Off-Label Use of Bevacizumab: Advanced Adenocarcinoma of the Pancreas

Assessment Program
Volume 24, No. 4
October 2009

Executive Summary

Background

In the U.S., pancreatic adenocarcinoma is the tenth most common cancer in men and the fourth leading cause of cancer deaths in men and women. Only 7% of cases are detected at an early stage, and more than 90% of patients develop metastases. The 1-year survival rate is 24%; the 5-year survival rate is 5% overall, and 20% for those diagnosed early with only local disease. For patients with advanced, unresectable disease, the standard of care is gemcitabine (Gemzar®, Eli Lilly and Co.). Gemcitabine is approved by the U.S. Food and Drug Administration (FDA) as single-agent first-line treatment for patients with locally advanced (stage II or stage III when surgery is not an option) or metastatic (stage IV) adenocarcinoma of the pancreas, including patients previously treated with 5-fluorouracil. Gemcitabine is sometimes given as part of combination therapy with another agent, such as erlotinib (Tarceva®, Genentech Bio-Oncology/OSI Oncology), which is approved by the FDA for first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer, in combination with gemcitabine.

Objective

To determine the incremental net benefit of using bevacizumab (Avastin®, Genentech Bio-Oncology) among patients with pancreatic adenocarcinoma. This Assessment updates part of an earlier Assessment on "Off-Label Uses of Bevacizumab: Renal Cell Carcinoma and Other Miscellaneous Non-Colorectal Cancer Indications" (Vol. 21, No. 9).

Search Strategy

A literature search was conducted in MEDLINE® (via PubMed) through April 2009, using the following search terms: (avastin OR bevacizumab) AND (pancreas OR pancreatic), limited to English-language studies involving human subjects. The search yielded 118 references, 42 of which were retrieved. In addition, literature searches were conducted in EMBASE and the Cochrane Central Register of Controlled Trials using the same search terms. Reference lists of pertinent articles were also reviewed, as well as abstracts from recent meetings of the American Society of Clinical Oncology (ASCO). The literature search was updated in July 2009, and no additional Phase III studies were found.

Selection Criteria

All Phase III trials evaluating bevacizumab for patients with advanced adenocarcinoma of the pancreas are included. No comparable data are available on the use of bevacizumab in earlier stages of the disease, so this topic is not addressed further in this Assessment.

BlueCross BlueShield Association

An Association of Independent Blue Cross and Blue Shield Plans

KAISER PERMANENTE®

Main Results

Results are available on two Phase III trials. The first, Cancer and Leukemia Group B (CALGB) 80303, compared gemcitabine with or without bevacizumab in 602 patients with locally advanced or metastatic adenocarcinoma of the pancreas. The trial was stopped early in June 2006 after a protocol-specified interim analysis with 64% of the information on overall survival and 436 deaths, or 93% of the deaths expected at final analysis. The CALGB Data Safety Monitoring Board concluded that a futility boundary had been crossed, i.e., it was unlikely that significant differences between treatment arms in overall survival would be detected with further follow-up. No statistically significant difference in progression-free survival was found.

The second Phase III trial, published in April 2009, compared gemcitabine and erlotinib with or without bevacizumab. Adding bevacizumab to gemcitabine and erlotinib[1] did not yield a statistically significant increase in overall survival. A statistically significant increase of 1 month was reported in progression-free survival.

Author's Conclusions and Comments

Adenocarcinoma of the pancreas is a grim disease with limited life expectancy after diagnosis, even after the best treatment current practice can offer. Multiple drugs have been tested as combination therapy with gemcitabine for advanced disease, including both more traditional chemotherapies such as cisplatin and newer, targeted therapies such as erlotinib. Unfortunately, the impact of these additional therapies has been limited or nonexistent. In this type of clinical situation, even small net benefits are often accepted. Bevacizumab was considered promising because it targets vascular endothelial growth factors (VEGFs), which stimulate angiogenesis and are thought to play an important role in pancreatic cancer, and because of an apparently positive effect in a Phase II trial. Unfortunately, the results of two Phase III trials, one of which was stopped early because of the lack of an effect on overall survival and the second of which was recently released, show no incremental benefit in overall survival.

The findings on progression-free survival were inconsistent, although the earlier Phase III trial was cut short. The more recently published trial did report a statistically significant difference in progression-free survival: median of 4.6 months in patients receiving bevacizumab plus gemcitabine and erlotinib versus 3.6 months in the group receiving only gemcitabine and erlotinib. However, few details were given on the methods used to assess progression-free survival, which may be subject to greater measurement error than overall survival. Data on quality of life would also be helpful to assess the value of this difference, but none were reported. In a disease such as advanced pancreatic cancer, where unfortunately life expectancy is short and secondary treatments used after failure of the first course have shown limited efficacy and often are not used, overall survival is the most meaningful primary outcome.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether the use of bevacizumab in patients with advanced adenocarcinoma of the pancreas meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

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

The U.S. Food and Drug Administration (FDA) has approved bevacizumab for first- or second-line treatment of metastatic colorectal cancer; for first-line treatment of unresectable, non-squamous, non-small cell lung cancer; for patients who have not received chemotherapy for metastatic, HER2-negative breast cancer; and, as of May 5, 2009, for patients with glioblastoma, with progressive disease after prior therapy. Bevacizumab has not been approved for use in pancreatic cancer.

[1] Another trial showed that the addition of erlotinib to gemcitabine resulted in a small but statistically significant difference in overall survival among patients receiving erlotinib (HR=0.82, p=0.038, adjusted for stratification factors).

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

Sufficient scientific evidence is available on the use of bevacizumab for patients with advanced adenocarcinoma of the pancreas in the form of two Phase III trials.

3. The technology must improve the net health outcome.

The addition of bevacizumab to a treatment regimen does not increase overall survival among patients with locally advanced or metastatic disease.

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

The established alternatives provided a benefit compared to the previously used regimens (gemcitabine vs. fluorouracil and erlotinib plus gemcitabine vs. gemcitabine alone). The addition of bevacizumab does not provide additional benefit in terms of the primary outcome of interest, overall survival.

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

Whether the addition of bevacizumab to chemotherapy regimens for advanced pancreatic adenocarcinoma improves health outcomes has not been established in the investigational settings.

