AETNA BETTER HEALTH®

Clinical Policy Bulletin:
Bevacizumab (Avastin) for Non-Ocular Indications

Number: 0685

Policy

Aetna considers bevacizumab (Avastin) medically necessary for the following non-ocular indications:

Angiosarcoma
Appendiceal cancer
Endometrial cancer (endometrioid, papillary serous, or clear cell) (for members who have progressed on prior cytotoxic chemotherapy)
Gliomas including anaplastic gliomas, anaplastic astrocytomas (grade 3) and recurrent or salvage therapy of glioblastoma
Hemangiopericytoma
Mesothelioma
Metastatic anal adenocarcinoma
Metastatic or recurrent breast cancer
Metastatic renal cell carcinoma
Metastatic small bowel adenocarcinoma
Non-squamous, non-small cell lung cancer
Persistent or recurrent epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer
Progressive ependymoma
Unresectable advanced or metastatic cancer of the colon or rectum
Recurrent or metastatic cervical cancer
Relapsed granulosa-cell tumors of the ovary
Second-line therapy of cervical cancer
Solitary fibrous tumors
For intravitreal bevacizumab for neovascular (wet) age-related macular degeneration and other ophthalmologic indications, see CPB 0701 - Vascular Endothelial Growth Factor Inhibitors for Ocular Indications.
These products are NOT covered for members with the following criteria:

• Use not approved by the FDA; AND

• The use is unapproved and not supported by the literature or evidence as an accepted off-label use.

Acoustic neuroma
Adrenocortical carcinoma
Bladder cancer
Cancer of unknown origin (primary occult)
Carcinoid tumors
Cholangiocarcinoma
Coat's disease
Desmoid tumor (e.g., fibromatosis and fibrosarcoma)
Esophageal cancer
Gallbladder cancer
Gastric cancer
Gastroesophageal junction adenocarcinoma
Gastrointestinal stromal tumors
Hepatocellular cancer
Hereditary hemorrhagic telangiectasia
Hydatidiform mole Islet cell cancer Laryngeal papillomatosis Melanoma Meningioma Mucoepidermoid carcinoma of the salivary gland Multiple myeloma Neuroendocrine tumors Neurofibromatosis Pancreatic cancer Pelvic bone cancer Prostate cancer Radiation necrosis/radiation-induced brain edema Sarcomas (e.g., Ewing sarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, and osteosarcoma) other than angiosarcoma, solitary fibrous tumors, and hemangiopericytoma Squamous cell carcinoma of the head and neck Urachal carcinoma Vaginal cancer Vogt-Koyanagi-Harada syndrome von Hippel Lindau disease

For bevacizumab for ocular indications, see CPB 0701 - Vascular Endothelial Growth Factor Inhibitors for Ocular Indications.

See also CPB 0371 - Brachytherapy, CPB 0375 - Photodynamic Therapy, CPB 0516 - Colorectal Cancer Screening, CPB 0535 - Virtual Gastrointestinal Endoscopy, CPB 0683 - Oxaliplatin (Eloxatin), and CPB 0684 - Cetuximab (Erbitux).
Background

Colorectal cancer is the second-leading cause of cancer death in the United States. It is the nation’s third most common cancer accounting for approximately 15% of all new cancer cases. Metastatic disease is present at diagnosis in 30% of the patients, and about 50% of early-stage patients will eventually present with metastatic disease. For many years, standard treatment of colorectal cancer was 5-fluorouracil (5-FU)-based therapy. Recent availability of newer agents, including capecitabine, irinotecan, oxaliplatin, and cetuximab has significantly expanded the options available for the management of patients with advanced colorectal cancer, with consequent improvements in survival.

Bevacizumab is a recombinant humanized monoclonal antibody to vascular endothelial growth factor (VEGF). It is designed to bind to and inhibit VEGF, which plays an important role in tumor angiogenesis, a process critical for tumor growth and metastasis. On February 26, 2004, the U.S. Food and Drug Administration (FDA) approved bevacizumab (Avastin) (Genentech, Inc., South San Francisco, CA) for use in combination with intravenous 5-FU based chemotherapy as a first-line treatment for patients with metastatic colorectal cancer. It is the first FDA-approved therapy designed to inhibit angiogenesis. In clinical trials, bevacizumab has been shown to extend patients' lives by approximately 5 months when given intravenously as a combination treatment along with standard chemotherapy drugs for colon cancer (e.g., the "Saltz regimen", also known as IFL, which includes irinotecan, 5-FU and leucovorin).

Bevacizumab is administered intravenously. In clinical trials, the most common side effects associated with the use of bevacizumab were asthenia, pain, abdominal pain, headache, hypertension, diarrhea, nausea, vomiting, anorexia, stomatitis, constipation, upper respiratory infection, epistaxis, dyspnea, exfoliative dermatitis, and proteinuria. The most serious adverse events were gastrointestinal perforations/wound healing complications, hemorrhage, hypertensive crises, nephrotic syndrome, and congestive heart failure.

In a phase II clinical study (n = 104), Kabbinavar and colleagues (2003) examined the safety and effectiveness of two doses of bevacizumab, in combination with 5-FU/leucovorin (LV) versus 5-FU/LV alone in patients with metastatic colorectal cancer. Previously untreated patients with measurable metastatic colorectal cancer were randomly assigned to one of the following three treatment groups: (i) 5-FU (500 mg/m2)/LV (500 mg/m2) alone (n = 36), (ii) 5-FU/LV plus low-dose bevacizumab (5 mg/kg every 2 weeks) (n = 35), and (iii) 5-FU/LV plus high-dose bevacizumab (10 mg/kg every 2 weeks) (n = 33). 5-FU/LV was given weekly for the first 6 weeks of each 8-week cycle. Compared with the 5-FU/LV control arm, treatment with bevacizumab (at both dosages) plus 5-FU/LV resulted in higher response rates (control arm, 17 %, 95 % confidence interval [CI]: 7 to 34 %; low-dose arm, 40 %, 95 % CI: 24 to 58 %; high-dose arm, 24 %, 95 % CI: 12 to 43 %), longer median time to disease progression (control arm, 5.2 months, 95 % CI: 3.5 to 5.6 months; low-dose arm, 9.0 months, 95 % CI: 5.8 to 10.9 months; high-dose arm, 7.2 months, 95 % CI: 3.8 to 9.2 months), and longer median survival (control arm, 13.8 months; 95 % CI: 9.1 to 23.0 months; low-dose arm, 21.5 months, 95 % CI: 17.3 to undetermined; high-dose arm, 16.1 months; 95 % CI: 11.0 to 20.7 months). After crossover, 2 of 22 patients had a partial response to bevacizumab alone. The authors concluded that the encouraging results of this randomized trial support further study of
bevacizumab 5 mg/kg plus chemotherapy as first-line therapy for metastatic colorectal cancer.

