCLC. Patients are stratified based on chemotherapy regimen selected: carboplatin plus paclitaxel or cisplatin plus vinorelbine, docetaxel or gemcitabine. The web site also lists two open phase II trials of neoadjuvant therapy using bevacizumab with cisplatin-based chemotherapy (NCT00130780) or with carboplatin plus paclitaxel (NCT00293332) for operable NSCLC. Additionally, the site lists

one closed phase II study of bevacizumab with carboplatin plus paclitaxel as neoadjuvant therapy (NCT00025389).

Summary of Application of the Technology Evaluation Criteria

For reasons discussed previously, the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) deferred decision on outcomes of bevacizumab as first-line therapy for advanced or metastatic NSCLC, pending availability of final results from the ECOG E4599 trial. Based on available evidence, the MAP made the following judgments about whether bevacizumab meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria as therapy for the remaining two NSCLC indications:

- A. second- or subsequent-line therapy for inoperable locally advanced, recurrent or metastatic disease; and
- C. adjuvant therapy for operable, early stage disease.

1. The technology must have final approval from the appropriate governmental regulatory bodies.

The U.S. Food and Drug Administration (FDA) approved bevacizumab (Avastin®) in February 2004 as first-line therapy, and in June 2006 as second-line therapy, when used in combination with intravenous fluorouracil-based chemotherapy for metastatic carcinoma of the colon or rectum. As of this writing, these are the only FDA-approved indications for bevacizumab. Use of bevacizumab to treat NSCLC patients is an off-label indication whether it is given as second- or subsequent-line therapy for advanced or metastatic disease, first-line therapy for advanced or metastatic disease, or as adjuvant therapy for an earlier disease stage.

2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.

Available evidence did not permit conclusions for either indication. One uncontrolled study (n=34) of bevacizumab plus erlotinib was the only evidence found on second- or subsequent-line therapy of inoperable advanced, recurrent or metastatic NSCLC. Since controls managed with erlotinib alone were lacking, this study did

not permit conclusions on benefits or harms of adding bevacizumab. No evidence was found on outcomes of bevacizumab as a component of adjuvant therapy for operable, early stage NSCLC.

- 3. The technology must improve the net health outcome; and**
- 4. The technology must be as beneficial as any established alternatives.**

Since available evidence is insufficient to permit conclusions, it cannot be determined whether bevacizumab as second-line therapy for advance or metastatic disease, or as adjuvant therapy for operable disease, improves health outcomes of patients with NSCLC, or whether the improvement from use of bevacizumab is as beneficial as any established alternatives.

- 5. The improvement must be attainable outside the investigational settings.**

Whether bevacizumab improves health outcomes of patients with NSCLC undergoing either second-line therapy for advanced or metastatic disease, or adjuvant therapy for early stage disease, and whether the improvement from use of bevacizumab is as beneficial as any established alternatives, has not yet been determined in the investigational setting.

Based on the above, bevacizumab does not meet the TEC criteria as either second-line therapy for advanced, recurrent or metastatic NSCLC, or adjuvant therapy for operable, early stage NSCLC. The MAP deferred decision on outcomes of bevacizumab as first-line therapy for advanced or metastatic NSCLC, pending availability of final results from the ECOG E4599 trial.