Based on the above, use of bevacizumab for patients with advanced adenocarcinoma of the pancreas does not meet the TEC criteria.

Contents

Published in cooperation with Kaiser Foundation Health Plan and Southern California Permanente Medical Group.

Assessment Objective

To determine the incremental benefit of using bevacizumab (Avastin®, Genentech Bio-Oncology) among patients with advanced adenocarcinoma of the pancreas. This Assessment updates part of an earlier Assessment on "Off-Label Uses of Bevacizumab: Renal Cell Carcinoma and Other Miscellaneous Non-Colorectal Cancer Indications" (Vol. 21, No. 9).

Background

Pancreatic Cancer

Pancreatic cancer, mostly adenocarcinoma, is the tenth leading site of new cancer cases in the U.S. among men; it is the fourth leading site of cancer deaths among both men and women (after lung/bronchus, prostate or breast, and colon/rectum). In 2008, an estimated 37,680 new cases were reported and 34,290 deaths, both of which are roughly equally divided between men and women (American Cancer Society 2008). The prognosis is grim for most patients, in part because only 7% of cases are detected at an early stage. More than 90% of patients develop metastases (Van Cutsem et al. 2009). The 1-year survival rate is 24%; the 5-year survival rate is 5% overall and 20% for those diagnosed early with only local disease. Age-adjusted death rates are generally higher among men than among women (12.2% vs. 9.2%). A higher risk of contracting pancreatic cancer is associated with smoking history or use of smokeless tobacco, obesity, chronic pancreatitis, diabetes, cirrhosis, and having a family history of the disease (American Cancer Society 2008).

For patients with advanced, unresectable disease, the standard of care is gemcitabine (Gemzar®, Eli Lilly and Co.). Gemcitabine is approved by the U.S. Food and Drug Administration (FDA) as single-agent first-line treatment for patients with locally advanced (stage II or stage III when surgery is not an option) or metastatic (stage IV) adenocarcinoma of the pancreas, including patients previously treated with 5-fluorouracil. The initial Phase III trial of gemcitabine reported both a small benefit in survival and a statistically significant improvement in "clinical benefit response" (measured by Karnofsky improvement status, pain, or weight; Burris et al. 1997). Gemcitabine is sometimes given as part of combination therapy with another agent, such as erlotinib (Tarceva®, Genentech Bio-Oncology/OSI Oncology), which is approved by the FDA for first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer, in combination with gemcitabine.

According to the National Comprehensive Cancer Network (NCCN 2009) guidelines, gemcitabine is recommended for pancreatic cancer patients with locally advanced or metastatic disease, and studies have suggested some benefit from adding another chemotherapy agent (such as cisplatin or fluoropyrimidine). The guidelines state that the only new targeted drug (such as bevacizumab) for which there is evidence of a statistically significant increase in survival when combined with gemcitabine is erlotinib. NCCN therefore "recommends gemcitabine-erlotinib combination therapy as an option for patients with locally advanced or metastatic disease and good performance status" (NCCN 2009).

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; Rini and Small 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).

For further information regarding VEGF pharmacology in general and additional uses of bevacizumab, please refer to the 2006 TEC Assessments, "Off-Label Uses of Bevacizumab: Breast and Lung Cancer Indications" (Vol. 21, No. 8) and "Off-Label Uses of Bevacizumab: Renal Cell Carcinoma and Other Miscellaneous Non-Colorectal Cancer Indications" (Vol. 21, No. 9).

Bevacizumab

Bevacizumab is a humanized monoclonal antibody directed against VEGF-A (Hicklin and Ellis 2005; Verheul and Pinedo 2005; Rhee and Hoff 2005; Rini and Small 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. In animal model systems (e.g., human tumor xenotransplants in athymic mice), bevacizumab decreases growth of tumor microvasculature and inhibits progression of metastatic disease.

Bevacizumab was considered a promising therapy for pancreatic cancer because it targets VEGF, which stimulates angiogenesis and is thought to play an important role in pancreatic cancer (Ko and Tempero 2005; Ducreux et al. 2007). About 89–93% of pancreatic patients have a VEGF mutation, which is associated with early recurrence after surgery, liver metastases, and poor prognosis. Finding VEGF in tumors is also correlated with tumor size (Borja-Cacho et al. 2008).

Results of two Phase II trials were also promising. Kindler et al. (2005) reported on 52 patients with stage IV pancreatic cancer who received gemcitabine and bevacizumab. The median survival was 8.8 months, with a 1-year survival of 29%, which is considered relatively large for this stage and disease. One patient had lethal gastrointestinal bleeding and 4 had visceral perforations. However, this group of patients was favorably selected in that patients were excluded who were at higher risk of bleeding; had tumor involvement of major blood vessels; had prior cerebrovascular accident, pulmonary embolus, or deep vein thrombosis; or had myocardial infarction, ischemia, or uncompensated coronary artery disease in the last 6 months; among other factors.

A second Phase II study (Ko et al. 2008) treated 52 patients with metastatic pancreatic cancer with bevacizumab, fixed-dose rate gemcitabine, and low-dose cisplatin. Fourteen patients (28.0%) received secondary therapy. Median time to progression was 6.6 months; median survival was 8.2 months, with an estimated 1-year survival of 36%. The most common Grade 3/4 toxicities were thromboembolic events (15.1%), hypertension (13.2%), gastrointestinal bleeding (9.4%), cardiac events (7.5%) and bowel perforation (5.7%). Exclusion criteria included history of myocardial infarction or stroke within 6 months, uncontrolled hypertension, unstable angina and other cardiac and vascular diagnoses, nonhealing wounds, and an elevated bleeding risk. Five patients (approximately 10%) died from myocardial infarctions or bowel perforations that may have been due to therapy. A post-hoc analysis suggested that patients with an Eastern Cooperative Oncology Group (ECOG) performance score of 0 (i.e., healthy; see http://ecog.dfci.harvard.edu/general/perf_stat.html) had a longer median survival than those who were sicker at baseline. This may not be surprising given the potential toxicities of the treatments used. The authors recommended that further research focus on an effort to identify subsets of patients who may benefit from bevacizumab.