The FDA approval of bevacizumab is based on the findings of a large, randomized, double-blind, placebo-controlled study (more than 800 patients) showing prolongation in the median survival of patients treated with bevacizumab plus the IFL chemotherapy regimen by about 5 months, compared to patients treated with the IFL chemotherapy regimen alone (20.3 months versus 15.6 months). The overall response rate to the treatment was 45% compared to 35% for the control arm of the trial.

A recent randomized controlled clinical study has shown that the addition of bevacizumab to a standard chemotherapy regimen for colorectal cancer has not resulted in an improvement in disease-free survival. Wolmark et al (2009) reported on the results of a 2-arm randomized prospective study to determine whether infusional 5-FU, leucovorin, and oxaliplatin (mFOLFOX6) plus bevacizumab (mFF6+B) would prolong disease-free survival (DFS) compared to mFOLFOX6 (mFF6) alone. Between September 2004 and October 2006, 2,672 patients with follow-up (1,338 and 1,334 in respective arms) with stage II (24.9%) or III carcinoma of the colon were randomized to receive either mFF6 or mFF6+B. The primary end point was DFS. Events were defined as first recurrence, second primary cancer, or death. The median follow-up for patients still alive was 36 months. The hazard ratio (HR: FF6+B versus. mFF6) was 0.89; 95% CI: 0.76 to 1.04; p = 0.15. The investigators reported that data censored at intervals disclosed an initial benefit for bevacizumab that diminished over time: The smoothed estimate of the DFS HR over time indicated that bevacizumab significantly reduced the risk of a DFS event during the interval from 0.5 to 1.0 year. There was no evidence that patients receiving bevacizumab had a worse DFS compared to those receiving mFF6 alone following treatment. The addition of bevacizumab to mFF6 did not result in an overall statistically significant prolongation in DFS. There was a transient benefit in DFS during the 1-year interval that bevacizumab was utilized. Consideration may be given to clinical trials assessing longer duration of bevacizumab administration.

Fluoropyrimidine-based chemotherapy plus the anti-VEGF antibody bevacizumab is standard first-line treatment for metastatic colorectal cancer. Tol and colleagues (2009) studied the effect of adding the anti-epidermal growth factor receptor (EGFR) antibody cetuximab to a combination of capecitabine, oxaliplatin, and bevacizumab for metastatic colorectal cancer. These investigators randomly assigned 755 patients with previously untreated metastatic colorectal cancer to capecitabine, oxaliplatin, and bevacizumab (CB regimen, 378 patients) or the same regimen plus weekly cetuximab (CBC regimen, 377 patients). The primary end point was PFS. The mutation status of the KRAS gene was evaluated as a predictor of outcome. The median PFS was 10.7 months in the CB group and 9.4 in the CBC group (p = 0.01). Quality-of-life scores were lower in the CBC group. The overall survival (OS) and response rates did not differ significantly in the 2 groups. Treated patients in the CBC group had more grade 3 or 4 adverse events, which were attributed to cetuximab-related adverse cutaneous effects. Patients treated with cetuximab who had tumors bearing a mutated KRAS gene had significantly decreased PFS as compared with cetuximab-treated patients with wild-type-KRAS tumors or patients with mutated-KRAS tumors in the CB group. The authors concluded that the addition of cetuximab to capecitabine, oxaliplatin, and bevacizumab resulted in significantly shorter PFS and inferior quality of life. Mutation status of the KRAS gene was a predictor of outcome in the cetuximab group.
In an accompanying editorial of the afore-mentioned article, Mayer (2009) stated that the findings of Tol et al (2009) serve as a reminder that anti-tumor activity observed in preclinical and also uncontrolled clinical contexts may not be validated when examined in randomized trials. Furthermore, the data suggest that combining multiple forms of targeted therapies may not be analogous to combining different types of cytotoxic chemotherapy, presumably because of subtle interactions in intra-cellular signaling. Finally, these results underscore the fundamental importance of subjecting hypotheses to carefully conducted clinical trials. As was observed in this situation, more is not always better.

The addition of bevacizumab to oxaliplatin or irinotecan based doublet chemotherapy has shown benefit in metastatic colorectal cancer. Capecitabine (Cap) with or without mitomycin C (MMC) are alternate chemotherapy regimens suitable for patients who are either unfit for or who do not require initial oxaliplatin/irinotecan. Tebbutt et al (2009) reported on a phase III study comparing Cap with Cap Bev and Cap Bev MMC. The aim of this study was to develop a low toxicity regimen suitable for a broad population of patients with metastatic colorectal cancer. Previously untreated patients with unresectable metastatic colorectal cancer considered suitable for Cap monotherapy were randomised to arm A (Cap), arm B (Cap Bev) or arm C (Cap Bev MMC). The primary endpoint was progression free survival (PFS); secondary endpoints were response rate (RR), toxicity, overall survival (OS), and quality of life (QoL). Randomization was stratified by age, performance status (PS), center and Cap dose. Response was assessed every 6 weeks. A total of 471 patients were randomized from July 2005 to June 2007. The most common grade 3/4 toxicities were dermatologic (palmar-plantar erythrodysesthesia, PPE) (16 %, 26 %, 28 %) and diarrhea (11 %, 17 %, 16 %) for arms (A, B, C). However, adjusted rates per cycle were similar as arms B and C received more cycles of Cap (A = 8.3, B = 10.8, and C = 10.5). Other toxicity rates were generally less than 10 %. The study achieved its primary endpoint with a highly significant improvement in PFS for arms B and C. However, OS was similar in all arms. The authors concluded that all treatment regimens were well-tolerated. The addition of Bev +/- MMC to Cap significantly improved PFS without significant additional toxicity. However, OS was similar for all arms.