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References

- American Cancer Society (2006).** Cancer Facts and Figures 2006. Atlanta, GA: American Cancer Society. Also available online at: http://www.cancer.org/docroot/STT/stt_0.asp.
- Bouis D, Kusumanto Y, Meijer C et al. (2006).** A review on pro- and anti-angiogenic factors as targets of clinical intervention. *Pharmacol Res*, 55(2):89-105.
- Carlson RW, Brown E, Burstein HJ et al. (2006).** NCCN Task Force Report: Adjuvant Therapy for Breast Cancer. *J Natl Compr Canc Netw*, 4 (Suppl 1):S1-26.
- Cebe-Suarez S, Zehnder-Fjallman A, Ballmer-Hofer K. (2006).** The role of VEGF receptors in angiogenesis; complex partnerships. *Cell Mol Life Sci*, 63(5):601-15.
- Cobleigh MA, Langmuir VK, Sledge GW et al. (2005).** A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. *Semin Oncol*, 30(5 Suppl 16):117-24.
- Culy C. (2005).** Bevacizumab: antiangiogenic cancer therapy. *Drugs Today (Barc)*, 41(1):25-56.
- Dooms CA, Pat KE, Vansteenkiste JF. (2006).** The effect of chemotherapy on symptom control and quality of life in patients with advanced non-small cell lung cancer. *Expert Rev Anticancer Ther*, 6(4):531-44.
- Early Breast Cancer Trialists' Collaborative Group (EBCTCG). (1998).** Polychemotherapy for early breast cancer: an overview of the randomised trials. *Lancet*, 352(9152):930-42.
- Early Breast Cancer Trialists' Collaborative Group (EBCTCG). (2005).** Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*, 365(9472):1687-717.
- Fidler IJ, Langley RR, Kerbel RS et al. (2005).** Angiogenesis (Chapter 5). In: *Cancer: Principles and Practice of Oncology* 7th edition; DeVita Jr VT, Hellman S, Rosenberg SA, eds. Philadelphia: Lippincott Williams and Wilkins, pp. 129-57.
- Flanigan RC, Mickisch G, Sylvester R et al. (2004).** Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. *J Urol*, 171(3):1071-6.
- Flanigan RC, Salmon SE, Blumenstein BA et al. (2001).** Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med*, 345(25):1655-9.
- Folkman J. (2006).** Angiogenesis. *Annu Rev Med*, 57:1-18.
- Folkman J. (2005).** Antiangiogenesis agents (Chapter 65). In: *Cancer: Principles and Practice of Oncology* 7th edition; DeVita Jr VT, Hellman S, Rosenberg SA, eds. Philadelphia: Lippincott Williams and Wilkins, pp. 2865-82.
- Fossella FV, DeVore R, Kerr RN et al. (2000).** Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 520 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol*, 18(12):2554-62.
- Genentech Biooncology. (2006).** Avastin® (bevacizumab). Package insert. Available online at <http://www.gene.com/gene/products/information/oncology/avastin/insert.jsp>.
- Giantonio BJ, Catalano PJ, Meropol NJ et al. (2005).** High-dose bevacizumab in combination with FOLFOX4 improves survival in patients with previously treated advanced colorectal cancer: results from the Eastern Cooperative Oncology Group (ECOG) study E3200. Presentation at May, 2005 annual meeting of the American Society of Clinical Oncology; Orlando, Florida (slides and video available online at http://www.asco.org/portal/site/ASCO/menuitem.64cfbd0f85cb37b2eda2be0aee37a01d/?vnextoid=09f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=vm_session_presentations_view&index=y&co nflID=54&trackID=201&sessionID=806).
- Glusker P, Recht L, Lane B. (2006).** Reversible posterior leukoencephalopathy syndrome and bevacizumab. *N Engl J Med*, 354(9):980-2; discussion 980-2.
- Goldhirsch A, Glick JH, Gelber RD et al. (2005).** Meeting Highlights: International Expert Consensus on the Primary Therapy of Early Breast Cancer 2005. *Ann Oncol*, 16(10):1569-1585.
- Hanna N, Shepherd FA, Fossella FV et al. (2004).** Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol*, 22(9):1589-97.
- Herbst RS, Johnson DH, Mininberg E et al. (2005).** Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer. *J Clin Oncol*, 23(11):2544-55.
- Hicklin DJ, Ellis LM. (2005).** Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol*, 23(5):1011-27.
- Hotta K, Matsuo K, Ueoka H et al. (2004a).** Role of adjuvant chemotherapy in patients with resected non-small-cell lung cancer: reappraisal with a meta-analysis of randomized controlled trials. *J Clin Oncol*, 22(19):5860-7.