Two more Phase II studies were published in the summer of 2009. Crane et al. (2009) reported on a study on bevacizumab plus capecitabine and radiotherapy, followed by maintenance gemcitabine and bevacizumab (RTOG 0411) among patients with locally advanced pancreatic cancer. Patients with a history of certain gastrointestinal, cardiac, and other health problems were excluded. Median survival was 11.9 months, with 47% surviving 1 year and progression-free survival of 8.6 months. About 35% of patients had Grade 3 or higher treatment-related gastrointestinal toxicity, with a higher percentage among patients undergoing chemoradiotherapy (22% vs. 13%, statistical significance of difference not reported). This difference may be due in part to unacceptable protocol deviations during radiotherapy in 13.4% of patients. The investigators believe that this was due, in turn, to poor tumor visualization on the diagnostic images. The authors conclude that "The 1-year overall survival rate in this study is comparable to that of prior RTOG Phase II studies. Therefore, the primary end point was negative, and additional study of this regiment in locally advanced pancreatic cancer is not warranted."

The second Phase II study published recently also examined the combination of gemcitabine, capecitabine, and bevacizumab (Javle et al. 2009). The 50 patients had advanced pancreatic cancer; patients at high risk for bleeding, cardiac events, and other adverse events were excluded. The primary endpoint was progression-free survival, and patients were followed a median of 8.9 months. There were 13 Grade 3 or 4 toxicities potentially associated with bevacizumab. One patient with cancer

involvement in the gastric wall and varices had a Grade 5 hemorrhage. As a result, the protocol was amended to exclude such patients, and no additional Grade 5 toxicities occurred. Median progression-free survival was 5.8 months; overall survival was 9.8 months. Based on the results of this and other published studies, the authors concluded that the role of bevacizumab in these patients is questionable, and they did not proceed to a Phase III trial.

Pancreatic cancer involves multiple genetic mutations (Philip 2008), which has led to its being targeted by a number of therapies, both alone and in combination. Erlotinib, for example, targets epidermal growth factor receptors (EGFR), and has been found to have a small beneficial incremental effect over the use of gemcitabine alone (Moore et al. 2007). Bevacizumab has been assessed in addition to gemcitabine alone or with erlotinib. A study currently underway treats patients with gemcitabine and bevacizumab with either cetuximab (Erbitux®, ImClone Systems, Inc.) or erlotinib (Phillip 2008).

As Borja-Cacho et al. (2008) write:

> Even although there is an initial response after anti-EGF[R] and anti-VEGF therapies, some epithelial tumors, including pancreatic cancer, have intrinsic mutations that make them primarily resistant or eventually resistant during the course of the treatment. The mutations give the tumor the ability to bypass the blockage of 1 pathway and because most pathways are redundant, tumors are still able to grow….In an effort to decrease resistance to these targeted therapies, combinations using both anti-EGFR and anti-VEGF therapy have been assayed in vitro, and the combination has yielded a better response compared with therapy using either drug alone.

FDA Status. The U.S. Food and Drug Administration (FDA) has approved bevacizumab (Avastin®, Genentech Bio-Oncology, Inc; South San Francisco, CA) for first- or second-line treatment of metastatic colorectal cancer; first-line treatment of unresectable, non-squamous, non-small cell lung cancer; and for patients who have not received chemotherapy for metastatic, HER2-negative breast cancer (based on improvement in progression-free survival only) (Genentech Bio-Oncology, Inc. 2009). Most recently, on May 5, 2009, the FDA granted accelerated approval to bevacizumab for patients with glioblastoma, with progressive disease after prior therapy, based on two single-arm studies.

The bevacizumab FDA-approved label includes a black box warning about gastrointestinal perforations, wound healing complications, and hemorrhage. Other potential adverse events listed on the label include non-gastrointestinal fistula, arterial thromboembolic events (including cerebral infarction, transient ischemic attacks, myocardial infarction, and angina), hypertension, reversible posterior leukoencephalopathy syndrome, neutropenia and infection, proteinuria, and congestive heart failure. Bevacizumab should not be given for at least 28 days following major surgery, and the surgical incision should be fully healed. In July 2008, Genentech sent a letter to healthcare providers indicating that the use of bevacizumab in combination with sunitinib maleate (Sutent®, Pfizer Oncology) was not recommended, because of the potential for microangiopathic hemolytic anemia seen in a Phase I dose-escalation study using both medications.

Methods

Search Methods

A literature search was conducted in MEDLINE® (via PubMed) through April 2009, using the following search terms: (avastin OR bevacizumab) AND (pancreas OR pancreatic), limited to English-language studies involving human subjects. The search yielded 118 references, 42 of which were retrieved. In addition, literature searches were conducted in EMBASE and the Cochrane Central Register of Controlled Trials using the same search terms. Reference lists of pertinent articles were also reviewed, as well as abstracts from recent meetings of the American Society of Clinical Oncology (ASCO). The literature search was updated in July 2009, and no additional Phase III studies were found.

Study Selection

All Phase III trials using bevacizumab for patients with adenocarcinoma of the pancreas are included. No comparable data are available on the use of bevacizumab in earlier stages of the disease, so this topic is not addressed further in this Assessment.

Medical Advisory Panel Review

This Assessment was reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on June 25, 2009. To maintain the timeliness of the Assessment's scientific information, 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 tables and text where appropriate.

Formulation of the Assessment

Patient Indications

Patients are those with adenocarcinoma of the pancreas.

Technologies to be Compared

Treatment with or without bevacizumab.

Health Outcomes

Benefits. Increased overall survival, longer progression-free survival (PFS), greater tumor response.

Harms. Adverse events due to bevacizumab.

For benefits and harms, the focus is on the incremental impact of bevacizumab, compared to standard treatment (gemcitabine; erlotinib or other chemotherapy agent sometimes added).

Specific Assessment Question

What is the incremental net benefit of using bevacizumab among patients with advanced adenocarcinoma of the pancreas, taking into account potential increases in survival or improvements in quality of life, as well as adverse events due to the treatment?

Review of Evidence

Five studies were identified that tested the use of bevacizumab in patients with advanced adenocarcinoma of the pancreas: two Phase III trials, two Phase II trials, and a single Phase I trial. Abstracts of additional Phase I or Phase II trials were not counted. In each case, bevacizumab was added to gemcitabine, which is the current standard of care for these patients. Some studies included other chemotherapeutic agents, as well, e.g., cisplatin or erlotinib.