There is a lack of evidence to support the combinational use of bevacizumab with cetuximab for metastatic colorectal cancer (Tol et al, 2009; Mayer, 2009). Current guidelines from the National Comprehensive Cancer Network (2009) recommends or lists as an option the addition of bevacizumab or cetuximab, but not both, to some regimens for metastatic colorectal cancer, based upon available data.

Preliminary results from a National Cancer Institute (NCI)-sponsored phase III randomized, controlled, multi-center clinical study of bevacizumab in patients with newly diagnosed non-small cell lung cancer (NSCLC) found that subjects treated with chemotherapy plus bevacizumab survived an average of 12.5 months, compared with 10.2 months among patients receiving paclitaxel and carboplatin alone (NCI, 2005). This difference was statistically significant. The data monitoring committee overseeing the trial recommended that the results of a recent interim analysis be made public because the study had met its primary endpoint of improving overall survival. A total of 878 patients with advanced non-squamous, NSCLC who had not previously received systemic chemotherapy were enrolled in this study between July 2001 and April 2004. Patients were randomized to 1 of the 2 treatment arms. One patient group received standard treatment -- 6 cycles of paclitaxel and carboplatin. The second group received the same 6-cycle chemotherapy regimen with the addition of bevacizumab, followed by bevacizumab alone until disease progression.
Patients with squamous cell carcinoma of the lung were excluded from the study because previous clinical experience suggested that these patients had a higher risk of serious bleeding from the lung after bevacizumab therapy. Patients with a prior history of frank hemoptysis were also excluded from the trial. The most significant adverse event observed in this study was life-threatening or fatal bleeding, primarily from the lungs. This infrequent adverse event was more common in the patient group that received bevacizumab in combination with chemotherapy than in the patient group that received only chemotherapy. In October 2006, the FDA approved the use of bevacizumab in combination with carboplatin and paclitaxel for the initial systemic treatment of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous, NSCLC. This approval was based on an improvement in survival time when bevacizumab was added to a standard chemotherapy regimen.

A randomized phase III study (BeTa Lung) evaluating bevacizumab in combination with erlotinib (Tarceva) in patients with advanced NSCLC whose disease had progressed following platinum-based chemotherapy did not meet its primary endpoint of improving OS compared to erlotinib in combination with placebo (Genentech, 2008). This multi-center, randomized, controlled phase III study enrolled 636 patients with advanced NSCLC who experienced disease progression during or following first-line standard chemotherapy or chemoradiotherapy. Patients who had received previous treatment with an epidermal growth factor receptor (EGFR) inhibitor or anti-angiogenesis agent were not eligible for this trial. Patients were randomized to receive erlotinib in combination with bevacizumab or erlotinib in combination with placebo. The primary endpoint of the study was improvement in OS. Secondary endpoints included PFS, objective response and an evaluation of exploratory biomarkers. Median survival was reported to be similar in both arms of this study. However, the study found improvements in the secondary endpoints of PFS and response rate when bevacizumab was added to erlotinib compared to erlotinib alone in this study.

A randomized, double-blind, phase II trial was conducted comparing placebo with bevacizumab at doses of 3 and 10 mg per kilogram of body weight, given every 2 weeks in 166 patients with renal cancer (Yang et al, 2003). Subjects were randomized to 3 groups: (i) 40 to placebo, (ii) 37 to low-dose bevacizumab, and (iii) 39 to high-dose bevacizumab. The investigators reported that there was a significant prolongation of the time to progression of disease in the high-dose-antibody group as compared with the placebo group (HR, 2.55; p < 0.001). There was a small difference, of borderline significance, between the time to progression of disease in the low-dose-antibody group and that in the placebo group (HR, 1.26; p = 0.053). The probability of being progression-free for patients given high-dose antibody, low-dose-antibody, and placebo was 64 %, 39 %, and 20 %, respectively, at 4 months and 30 %, 14 %, and 5 % at 8 months. There was, however, no significant differences in OS between groups (p > 0.20 for all comparisons). Although there were no significant differences in survival, this study cannot rule out such a benefit due to the fact that the study was too underpowered to detect differences in survival between treatment groups that may be clinically significant (Chen, 2004). A phase III study of bevacizumab in renal cell carcinoma is currently ongoing.

In July 2009, the FDA granted approval for the use of bevacizumab in combination with interferon alfa for the treatment of patients with metastatic renal cell carcinoma.

Preliminary results from a NCI-sponsored multi-center randomized controlled clinical trial conducted by the Eastern Cooperative Oncology Group (ECOG) of 722 women with
previously untreated recurrent or metastatic breast cancer show that women who received bevacizumab in combination with paclitaxel had a statistically significant increase in PFS of 4 months than women who received paclitaxel alone. The data monitoring committee overseeing the trial recommended that the results of a recent interim analysis be made public because the study had met its primary endpoint of increasing PFS. Women whose tumors over-expressed HER-2 were not included in the study unless they had previously received trastuzumab (Herceptin) or were unable to receive trastuzumab. Also excluded were women who had received preventive chemotherapy treatment with paclitaxel within the previous 12 months, as well as women with a prior history of thrombosis or who were on anticoagulants. Serious hemorrhage and thrombosis were rare in this study. Women receiving the combination of paclitaxel and bevacizumab had small increases in rates of neuropathy, hypertension and proteinuria than women receiving paclitaxel alone. Other side effects were similar between the 2 treatment groups.