- Hotta K, Matsuo K, Ueoka H et al. (2004b).** Meta-analysis of randomized clinical trials comparing cisplatin to carboplatin in patients with advanced non-small-cell lung cancer. *J Clin Oncol*, 22(19):5852-9.
- Hurwitz H, Fehrenbacher L, Novotny W et al. (2004).** Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*, 350(25):2335-42.
- Hurwitz HI, Fehrenbacher L, Hainsworth JD et al. (2005).** Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer. *J Clin Oncol*, 23(15):5502-8.
- Johnson DH, Fehrenbacher L, Novotny WF et al. (2004).** Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol*, 22(11):2184-91.
- Kabbinavar F, Hurwitz HI, Fehrenbacher L et al. (2005).** Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol*, 21(1):60-5.
- Kabbinavar FF, Schulz J, McCleod M et al. (2005a).** Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. *J Clin Oncol*, 23(16):5697-705.
- Kabbinavar FF, Hambleton J, Mass RD et al. (2005b).** Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol*, 23(16):3706-12.
- Karp JE, Gojo I, Pili R et al. (2004).** Targeting vascular endothelial growth factor for relapsed and refractory adult acute myelogenous leukemias: therapy with sequential 1-beta-d-arabinofuranosylcytosine, mitoxantrone, and bevacizumab. *Clin Cancer Res*, 10(11):5577-85.
- Kindler HL, Friberg G, Singh DA et al. (2005).** Phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer. *J Clin Oncol*, 23(31):8033-40.
- Midgley R, Kerr D. (2005).** Bevacizumab--current status and future directions. *Ann Oncol*, 16(7):999-1004.
- Miller KD. (2005).** E2100: a phase III trial of paclitaxel versus paclitaxel/bevacizumab for metastatic breast cancer. *Clin Breast Cancer*, 5(6):421-2.
- Miller KD, Chap LI, Holmes FA et al. (2005a).** Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. *J Clin Oncol*, 23(4):792-9.
- Miller KD, Wang M, Gralow J et al. (2005b).** E2100 study: A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer. Presentation at May, 2005 annual meeting of the American Society of Clinical Oncology; Orlando, Florida (slides and video available online at http://www.asco.org/portal/site/ASCO/menuitem.64cfbd0f85cb37b2eda2be0aee37a01d/?vgnextoid=09f8201eb61a7010VgnVCM100000ed730ad1RCRD&vmview=vm_session_presentations_view&index=y&confID=54&trackID=1&sessionID=954).
- Miller KD, Wang M, Gralow J et al. (2005c).** E2100 study: A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer. Presentation at December, 2005 San Antonio Breast Cancer Symposium; San Antonio, Texas (streaming webcast available on-line at <http://www.sabcs.org/SymposiumOnline/index.asp#webcast>).
- National Comprehensive Cancer Network (NCCN) (2006a).** Breast cancer. In: Practice Guidelines in Oncology (v.2.2006). Jenkintown, PA: NCCN. Available on-line at: http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf.
- National Comprehensive Cancer Network (NCCN) (2006b).** Non-small cell lung cancer. In: Practice Guidelines in Oncology (v.2.2006). Jenkintown, PA: NCCN. Available online at: http://www.nccn.org/professionals/physician_gls/PDF/nscl.pdf.
- Non-small Cell Lung Cancer (NSCLC) Collaborative Group. (1995).** Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. *BMJ*, 311(7010):899-909.
- Novick AC. (2002).** Nephron-sparing surgery for renal cell carcinoma. *Annu Rev Med*, 53(395-407).
- O'Shaughnessy J. (2005).** Extending survival with chemotherapy in metastatic breast cancer. *Oncologist*, 10 (Suppl 5):20-9.
- Ozcan C, Wong SJ, Hari P. (2006).** Reversible posterior leukoencephalopathy syndrome and bevacizumab. *N Engl J Med*, 354(9):980-2; discussion 980-2.
- Physician Data Query (PDQ). (2006a).** Breast cancer (PDQ®): treatment. National Cancer Institute, U.S. National Institutes of Health. Available online at: <http://cancernet.nci.nih.gov/cancertopics/pdq/treatment/breast/healthprofessional>.
- Physician Data Query (PDQ). (2006b).** Non-small cell lung cancer (PDQ®): treatment. National Cancer Institute, U.S. National Institutes of Health. Available online at: <http://cancernet.nci.nih.gov/cancertopics/pdq/treatment/non-small-cell-lung/healthprofessional>.
- Piccart-Gebhart MJ, Procter M, Leyland-Jones B et al. (2005).** Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med*, 353(16):1659-72.