Because of their research design, the two Phase III studies (Kindler et al. 2007, Van Cutsem et al. 2009; Table 1) provide the strongest evidence. The Kindler et al. (2007) Cancer and Leukemia Group B (CALGB) 80303 trial was stopped before completion when the Data Safety Monitoring Board determined that the gemcitabine plus bevacizumab arm could not achieve longer survival than the control arm receiving gemcitabine alone. The results were presented at an ASCO conference in 2007, but were not published in a peer-reviewed journal.

The most important outcome is overall survival, especially for a medication like bevacizumab, which can cause serious adverse effects, sometimes resulting in death. Prolonging the interval before progression may or may not extend life, depending on the magnitude and timing of adverse events and the course of the disease once progression resumes. Also of great importance, especially in a usually fatal disease, is the impact on the quality of life following treatment.

As is shown in Table 1, Kindler et al. (2007) randomized 602 patients with advanced cancer (locally advanced or metastatic) to gemcitabine with or without bevacizumab. Patients were stratified by performance status, disease extent, and whether or not they received radiation therapy. Patients with a number of comorbidities were excluded, including factors like elevated risk of bleeding and clinically significant cardiovascular disease, some of which might make it more difficult to tolerate potential adverse events from bevacizumab. The trial was halted after a protocol-specified interim analysis, with 64% of the expected overall survival data available and 436 deaths, or 93% of the deaths expected at final analysis. The Data Safety Monitoring Board decided that "it was unlikely that there would be significant differences in overall survival between treatment arms with further follow-up." The authors speculated that the reason their Phase III results differed from their Phase II trial was that in the latter, they had more healthy patients (ECOG performance status=0, 60% vs. approximately 38%), they excluded patients with prior thrombosis, and more patients had received prior adjuvant therapy (23% vs. 11% had prior radiation). They also reiterated the importance of conducting randomized, controlled trials in this disease.

Table 1. Phase III Studies on Use of Bevacizumab for Advanced Adenocarcinoma of the Pancreas

Row No.	Category	Kindler et al. 2007 (preliminary analysis presented at ASCO meeting)*	Van Cutsem et al. 2009
A. Design			
1	Treatments compared	Gemcitabine + bevacizumab	Gemcitabine + erlotinib ± bevacizumab
2	Randomization method	Not reported	Interactive voice recording device
3	Stratification	PS (0/1 or 2), disease extent (locally advanced or metastatic), prior radiation (y/n)	KPS, albumin
4	Sample size calculation	90% power to detect a difference in median OS of 6 vs. 8.1 months.	Assuming 6.9 months median survival in control arm and 9 months in Tx arm (HR=0.767), need 446 events to achieve 80% power for log-rank test with two-sided overall α of 5%
5	Study population	Pts with locally advanced or metastatic pancreatic cancer. Exclusions: no prior therapy for advanced disease, PS 0-2, no tumor invasion of adjacent organs, no bleeding risk.	Pts. 18+ years w/ histologically or cytologically documented metastatic adenocarcinoma of the pancreas. Also KPS >60%, adequate blood counts and kidney and liver function, and proteinuria dipstick <2+. Excluded if certain prior Tx, clinically significant cardiovascular disease, risk of bleeding (details in article), major surgery w/in 28 days, etc.
6	Location and time period	6/30/04-4/14/06. Based on a protocol-specified interim analysis with 64% of information on OS, the CALGB Data Safety Monitoring Board released study data in 6/06 because a futility boundary was crossed.	Multicenter (92 institutions in 20 countries; none in U.S.), July 2005-September 2006
7	Sample size	n=602; n=518 pts (Tx: 264; Ctl: 254) evaluable for toxicity	n=607 for efficacy outcomes; n=583 for safety (24 of those recruited received no Tx)
8	Outcomes	Primary: overall survival	Primary: overall survival Secondary: – progression-free survival – ORR (CR+PR) and disease control rate (CR+PR+SD) (tumor response measured using RECIST) – tolerability (adverse events measured using NCI-CTCAE v3)

*There are some minor differences in the numbers reported in the abstract and those included in the slides.

Table 1. Phase III Studies on Use of Bevacizumab for Advanced Adenocarcinoma of the Pancreas (cont'd)

Row No.	Category	Kindler et al. 2007 (preliminary analysis presented at ASCO meeting)	Van Cutsem et al. 2009
A. Design (cont'd)			
9	Median follow-up duration	Tx: 8.4 months Ctl: 8.1 months	Not reported
10	Follow-up frequency	CT scans: every 2 cycles	8, 16, 24, 32, 40 weeks and every 12 weeks thereafter (KPS, weight, hematology and coagulation tests, blood chemistry and urinalysis every 1–2 weeks; biomarkers collected before trial, week 9, and at disease progression)
11	Multivariate analysis plan (MVA)	Not reported	Prespecified prognostic factors: region; KPS; baseline albumin; gender; age; race; tumor location w/in pancreas; jaundice at time of Dx; baseline levels of LDH, alkaline phosphatase, platelet count, C-reactive protein, total bilirubin, CA19.9, neutrophils, and no. lesions; smoking status, liver lesions (y/n) No further description of analysis methods.
B. Results			
12	Gender (% female)	Tx: 42% Ctl: 49%	Tx: 43 Ctl: 38 p not reported
13	Baseline median age (range) in yrs	Tx: 63.8 Ctl: 65.0	Tx: 62 (20–85) Ctl: 61 (33–85)
14	Performance status	ECOG PS 2=9% for both arms	KPS <80% Tx: 13% Ctl: 13%
15	Stage or location	Stage IV: Tx: 85% Ctl: 84%	Primary tumor location in pancreas Head: Tx: 51%; Ctl: 55% Body: Tx: 26%; Ctl: 22% Tail: Tx: 22%; Ctl: 22%
16	Prior Tx for pancreatic cancer	Prior radiotherapy 11% for both groups	Antimetabolites: Tx: 4%; Ctl: 5% Radiotherapy: Tx: 3%; Ctl: 2%
17	Median dose received: % of planned (range)	Not reported; Median cycles: Tx: 3.0; Ctl: 2.6	Tx: 89% (20–108%) Ctl: 91% (9–110%)

Table 1. Phase III Studies on Use of Bevacizumab for Advanced Adenocarcinoma of the Pancreas (cont'd)