A previous phase III study of bevacizumab in metastatic breast cancer found that the addition of bevacizumab to capecitabine produced a significant increase in response rates, but this did not translate into improved PFS or OS (Miller et al, 2005). This randomized phase III trial compared the efficacy and safety of capecitabine with or without bevacizumab in 462 patients with metastatic breast cancer previously treated with an anthracycline and a taxane. Patients were randomly assigned to receive capecitabine (2,500 mg/m2/d) twice-daily on day 1 through 14 every 3 weeks, alone or in combination with bevacizumab (15 mg/kg) on day 1. Combination therapy significantly increased the response rates (19.8 % versus 9.1 %; p = 0.001); however, this did not result in a longer PFS (4.86 versus 4.17 months; HR= 0.98). Overall survival (15.1 versus 14.5 months) and time to deterioration in quality of life as measured by the Functional Assessment of Cancer Treatment-Breast were comparable in both treatment groups. The investigators reported that bevacizumab was well-tolerated in this heavily pretreated patient population (Miller et al, 2005). No significant differences were found in the incidence of diarrhea, hand-foot syndrome, thromboembolic events, or serious bleeding episodes between treatment groups. Of other grade 3 or 4 adverse events, only hypertension requiring treatment (17.9 % versus 0.5 %) was more frequent in patients receiving bevacizumab.

In July 2010, Federal health scientists said that follow-up studies of Avastin showed that it failed to extend patient lives, opening the door for it to be potentially withdrawal for use in treating that disease. The FDA approved Avastin in 2008 based on a trial showing it slowed growth of tumors caused by breast cancer. The decision was controversial because drugs for cancer patients who have never been treated before must usually show evidence they extend lives. Avastin's so-called "accelerated approval" was based on the condition that later studies would show a survival benefit. But in briefing documents posted online, FDA reviewers said 2 follow-up studies recently submitted by Roche failed to show that Avastin significantly extended lives compared to chemotherapy alone. Additionally, the FDA said that in follow-up studies the drug did not slow tumor growth to the same degree as in earlier studies. Furthermore, patients taking Avastin showed significantly more side effects, including high blood pressure, fatigue and abnormal white blood cell levels.

On July 20, 2010, an advisory panel has voted 12 to 1 to recommend that the FDA remove the advanced breast cancer indication from Avastin. The Oncologic Drugs Advisory Committee voted that bevacizumab, when added to standard chemotherapy, does not extend PFS long enough to be clinically meaningful in patients with HER2-negative, metastatic breast cancer. If the FDA follows the advice of its advisory committee -- and it
usually does -- bevacizumab would still be indicated for the treatment of colon, kidney, and lung cancer. The FDA will make a final decision by September 17 (Walker, 2010).

Guidelines from the National Comprehensive Cancer Network (NCCN, 2006) stated that bevacizumab is an acceptable alternative chemotherapeutic regimen for recurrent epithelial ovarian cancer for stage II, III, and IV patients with partial responses to their primary paclitaxel and platinum-based chemotherapeutic regimens. The guidelines noted that bevacizumab has been demonstrated to be active in recurrent epithelial ovarian cancer, although it may cause arterial thrombosis and intestinal perforation. NCCN guidelines also indicate bevacizumab as therapy for clinical relapse in patients with stage II to IV granulosa-cell tumors of the ovary.

Primary peritoneal carcinoma (also known as papillary serous carcinoma of the peritoneum) is an entity closely associated with, but distinct from, epithelial ovarian carcinoma (EOC). Histologically, this tumor is indistinguishable from papillary serous ovarian carcinoma, but morphologic distinctions have been described. The criteria established by the Gynecologic Oncology Group (GOG) to define primary peritoneal carcinoma are:

- A predominantly serous histology
- Extra-ovarian involvement greater than ovarian involvement
- Ovaries normal in size (4.0 cm in largest diameter) or enlarged by a benign process
- Surface involvement of less than 5 mm depth and width.

Using these criteria, between 7 and 20 % of patients previously identified with primary EOC may be re-classified as having primary peritoneal carcinoma. In some cases, they may be classified as adenocarcinomas of unknown primary site. The pattern of spread is similar to that in women with EOC. Women with papillary serous carcinoma of the peritoneum are treated similarly to those with EOC. Optimal surgical cytoreduction may be more difficult to achieve in the setting of widespread peritoneal disease without a predominant ovarian or pelvic mass. Chemotherapy regimens and response rates are similar to EOC (NCCN, 2009).

Bevacizumab appears to be an effective treatment for gliomas. Vredenburgh et al (2007) reported on a phase II clinical trial of bevacizumab and irinotecan in 32 patients with recurrent gliomas, 23 with grade IV gliomas and 9 with grade III gliomas. Radiographical responses were noted in 63 % of patients (14 of 23 grade IV patients and 6 of 9 grade III patients); 1 was a complete response and 19 were partial responses. The median PFS was 23 weeks for all patients (95 % CI: 15 to 30 weeks; 20 weeks for grade IV patients and 30 weeks for grade III patients). The 6-month PFS probability was 38 % overall, and 56 % in the grade III glioma patients and 30 % in the grade IV glioma patients. The 6-month OS probability was 72 %. The response and survival rates in this study are higher than what would have been expected.

In May 2009, the FDA approved bevacizumab for the treatment of patients with glioblastoma multiforme when this form of brain cancer continues to progress following standard therapy.

Packer et al (2009) noted that chemotherapy has taken on a prominent role in the treatment of pediatric low-grade gliomas not amenable to gross total resections; however, there are few proven effective options for children with multiply recurrent tumors. Bevacizumab and irinotecan have been used with some success in adults with malignant
gliomas. A total of 10 children with multiply recurrent low-grade gliomas were treated with the combination of bevacizumab and irinotecan. Patients received treatment at a median of 5.2 years of age, range of 1.5 to 11.1 years. The majority of patients had diencephalic tumors, 3 had neurofibromatosis type 1, and 2 had disseminated disease at the time of treatment. Nine of 10 patients had progressed after 3 or greater chemotherapy regimens and 1 patient also had received radiation therapy. Seven patients had an objective neuro-radiographical response, which was a complete response in 1, partial response in 3, and minor response in 3. Clinical improvements were noted in 7, including improved visual acuity (n = 2), improved motor function (n = 2), weight gain in 4 with a diencephalic syndrome, and reversal of psychomotor retardation (n = 3). Dose-limiting toxicities included transient leukoencephalopathy (n = 1) and grade 3 proteinuria (n = 1). Response was durable in the majority of patients and 6 remained on treatment, for up to 22 months. The authors concluded that multiple recurrent low-grade gliomas in children are responsive to the combination of bevacizumab and irinotecan. The drug combination of bevacizumab and irinotecan has been relatively well-tolerated, including in patients with neurofibromatosis type 1, and warrants further study.