Pujol JL, Barlesi F, Daures JP. (2006). Should chemotherapy combinations for advanced non-small cell lung cancer be platinum-based? A meta-analysis of phase III randomized trials. *Lung Cancer*, 51(3):335-45.

Ramaswamy B, Elias AD, Kelbick NT et al. (2006). Phase II trial of bevacizumab in combination with weekly docetaxel in metastatic breast cancer patients. *Clin Cancer Res* 12(10):5124-9.

Rhee J, Hoff PM. (2005). Angiogenesis inhibitors in the treatment of cancer. *Expert Opin Pharmacother*, 6(10):1701-11.

Romond EH, Perez EA, Bryant J et al. (2005). Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*, 355(16):1673-84.

Sanborn RE, Sandler AB. (2006). The safety of bevacizumab. *Expert Opin Drug Saf*, 5(2):289-301.

Sandler AB, Gray R, Brahmer J et al. (2005). A randomized phase III trial of paclitaxel (P) plus carboplatin (C) with or without bevacizumab (NSC #704865) in patients with advanced non-squamous non-small cell lung cancer (NSCLC). An Eastern Cooperative Oncology Group trial – E4599. *J Clin Oncol* 23(16S, part 1):2s (abstract LBA4). Presentation at May, 2005 annual meeting of the American Society of Clinical Oncology; Orlando, Florida (slides and video available online at http://www.asco.org/portal/site/ASCO/menuitem.64cfbd0f85cb57b2eda2be0aee57a01d/?vgnnextoid=09f8201eb61a7010VgnVCM100000ed750ad1RCRD&vmview=vm_session_presentations_view&index=y&confID=54&trackID=201&sessionID=806).

Schneider BP, Miller KD. (2005). Angiogenesis of breast cancer. *J Clin Oncol*, 23(8):1782-90.

Schrump DS, Altorki NK, Henschke CL et al. (2005). Non-small cell lung cancer (Chapter 27 section 2). In: *Cancer: Principles and Practice of Oncology* 7th edition; DeVita Jr VT, Hellman S, Rosenberg SA, eds. Philadelphia: Lippincott Williams and Wilkins, pp. 755-810.

Shepherd FA, Rodrigues Pereira J, Ciuleanu T et al. (2005). Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*, 355(2):125-32.

Tuma RS. (2006). Accrual delayed in adjuvant bevacizumab trial. *J Natl Cancer Inst*, 98(7):459-40.

Tyagi P, Tripathy D. (2005). First-line treatment with bevacizumab and paclitaxel prolongs progression-free survival in metastatic breast cancer. *Clin Breast Cancer*, 6(2):105-107.

Verheul HM, Pinedo HM. (2005). Inhibition of angiogenesis in cancer patients. *Expert Opin Emerg Drugs*, 10(2):405-12.

Wakelee H, Belani CP. (2005). Optimizing first-line treatment options for patients with advanced NSCLC. *Oncologist*, 10 (Suppl 3):1-10.

Wedam SB, Low JA, Yang SX et al. (2006). Antiangiogenic and antitumor effects of bevacizumab in patients with inflammatory and locally advanced breast cancer. *J Clin Oncol*, 24(5):769-77.

Wood WC, Muss HB, Solin LJ et al. (2005). Malignant tumors of the breast (Chapter 35 section 2). In: *Cancer: Principles and Practice of Oncology* 7th edition; DeVita Jr VT, Hellman S, Rosenberg SA, eds. Philadelphia: Lippincott Williams and Wilkins, pp. 1415-77.



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