Row No.	Category	Kindler et al. 2007 (preliminary analysis presented at ASCO meeting)	Van Cutsem et al. 2009
B. Results (cont'd)			
18	Pts receiving second-line therapy (mostly antimetabolites or platinum compounds)	Not reported	Tx: 30% Ctl: 39%
19	# (%) deaths when analysis performed	Tx: 196/302 (64.9%) Ctl: 181/300 (60.3%) (80% of total expected deaths at planned final analysis)	Tx: 221 (72.2%) Ctl: 233 (77.4%)
20	Median overall survival (months)	Tx: 5.7 95% CI: 4.9–6.5 Ctl: 6.0 95% CI: 5.0–6.9 HR: 1.09 p=0.40	Tx: 7.1 Ctl: 6.0 HR: 0.89 95% CI: 0.74–1.07 p=0.2087 (NS)
21	Median progression-free (or failure-free) survival (months)	Tx: 4.8 95% CI: 4.3–5.7 Ctl: 4.3 95% CI: 3.8–5.6 HR: 1.0 p=0.99	Tx: 4.6 Ctl: 3.6 HR: 0.73 95% CI: 0.61–0.86 p=0.0002
22	Tumor response	Complete: Tx: 1.1%; Ctl: 2.8% Partial: Tx: 12.4%; Ctl: 7.5% Stable disease: Tx: 40.9%; Ctl: 33.6% (includes unconfirmed responses; no statistics reported)	Tx: 2 CRs, 38 PRs, n=297 Ctl: 0 CRs, 25 PRs, n=292 ORR Tx: 13.5% Ctl: 8.6% p=0.0574 (NS) Disease control rate Tx: 62.1% Ctl: 58.5% p=0.3621 (NS)

Table 1. Phase III Studies on Use of Bevacizumab for Advanced Adenocarcinoma of the Pancreas (cont'd)

Row No.	Category	Kindler et al. 2007 (preliminary analysis presented at ASCO meeting)	Van Cutsem et al. 2009
B. Results (cont'd)			
23	Subgroup analysis of overall survival (months)	Not reported	Tumors in tail of pancreas Tx: 9.0 Ctl: 5.5 HR: 0.54 95% CI: 0.36–0.81 p=0.0025 Baseline CRP >1.4 mg/L Tx: 4.8 Ctl: 3.6 HR: 0.65 95% CI: 0.51–0.84 p=0.0009 Baseline LDH > Upper limit of normal Tx: 4.7 Ctl: 3.6 HR: 0.59 95% CI: 0.43-0.82 p=0.0013 Pts with skin rash (Figure to be abstracted; survival appears better for pts with Grade 1+ vs. Grade 0; no statistics reported) Pts from "other region" (not Asia/Pacific or Western European—not defined but may include Canada, Peru, Israel) may have benefited from bevacizumab (HR: 0.62; 95% CI: 0.41–0.95; p not reported; n=123) No subgroups with Ctl outcomes better than Tx outcomes.

Table 1. Phase III Studies on Use of Bevacizumab for Advanced Adenocarcinoma of the Pancreas (cont'd)

Row No.	Category	Kindler et al. 2007 (preliminary analysis presented at ASCO meeting)	Van Cutsem et al. 2009
B. Results (cont'd)			
24	Adverse events (AE)	Grade 3/4 toxicity: Neutropenia: Tx=31%; Ctl=29% Anemia: Tx=5%; Ctl=8% Thrombocytopenia: Tx=12%; Ctl=11% Hypertension: Tx=8%; Ctl=2% Perforation: Tx & Ctl=0% GI bleed: Tx=3%; Ctl=2% CVA: Tx=1%; Ctl=2% Proteinuria: Tx=2%; Ctl=1% Venous thrombosis: both Tx and Ctl=9%	Grade 3–5 events: Tx=74%; Ctl=70% Top 6 most common Grade 3–5 AEs (%): Anemia: Tx=7; Ctl=9 Thrombocytopenia: Tx=8; Ctl=6 Neutropenia: Tx=21; Ctl=17 Diarrhea: Tx=4; Ctl=6 Nausea: Tx=4; Ctl=3 Rash: Tx=8; Ctl=3 No statistics reported. Adverse events resulting in death (including PE, GI bleeding, cerebrovascular events, septic shock/sepsis; respiratory failure): Tx=9%; Ctl=6%. No difference between groups in deaths w/in 30 days last Tx (3%) or 60-day all cause mortality (Tx=10%; Ctl=12%).
25	Result summary	Adding bevacizumab to gemcitabine does not improve survival in advanced pancreatic cancer.	Difference between treatment and control group favors bevacizumab for progression-free survival and for overall survival of some subgroups (tumor in tail, higher baseline CRP and LDH, patients with rash), but there is no statistically significant difference between groups for overall survival or tumor response.

Table 1. Phase III Studies on Use of Bevacizumab for Advanced Adenocarcinoma of the Pancreas (cont'd)

Row No.	Category	Kindler et al. 2007 (preliminary analysis presented at ASCO meeting)	Van Cutsem et al. 2009
C. Study Quality			
26	Key characteristics		Prospective, RCT, ITT; Adverse events counted for pts who received >1 dose of assigned Tx
27	Results published in peer-reviewed publication	No; study halted by data monitoring committee	Yes
28	U.S. Preventive Task Force (USPSTF) rating	No rating**	Good
29	Source of funding		Hoffman-La Roche

**No rating assigned because only preliminary results from ASCO presentation available.

Abbreviations:
AE: adverse events; CR: complete tumor response; Ctl: control group, i.e., did not receive bevacizumab; CVA: cerebrovascular accident; Dx: diagnosis; GI: gastrointestinal; ITT: intention to treat; KPS: Karnofsky Performance Status; LDH: lactate dehydrogenase; NCI-CTCAE v3: National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0; ORR: overall response rate ; OS: overall survival; PE: pulmonary embolism; PR: partial tumor response; PS: performance status; RCT: randomized, controlled trial; RECIST: Response Evaluation Criteria in Solid Tumors; SD: table disease (tumor response measure); Tx: treatment group, i.e., received bevacizumab; y/n: yes or no

In the second Phase III trial (Table 1), Van Cutsem et al. (2009) randomized 607 patients with metastatic adenocarcinoma of the pancreas to treatment with bevacizumab; all patients also received gemcitabine and erlotinib. Patients with Karnofsky Performance Status (KPS) less than 60%, poor blood counts, poor kidney or liver function, or proteinuria were excluded. The sample size was selected to achieve 80% power for a log rank test with an assumed hazard ratio of 0.767 (9 months' median survival for bevacizumab group versus 6.9 months for "control" group receiving only gemcitabine and erlotinib) and a two-sided of 5%. Intent-to-treat analysis was used for efficacy outcomes, but 24 patients received no treatment and were not included in the safety data. The median dose received, as a percentage of planned dose, was 89% (range: 20–108%) for the bevacizumab group and 91% (range: 9–110%) for the control group. Thirty percent of the treatment group and 39% of the control group received second-line therapy.