Gonzalez et al (2007) reported the findings of 15 patients with malignant brain tumors who were treated with bevacizumab or bevacizumab in combination with other agents on either a 5 mg/kg/2-week or 7.5 mg/kg/3-week schedule. Radiation necrosis was diagnosed in 8 of these patients on the basis of magnetic resonance imaging (MRI) and biopsy; MRI studies were obtained before treatment and at 6-week to 8-week intervals. Of the 8 patients with radiation necrosis, post-treatment MRI performed an average of 8.1 weeks after the start of bevacizumab therapy showed a reduction in all 8 patients in both the MRI fluid-attenuated inversion-recovery (FLAIR) abnormalities and T1-weighted post-Gd-contrast abnormalities. The average area change in the T1-weighted post-Gd-contrast abnormalities was 48 % (+/- 22 SD), and the average change in the FLAIR images was 60 % (+/- 18 SD). The average reduction in daily dexamethasone requirements was 8.6 mg (+/- 3.6). The authors concluded that bevacizumab, alone and in combination with other agents, can reduce radiation necrosis by decreasing capillary leakage and the associated brain edema. Moreover, they stated that these findings will need to be confirmed in a randomized trial to determine the optimal duration of treatment.

Liu et al (2009) stated that diffuse pontine gliomas are a pediatric brain tumor that is fatal in nearly all patients. Given the poor prognosis for patients with this tumor, their quality of life is very important. Radiation therapy provides some palliation, but can result in radiation necrosis and associated neurologic decline. The typical treatment for this necrosis is steroid therapy. Although steroids are effective, they have many adverse effects that can often significantly compromise quality of life. Bevacizumab has been suggested as a treatment for radiation necrosis. These investigators reported on their initial experience with bevacizumab therapy for radiation necrosis in pediatric pontine gliomas. A total of 4 children with pontine gliomas treated at the Children’s Hospital in Denver and the University of Colorado Denver developed evidence of radiation necrosis both clinically and on imaging. They received bevacizumab as a treatment for the radiation necrosis. These researchers reviewed the clinical outcome and imaging findings. After bevacizumab therapy, 3 children had significant clinical improvement and were able to discontinue steroid use. One child continued to decline, and, in retrospect, had disease progression, not radiation necrosis. In all cases, bevacizumab was well-tolerated. The authors concluded that in children with pontine gliomas, bevacizumab may provide both therapeutic benefit and diagnostic information. They stated that more formal evaluation of bevacizumab in these children is needed.
Guidelines from the NCCN (2010) indicated bevacizumab as a single agent for disease progression after radiation therapy for spine or brain ependymoma recurrence.

Bevacizumab is being investigated as a treatment for pancreatic cancer. An assessment by the BlueCross BlueShield Technology Evaluation Center (TEC) (BCBSA, 2006) concluded that bevacizumab for pancreatic cancer does not meet the TEC criteria. Regarding use of bevacizumab as first-line therapy, TEC assessment notes "On June 26, 2006, the drug's manufacturer announced that, after interim analysis of a phase III randomized controlled trial (RCT; n = 602) comparing gemcitabine with versus without bevacizumab as first-line therapy for pancreatic cancer, the trial's data safety monitoring board concluded that it was very unlikely that significant differences in overall survival will be shown as the data mature. Consequently, the trial was stopped early." Regarding use of bevacizumab as second line therapy, the TEC assessment identified 2 published uncontrolled studies on pancreatic cancer. One study on pancreatic cancer also included radiation therapy. Each study used bevacizumab as part of a combination regimen, but none provided data for comparison on concurrent or historical controls managed with the same regimen minus bevacizumab. The TEC assessment concluded that current evidence does not permit conclusions on outcomes of bevacizumab for any stage of pancreatic carcinoma.

In September 2009, the TEC assessment (BCBSA, 2009) on the off-label use of bevacizumab for advanced adenocarcinoma of the pancreas concluded that whether the addition of bevacizumab to chemotherapy regimens for advanced pancreatic adenocarcinoma improves health outcomes has not been established in the investigational settings. Thus, the use of bevacizumab for patients with advanced adenocarcinoma of the pancreas does not meet the TEC criteria.

In a phase III study, Van Cutsem et al (2009) examined the use of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. Patients were randomly assigned to receive gemcitabine (1,000 mg/m(2)/week), erlotinib (100 mg/day), and bevacizumab (5 mg/kg every 2 weeks) or gemcitabine, erlotinib, and placebo. Primary end point was OS; secondary end points included PFS, disease control rate, and safety. A total of 301 patients were randomly assigned to the placebo group and 306 to the bevacizumab group. Median OS was 7.1 and 6.0 months in the bevacizumab and placebo arms, respectively (HR, 0.89; 95 % CI: 0.74 to 1.07; p = 0.2087); this difference was not statistically significant. Adding bevacizumab to gemcitabine-erlotinib significantly improved PFS (HR, 0.73; 95 % CI: 0.61 to 0.86; p = 0.0002). Treatment with bevacizumab plus gemcitabine-erlotinib was well-tolerated: safety data did not differ from previously described safety profiles for individual drugs. The authors concluded that the primary objective was not met. The addition of bevacizumab to gemcitabine-erlotinib did not lead to a statistically significant improvement in OS in patients with metastatic pancreatic cancer. However, PFS was significantly longer in the bevacizumab group compared with placebo.

In a phase II clinical trial, Crane et al (2009) evaluated the 1-year survival of patients with locally advanced, unresectable pancreatic cancer treated with the combination of bevacizumab, capecitabine, and radiation. Secondary end points were toxicity, PFS, and RR. Patients with locally advanced pancreatic cancer without duodenal invasion were treated with 50.4 Gy per 28 fractions to the gross tumor with concurrent capecitabine 825 mg/m(2) orally twice-daily on days of radiation and bevacizumab 5 mg/kg on days 1, 15, and 29 followed by maintenance gemcitabine 1 g/m(2) weekly for 3 weeks and...
bevacizumab 5 mg/kg every 2 weeks, both in 4-week cycles until progression. Treatment plans were reviewed for quality assurance (QA). Between January 2005 and February 2006, 82 eligible patients were treated. The median and 1-year survival rates were 11.9 months (95 % CI: 9.9 to 14.0 months) and 47 % (95 % CI: 36 % to 57 %). Median PFS was 8.6 months (95 % CI: 6.9 to 10.5), and RR was 26 %. Overall, 35.4 % of patients had grade 3 or greater treatment-related gastro-intestinal toxicity (22.0 % during chemoradiotherapy, 13.4 % during maintenance chemotherapy). Unacceptable radiotherapy protocol deviations (i.e., inappropriately generous volume contoured) correlated with grade 3 or greater gastrointestinal toxicity during chemoradiotherapy (45 % versus 18 %; adjusted odds ratio, 3.7; 95 % CI: 0.98 to 14.1; p = 0.05). The authors concluded that the addition of bevacizumab to a regimen of capecitabine-based chemoradiotherapy followed by gemcitabine did not result in an improvement in overall survival in patients with locally advanced pancreatic cancer.

The effectiveness of bevacizumab for von Hippel Lindau disease, prostate cancer and other types of cancer (e.g., esophageal cancer, cervical cancer, gastric cancer, and cancer of unknown origin [primary occult]) is being studied.

Shad et al (2006) assessed the safety and effectiveness of the addition of bevacizumab to chemotherapy in the treatment of gastric and gastro-esophageal junction (GEJ) adenocarcinoma. A total of 47 patients with metastatic or unresectable gastric/GEJ adenocarcinoma were treated with bevacizumab 15 mg/kg on day 1, irinotecan 65 mg/m2, and cisplatin 30 mg/m2 on days 1 and 8, every 21 days. The primary end point was to demonstrate a 50 % improvement in time to progression over historical values. Secondary end points included safety, response, and survival. Patient characteristics were as follows: median age 59 years (range of 25 to 75 years); Karnofsky performance status 90 % (70 to 100 %); male:female, 34:13; and gastric/GEJ, 24:23. With a median follow-up of 12.2 months, median time to progression was 8.3 months (95 % CI: 5.5 to 9.9 months). In 34 patients with measurable disease, the overall response rate was 65 % (95 % CI: 46 to 80 %). Median survival was 12.3 months (95 % CI: 11.3 to 17.2 months). These researchers observed no increase in chemotherapy related toxicity. Possible bevacizumab-related toxicity included a 28 % incidence of grade 3 hypertension, 2 patients with a gastric perforation and 1 patient with a near perforation (6 %), and 1 patient with a myocardial infarction (2 %). Grade 3 to 4 thromboembolic events occurred in 25 % of patients. Although the primary tumor was unresected in 40 patients, these investigators observed only 1 patient with a significant upper gastrointestinal bleed. The authors concluded that bevacizumab can be safely given with chemotherapy even with primary gastric and GEJ tumors in place. The response rate, time to disease progression (TTP), and OS are encouraging, with TTP improved over historical controls by 75 %. Moreover, they stated that further development of bevacizumab in gastric and GEJ cancers is needed.

Abad (2008) noted that bevacizumab has been used to treat patients with gastric cancer in phase I and II clinical trials with good results, which need to be confirmed in new phase III studies. Also, Ohtsu (2008) stated that several targeting agents such as trastuzumab, bevacizumab, and lapatinib are now under investigation in international randomized studies to examine their effects on metastatic gastric cancer.

In a phase II clinical study, Hainsworth et al (2009) evaluated the efficacy and toxicity of the combination of paclitaxel, carboplatin, bevacizumab, and erlotinib in the first-line treatment of patients with carcinoma of unknown primary site (CUP). Patients with previously untreated CUP (adenocarcinoma, poorly differentiated carcinoma, poorly
differentiated squamous carcinoma) without clinical or pathological characteristics of a well-defined treatable subsets were eligible. All patients received paclitaxel, carboplatin, bevacizumab, and erlotinib. Treatment cycles were repeated at 21-day intervals. After 4 cycles, paclitaxel and carboplatin were discontinued; bevacizumab-erlotinib treatment was continued until tumor progression. Patients were initially evaluated for response after completion of 2 treatment cycles; re-evaluations occurred every 6 weeks thereafter. Overall, 49 of 60 patients (82%) completed 4 cycles of therapy, and 44 patients (73%) subsequently received maintenance bevacizumab and erlotinib. Thirty-two patients (53%) had major responses to treatment; an additional 18 patients had stable disease. After a median follow-up of 19 months, the median PFS time was 8 months, with 38% of patients progression free at 1 year. The median survival time and 2-year OS rate were 12.6 months and 27%, respectively. Treatment was generally well-tolerated, with a toxicity profile as predicted based on the known toxicities of each treatment component. The authors concluded that empiric treatment with paclitaxel, carboplatin, bevacizumab, and erlotinib is effective and well-tolerated as first-line treatment for patients with CUP. They stated that further development of this regimen is warranted.