The primary outcome was overall survival. No statistically significant difference was detected between the groups. The median survival was 7.1 months for the treatment group and 6.0 months for the control group (HR=0.89; 95% CI: 0.74–1.07; p=0.2087).

Secondary outcomes included progression-free survival, objective response rate (ORR=complete and partial tumor response, using Response Evaluation Criteria in Tumors [RECIST] criteria), disease control rate (DCR=ORR plus stable disease), and tolerability (i.e., adverse events measured using National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 [NCI-CTCAE v3]). Of PFS, ORR, and DCR, there was one statistically significant difference between groups: Median progression-free survival was 4.6 months for the bevacizumab group and 3.6 months for the control group (HR=0.73; 95% CI: 0.61–0.86; p=0.0002). The between-group differences for objective response and disease control response rates were not statistically significant (p=0.0574 and p=0.3621, respectively).

The authors also reported the results of a multivariate Cox survival model, with 18 prespecified prognostic factors (see Table 1, Row 11 for list). No additional details are provided on the methods used in this analysis. Hazard ratios are reported for each of them, and statistically significant differences between the bevacizumab and control groups were reported in the article: tumors in the tail of the pancreas (versus head or body; HR=0.54, p=0.0025), baseline C-reactive protein greater than 1.4 mg/L (HR=0.65; p=0.0009), and baseline LDH greater than the upper limit of normal (HR=0.59, p=0.0013). The authors also note that overall survival appears to be longer for patients with a Grade 1 or higher skin rash versus those with no rash (p value not reported). Visual inspection of the online table of results also shows that the bevacizumab:control hazard ratio is statistically significantly lower for patients from "other region" vs. patients from Asia/Pacific or Western European (HR=0.62, 95% CI: 0.41–0.95, p not reported). Finally, the authors note that the control group did not have better treatment outcomes than the bevacizumab group for any of the prognostic factors.

The adverse events by group are reported in Table 1, Row 24. The percentage of patients with Grade 3–5 events was 74% for the treatment group and 70% for the control group. There were no differences between groups in the deaths within 30 days of the last treatment or in 60-day all-cause mortality. The six most common Grade 3–5 adverse events were anemia, thrombocytopenia, neutropenia, diarrhea, nausea, and rash. No statistical tests were reported for any of these comparisons.

Discussion

The most important outcome in considering the use of bevacizumab for patients with advanced adenocarcinoma of the pancreas is overall survival. This outcome is especially significant for a medication like bevacizumab, which can cause serious adverse effects, sometimes resulting in death. Prolonging the interval before progression may or may not extend life, depending on the magnitude and timing of adverse events. Also of great importance, especially in a usually fatal disease, is the impact on the quality of life following treatment.

The results for overall survival between groups treated with and without bevacizumab in the two Phase III trials were the same: There was no statistically significant difference between the treatment and control arms in either study, even though one added bevacizumab or placebo to gemcitabine (Kindler et al. 2007) and the other added bevacizumab or placebo to gemcitabine and erlotinib (Van Cutsem et al.

2009). Thus, in terms of the primary outcome for both studies, the addition of bevacizumab did not yield any benefit.

Bevacizumab appeared to provide a benefit in terms of lengthening progression-free survival in one study (Van Cutsem et al. 2009) but not in the other (Kindler et al. 2007). In the former, progression-free survival was about 28% longer in the bevacizumab arm, but given the low baseline survival, that translates to a possible increase of one month, from 3.6 to 4.6 months. There are several issues that should be considered in interpreting this finding, including the following:

- How reliable is the measurement of progression? No details are provided in the paper on the methods used other than citing the RECIST criteria. The RECIST criteria (www.recist.com) state that randomization and double-blinding is ideal when progression-free survival is the primary endpoint, and if double-blinding is not possible that an independent reviewer may be added. It is not clear whether the evaluators in the Van Cutsem et al. (2009) study were blinded to treatment assignment or whether the assessments were performed by multiple evaluators and/or verified.
- What is the impact of an increase in progression-free survival on patients' quality of life, when targeted therapies may halt progression without shrinking tumor volume and the associated symptoms in a disease like pancreatic cancer? Quality-of-life measures were used in the CALGB 80303 (Kindler et al. 2007) study, but because the trial was stopped early, full results were never published. In an abstract presented at ASCO in 2007, health-related quality-of-life at 8 weeks was reported (Romanus et al. 2007) and no difference was found between the bevacizumab and treatment arms. Unfortunately, only the abstract is available; furthermore, results are not available on the full time period of interest (i.e., until disease progression).
- Was the lack of a significant impact on progression-free survival in Kindler et al. (2007) due to inadequate sample size, a different patient population, the addition of erlotinib in the Van Cutsem et al. trial or some other factor(s)?
- What accounts for the difference in results between progression-free and overall survival? The adverse event rates in each arm appeared to be roughly equivalent in both studies, although no statistical comparisons were reported.

These questions cannot all be answered, but they suggest the need for caution in generalizing from these results regarding progression-free survival from a single study with scantily described evaluation methods or using them to presume a net benefit for bevacizumab. Using progression-free survival as an endpoint generally avoids confounding by the use of additional therapies when the disease progresses. This fact is outweighed, however, by its lack of precision, i.e., progression-free survival may be affected by the methods used to collect the information (Mayfield 2008) and the timing of follow-up (although this issue is less germane in a well-conducted Phase III trial; Panagea et al. 2007). Radiologic measurement of tumor size is also complicated by the fact that tumors are composed of both cancer cells and "dense desmoplastic reaction with contributions from pancreatitis and a dilated pancreatic duct" (Conner and O'Reilly 2005). As Kulke noted in a commentary in 2005:

> However, the advantage and use of progression-free survival as a primary endpoint in trials of advanced pancreatic cancer, where the value of second-line therapy is less clear, is debatable. Indeed, with a median overall survival time of only about 6 months, a strong argument can be made for the continued use of overall survival as the primary endpoint for clinical trials in this disease.

Another secondary finding from the Van Cutsem et al. (2009) study that should be considered is the meaning of the statistically significant prognostic factors in the multivariate Cox model. Again, the paucity of details on methods in this paper makes the results difficult to interpret. In the methods section, the prespecified prognostic factors are listed, as described in Table 1, Row 11. Although the authors refer to their findings in the paper as a subgroup analysis, that is not the type of analysis they appeared to perform. The best way to identify subgroups that may benefit or be harmed disproportionately by a treatment is to identify patient characteristics that predict outcomes a priori and then include treatment by patient characteristic interaction terms in a multivariate analysis. Statistically significant interaction terms will indicate that the treatment has a differential effect in a distinct group of patients.

There are several additional concerns with the Van Cutsem et al. (2009) analysis. First, as mentioned above, insufficient details are provided

on the methods used to evaluate the validity and generalizability of the results. Second, even if the authors had used the appropriate statistical approach for a subgroup analysis, there are a number of potential pitfalls encountered with subgroup analyses, which are well described in Pocock et al. (2002). They note that:

> Biological plausibility, the number of subgroup analyses performed, their prespecification and the trial's size all need to be considered alongside the statistical strength of the evidence when weighing up the all too likely case that any particular subgroup finding, no matter how intriguing, is prone to be an exaggeration of the truth.

The Van Cutsem et al. (2009) trial was relatively large, and the covariates were prespecified. But the number of covariates included is large and the rationale (or biological plausibility) for including each one is not described. For example, is there a reason why one would expect a priori that bevacizumab would be more effective in treating tumors in the tail of the pancreas, which are often detected at a later stage, rather than one in the body or head? Moreover, it may be difficult to classify tumor location given the challenges of radiological imaging in this site. One significant covariate was not mentioned in the paper: geographic region. Patients in "other regions" had a lower hazard ratio than those from Asia/Pacific or two parts of Western Europe.

Identifying the subset of patients, if any, who may benefit most from an intervention should be an important part of any comparative clinical trial. If the group of patients who benefit disproportionately from a treatment are a relatively small proportion of the whole and/or if the treatment effect is modest, the treatment may not appear to be beneficial when analyzing the group as a whole and the treatment may be abandoned, thus foregoing the potential benefit for a subset of patients. But conducting valid subgroup analyses can be challenging; otherwise, the results are likely to be misleading.

The Kindler et al. (2007) trial is discussed briefly, because stopping the trial early means that full data are not available. A potential confounder in the study, however, is that patients with locally advanced disease should probably be studied separately from those with metastatic disease (on the latter point, see Chua and Zalcberg 2008; Philip 2008).

Summary

Adenocarcinoma of the pancreas is a grim disease with limited life expectancy after diagnosis, even after the best treatment current practice can offer. Multiple drugs have been tested as combination therapy with gemcitabine for advanced disease, including both more traditional chemotherapies such as cisplatin and newer, targeted therapies such as erlotinib. Unfortunately, the impact of these additional therapies has been limited or nonexistent. In this type of clinical situation, even small net benefits are often accepted. Bevacizumab was considered promising because it targets vascular endothelial growth factors, which stimulate angiogenesis and are thought to play an important role in pancreatic cancer, and because of an apparently positive effect in a Phase II trial. Unfortunately, the results of two Phase III trials (Kindler et al. 2007; Van Cutsem et al. 2009), one of which was stopped early because of the lack of an effect on overall survival and the second of which was recently released, show no incremental benefit in overall survival.

The findings on progression-free survival were inconsistent, although admittedly, the earlier Kindler trial was cut short. The Van Cutsem trial did report a statistically significant difference in progression-free survival: median of 4.6 months in patients receiving bevacizumab plus gemcitabine and erlotinib versus 3.6 months in the group receiving only gemcitabine and erlotinib. However, few details were given on the methods used to assess progression-free survival, which may be subject to greater measurement error than overall survival. Data on quality of life would also be helpful to assess the value of this difference, but none were reported. In a disease such as advanced pancreatic cancer, where unfortunately life expectancy is short and secondary treatments used after failure of the first course have shown limited efficacy and often are not used, overall survival is the most meaningful primary outcome.

Numerous clinical trials are currently under way, planned, or in the analysis phase using bevacizumab for pancreatic cancer; they are listed at www.clinicaltrials.gov. Most of them are relatively small (i.e., fewer than 100 subjects).

Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether the use of bevacizumab in patients with advanced adenocarcinoma of the pancreas meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

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

The U.S. Food and Drug Administration (FDA) has approved bevacizumab for first- or second-line treatment of metastatic colorectal cancer; for first-line treatment of unresectable, non-squamous, non-small cell lung cancer; for patients who have not received chemotherapy for metastatic, HER2-negative breast cancer; and, as of May 5, 2009, for patients with glioblastoma, with progressive disease after prior therapy. Bevacizumab has not been approved for use in pancreatic cancer.

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

Sufficient scientific evidence is available on the use of bevacizumab for patients with advanced adenocarcinoma of the pancreas in the form of two Phase III trials.

3. **The technology must improve the net health outcome.**

The addition of bevacizumab to a treatment regimen does not increase overall survival among patients with locally advanced or metastatic disease.

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

The established alternatives provided a benefit compared to the previously used regimens (gemcitabine vs. fluorouracil and erlotinib plus gemcitabine vs. gemcitabine alone). The addition of bevacizumab does not provide additional benefit in terms of the primary outcome of interest, overall survival.

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

Whether the addition of bevacizumab to chemotherapy regimens for advanced pancreatic adenocarcinoma improves health outcomes has not been established in the investigational settings.

Based on the above, use of bevacizumab for patients with advanced adenocarcinoma of the pancreas does not meet the TEC criteria.