Kamat and colleagues (2007) examined the clinical and therapeutic significance of VEGF in endometrial carcinoma using patient samples and an endometrioid orthotopic mouse model. Following Institutional Review Board approval, VEGF expression and microvessel density (MVD) counts were evaluated using immunohistochemistry in 111 invasive endometrial cancers by 2 independent investigators. Results were correlated with clinicopathologic characteristics. For the animal model, Ishikawa or Hec-1A cancer cell lines were injected directly into the uterine horn. Therapy experiments with bevacizumab alone or in combination with docetaxel were done and samples were analyzed for markers of angiogenesis and proliferation. Of 111 endometrial cancers, high expression of VEGF was seen in 56% of tumors. There was a strong correlation between VEGF expression and MVD (p < 0.001). On multi-variate analysis, stage (p = 0.04), grade (p = 0.003), VEGF levels (p = 0.03), and MVD (p = 0.037) were independent predictors of shorter disease-specific survival. In the murine model, whereas docetaxel and bevacizumab alone resulted in 61% to 77% tumor growth inhibition over controls, combination therapy had the greatest efficacy (85% to 97% inhibition over controls; p < 0.01) in both models. In treated tumors, combination therapy significantly reduced MVD counts (50% to 70% reduction over controls; p < 0.01) and percent proliferation (39% reduction over controls; p < 0.001). The authors concluded that increased levels of VEGF and angiogenic markers are associated with poor outcome in endometrioid endometrial cancer patients. Using a novel orthotopic model of endometrioid endometrial cancer, these researchers showed that combination of anti-vascular therapy with docetaxel is highly efficacious and should be considered for future clinical trials.

Gonzalez-Cao et al (2008) assessed the activity of the combination of weekly paclitaxel and bevacizumab in previously treated metastatic melanoma. Patients with previously treated metastatic melanoma received paclitaxel 70 mg/m(2) weekly and bevacizumab 10 mg/kg biweekly for 5 consecutive weeks every 6 weeks. A total of 12 patients were treated. Two patients (16.6%) achieved a partial response and 7 patients (58.3%) stable disease. Responses were seen in soft tissue, lung and brain metastases. Median disease-free and OS times were 3.7 and 7.8 months, respectively. Treatment was well-tolerated. Main toxicities were grade 3 asymptomatic lymphopenia in 6 patients, grade 3 leucopenia in 2 patients, and grade 3 thrombocytopenia in 1 patient. The authors concluded that these preliminary results suggested that the combination of bevacizumab and weekly
paclitaxel is active and safe in patients with metastatic melanoma, warranting further investigation.

In a phase II clinical trial, Siegel et al (2008) determined the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma (HCC). Adults with organ-confined HCC, ECOG performance status of 0 to 2, and compensated liver disease were eligible. Patients received bevacizumab 5 mg/kg (n = 12) or 10 mg/kg (n = 34) every 2 weeks until disease progression or treatment-limiting toxicity. The primary objective was to determine whether bevacizumab improved the 6-month PFS rate from 40 % to 60 %. Secondary end points included determining the effects of bevacizumab on arterial enhancement and on plasma cytokine levels and the capacity of patients’ plasma to support angiogenesis via an in vitro assay. The study included 46 patients, of whom 6 had objective responses (13 %; 95 % CI: 3 % to 23 %), and 65 % were progression-free at 6 months. Median PFS time was 6.9 months (95 % CI: 6.5 to 9.1 months); OS rate was 53 % at 1 year, 28 % at 2 years, and 23 % at 3 years. Grade 3 to 4 adverse events included hypertension (15 %) and thrombosis (6 %, including 4 % with arterial thrombosis). Grade 3 or higher hemorrhage occurred in 11 % of patients, including 1 fatal variceal bleed. Bevacizumab was associated with significant reductions in tumor enhancement by dynamic contrast-enhanced magnetic resonance imaging and reductions in circulating VEGF-A and stromal-derived factor-1 levels. Functional angiogenic activity was associated with VEGF-A levels in patient plasma. The authors concluded that these findings revealed significant clinical and biologic activity for bevacizumab in non-metastatic HCC and achieved the primary study end point. Serious bleeding complications occurred in 11 % of patients. They stated that further evaluation is needed in carefully selected patients (e.g., unresectable HCC).

In another phase II study, Thomas et al (2009) determined the proportion of patients with HCC treated with the combination of bevacizumab (B) and erlotinib (E) who were alive and progression free at 16 weeks (16-week PFS [PFS16]) of continuous therapy. Secondary objectives included response rate, median PFS, survival, and toxicity. Patients who had advanced HCC that was not amenable to surgical or regional therapies, up to 1 prior systemic treatment; Childs-Pugh score A or B liver function; ECOG performance status 0, 1, or 2 received B 10 mg/kg every 14 days and E 150 mg orally daily, continuously, for 28-day cycles. Tumor response was evaluated every 2 cycles by using Response Evaluation Criteria in Solid Tumors Group criteria. A total of 40 patients were treated. The primary end point of PFS16 was 62.5 %; 10 patients achieved a partial response for a confirmed overall response rate (intent-to-treat) of 25 %. The median PFS event was 39 weeks (95 % CI: 26 to 45 weeks; 9.0 months), and the median OS was 68 weeks (95 % CI: 48 to 78 weeks; 15.65 months). Grades 3 to 4 drug-related toxicity included fatigue (n = 8; 20 %), hypertension (n = 6; 15 %), diarrhea (n = 4; 10 %) elevated transaminases (n = 4; 10 %), gastrointestinal hemorrhage (n = 5; 12.5 %), wound infection (n = 2; 5 %), thrombocytopenia (n = 1; 2.5 %), and proteinuria, hyper-bilirubinemia, back pain, hyperkalemia, and anorexia (n = 1 each). The authors concluded that the combination of B + E in patients who had advanced HCC showed significant, clinically meaningful antitumor activity. They stated that bevacizumab plus erlotinib warrant additional evaluation in randomized controlled trials.