References

American Cancer Society (ACS). (2008). Cancer Facts & Figures 2008. Retrieved 04/29/09 from http://www.cancer.org/downloads/STT/2008CAFFfinalsecured.pdf.

Borja-Cacho D, Jensen EH, Saluja AK et al. (2008). Molecular targeted therapies for pancreatic cancer. *Am J Surg,* 196:430-41.

Bouis D, Kusumanto Y, Meijer C et al. (2006). A review on pro- and anti-angiogenic factors as targets of clinical intervention. *Pharmacol Res,* 53(2):89-103.

Burris HA III, Moore MJ, Andersen et al. (1997). Improvements in survival and clinical benefits with gemcitabine in first line therapy for patients with advanced pancreatic cancer: A randomized trial. *J Clin Oncol* 15:2403-13.

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.

Chua YJ, Zalcberg JR. (2008). Pancreatic cancer—is the wall crumbling? *Ann Oncol* 19:1224-30.

Conner JA, O'Reilly EM. (2005). Clinical trial design and methodology. In: *Pancreatic Cancer,* Von Huff DD et al., eds., pp. 451-68. Sudbury, MA: Jones and Bartlett Publishers.

Crane CH, Winter K, Regine WF, et al. (2009). Phase II study of bevacizumab with concurrent capecitabine and radiation followed by maintenance gemcitabine and bevacizumab for locally advanced pancreatic cancer: Radiation Therapy Oncology Group RTOG 0411. *J Clin Oncol,* epub 27 July 2009.

Culy C. (2005). Bevacizumab: antiangiogenic cancer therapy. *Drugs Today (Barc),* 41(1):23-36.

Ducreux M, Boige V, Malka D. (2007). Treatment of advanced pancreatic cancer. *Semin Oncol,* 34(suppl1):S25-S30.

Fidler IJ, Langley RR, Kerbel RS et al. (2005). Angiogenesis (Chapter 5). In: *Cancer: Principles and Practice of Oncology* 7th edition; VT DeVita Jr, S Hellman, SA Rosenberg, eds. Philadelphia: Lippincott Williams and Wilkins, pp. 129-37.

Folkman J. (2006). Angiogenesis. *Annu Rev Med,* 57:1-18.

Folkman J. (2005). Antiangiogenesis agents (Chapter 63). In: Cancer: *Principles and Practice of Oncology* 7th edition; VT DeVita Jr, S Hellman, SA Rosenberg, eds. Philadelphia: Lippincott Williams and Wilkins, pp. 2865-82.

Genentech Bio-Oncology, Inc. (2009). Avastin® (bevacizumab) prescribing information. South San Francisco, CA; last revised May 2009. Available online at http://www.gene.com/gene/products/information/pdf/avastin-prescribing.pdf. Last accessed May 2009.

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.

Javle M, Yu J, Garrett C, Pande A et al. (2009). Bevacizumab combined with gemcitabine and capecitabine for advanced pancreatic cancer: A phase II study. *Br JCancer,* 100:1842-5.

Kindler HD, 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.

Kindler HD, Niedzwiecki D, Hollis D et al. (2007). A double-blind, placebo-controlled, randomized phase III trial of gemcitabine plus bevacizumab versus gemcitabine plus placebo in patients with advanced pancreatic cancer: A preliminary analysis of CALGB 80303. Abstract and slide presentation from the 2007 meeting of the American Society of Clinical Oncology.

Ko AH, Dito E, Schillinger B et al. (2008). A phase II study evaluating bevacizumab in combination with fixed-dose rate gemcitabine and low-dose cisplatin for metastatic pancreatic cancer: Is an anti-VEGF strategy still applicable? *Invest New Drugs,* 26:463-71.

Ko AH, Tempero MA. (2005). Treatment of metastatic pancreatic cancer. J Natl *Comprehensive Cancer Network,* 3(5):627-36.

Kulke MH. (2005). Combination chemotherapy for advanced pancreatic cancer—has its time finally come? (Reflection and Reaction). *Lancet Oncol,* 6:352-3.

Mayfield E. (2008). Progression-free survival: Patient benefit or lower standard? *NCI Cancer Bull,* 5(10):8-9.

Midgley R, Kerr D. (2005). Bevacizumab—current status and future directions. *Ann Oncol,* 16(7):999-1004.

Moore MJ, Goldstein D, Hamm J et al. (2007). Erlotinib plus gemcitabine compare with gemcitabine alone in patients with advanced pancreatic cancer: A phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol,* 25(15):1960-6.

National Comprehensive Cancer Network® (NCCN). (2009). NCCN Clinical Practice Guidelines in Oncology™: Pancreatic adenocarcinoma. Accessed May 4, 2009, at www.nccn.org.

Panagea KS, Ben-Porat L, Dickler MN et al. (2007). When you look matters: The effect of assessment schedule on progression-free survival. *J Natl Cancer Inst,* 99:428-32.

Philip PA. (2008). Targeted therapies for pancreatic cancer. *Gastrointest Cancer Res,* 2(4, suppl 2):S16-S19.

Pocock SJ, Assmann SE, Enos LE et al. (2002). Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: Current practice and problems. *Statist Med,* 21:2917-30.

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

Rini BI, Small EJ. (2005). Biology and clinical development of vascular endothelial growth factor-targeted therapy in renal cell carcinoma. *J Clin Oncol,* 23(5):1028-43.

Romanus D, Archer L, Wang X et al. (2007). Does health-related quality of life (HRQOL) improve for patients who respond to chemotherapy? Analysis of patients with advanced pancreatic cancer (APC) receiving gemcitabine on Cancer and Leukemia Group B (CALGB) study #80303. *J Clin Oncol,* 25(18S):9008.

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

Van Cutsem E, Vervenne WL, Bennouna I et al. (2009). Phase III trial of bevacizumab in combination with gemcitabine and erlotinib for patients with metastatic pancreatic cancer. *J Clin Oncol,* 27(13):2231-7.

Verheul HM, Pinedo HM. (2005). Inhibition of angiogenesis in cancer patients. *Expert Opin Emerg Drugs,* 10(2):403-12.

Technology
Evaluation
Center

Blue Cross and
Blue Shield Association
225 North Michigan Avenue
Chicago, Illinois 60601-7680
www.bcbs.com/tec