Plotkin and co-workers (2009) determined the expression pattern of VEGF and 3 of its receptors, VEGFR-2, neuropilin-1, and neuropilin-2, in paraffin-embedded samples from 21 vestibular schwannomas associated with neurofibromatosis type 2 and from 22 sporadic schwannomas. A total of 10 consecutive patients with neurofibromatosis type 2 and progressive vestibular schwannomas who were not candidates for standard treatment
were treated with bevacizumab. An imaging response was defined as a decrease of at least 20% in tumor volume, as compared with baseline. A hearing response was defined as a significant increase in the word-recognition score, as compared with baseline. Vascular endothelial growth factor was expressed in 100% of vestibular schwannomas and VEGFR-2 in 32% of tumor vessels on immuno-histochemical analysis. Before treatment, the median annual volumetric growth rate for 10 index tumors was 62%. After bevacizumab treatment in the 10 patients, tumors shrunk in 9 patients, and 6 patients had an imaging response, which was maintained in 4 patients during 11 to 16 months of follow-up. The median best response to treatment was a volumetric reduction of 26%. Three patients were not eligible for a hearing response; of the remaining 7 patients, 4 had a hearing response, 2 had stable hearing, and 1 had progressive hearing loss. There were 21 adverse events of grade 1 or 2. The authors concluded that VEGF blockade with bevacizumab improved hearing in some, but not all, patients with neurofibromatosis type 2 and was associated with a reduction in the volume of most growing vestibular schwannomas. They stated that additional research is needed to determine the optimal drug regimen, duration, and adverse-effect profile for long-term anti-VEGF therapy for vestibular schwannomas associated with neurofibromatosis.

Wortmann et al (2010) evaluated the effects of bevacizumab plus capecitabine as salvage therapy in advanced adrenocortical carcinoma (ACC). Patients registered with the German ACC Registry with refractory ACC progressing after cytotoxic therapies were offered treatment with bevacizumab (5 mg/kg body weight i.v. every 21 days) and oral capecitabine (950 mg/m² twice-daily for 14 days followed by 7 days of rest) in 2006 to 2008. Evaluation of tumor response was performed by imaging according to response evaluation criteria in solid tumours every 12 weeks. A total of 10 patients were treated with bevacizumab plus capecitabine. None of them experienced any objective response or stable disease. Two patients had to stop therapy after few weeks due to hand-foot syndrome, and 3 patients died on progressive disease within 12 weeks. Other adverse events were mild (grade I to grade II). Median survival after treatment initiation was 124 days. The authors concluded that bevacizumab plus capecitabine has no activity in patients with very advanced ACC. Hence, this regimen cannot be recommended as a salvage therapy.

Age-related macular degeneration (AMD), characterized as a progressive degenerative disease of the macula, is the leading cause of blindness in developed countries afflicting approximately 15 million people in the United States. There are various options for the treatment of choroidal neovascularization (CNV) in patients with AMD. Classic CNV responds well to photodynamic therapy (PDT) with "off label" triamcinolone, while occult CNV can be treated by PDT, transpupillary thermotherapy, sub-retinal surgery, macular translocation, and anti-angiostatic therapy. Ladewig and colleagues (2006) stated that the safety and effectiveness of the therapeutic anti-VEGF concept has already been shown for pegaptanib (Macugen) and ranibizumab (Lucentis). Bevacizumab acts as an antibody against all VEGF-A isoforms and has been developed for oncological indications with intravenous application. Initial reports on intra-vitreal administration in patients with neovascular AMD have shown beneficial morphological and functional effects. In the meantime, bevacizumab has been used off-label in thousands of patients with AMD.

According to the manufacturer, however, there are a number of differences between bevacizumab and ranibizumab (Bandolier, 2007): (i) bevacizumab contains no preservatives, so there could be problems in keeping it sterile when split into small quantities required for retinal treatment; (ii) no preclinical trial toxicity data exists for use
of bevacizumab in retinal therapy; (iii) the half-life of bevacizumab is different from ranibizumab, in that it clears from the system 100 times slower; this is important for cancer use, but remaining in the retina for that length of time could be harmful; (iv) ranibizumab binds more strongly to the VGEF protein than bevacizumab; it is this binding that blocks the protein from developing blood vessel growth into the retina (neovascularization); (v) bevacizumab contains full-length antibodies, which can cause inflammation, whereas the antibody fragments in ranibizumab are 1/3 the size of bevacizumab antibodies, so they are capable of better penetration through the retinal layers; and (vi) manufacturing standards differ for cancer and ophthalmic drugs; particulate matter must be very low in drugs used in the eye, and bevacizumab is not manufactured with that in mind. It is also the case that there are some small case series, but little randomized trial evidence exists for benefit from bevacizumab (Avastin), nor much at all for harm, especially rare but serious harm (Bandolier, 2007).

Fung et al (2006) stated that off-label intra-vitreal injections of bevacizumab have been performed for the treatment of neovascular and exudative ocular diseases since May 2005. Since then, the use of intra-vitreal bevacizumab has spread worldwide, but the drug-related adverse events (AE) associated with its use have only been reported in a few retrospective reviews. The International Intra-vitreal Bevacizumab Survey was initiated to gather timely information regarding adverse events from physicians around the world via the internet. An internet based survey was designed to identify AE associated with intra-vitreal bevacizumab therapy. The survey web address was disseminated to the international vitreo-retinal community via email. Rates of AE were calculated from participant responses. A total of 70 centers from 12 countries reported on 7,113 injections performed on 5,228 patients. Physician-reported AE included corneal abrasion, lens injury, endophthalmitis, retinal detachment, inflammation/uveitis, cataract progression, acute vision loss, central retinal artery occlusion, sub-retinal hemorrhage, retinal pigment epithelium tears, blood pressure elevation, transient ischemic attack, cerebrovascular accident and death. None of the AE rates exceeded 0.21 %.

Spaide et al (2006) described the short-term anatomical and visual acuity responses after intra-vitreal injection of bevacizumab in patients with CNV secondary to AMD. These investigators performed a retrospective study of patients with CNV secondary to AMD who were treated with intra-vitreal injection of bevacizumab (1.25 mg) during a 3-month period. Patients underwent best-corrected Snellen visual acuity testing, optical coherence tomography, and ophthalmoscopic examination at baseline and follow-up visits. There were 266 consecutive eyes of 266 patients who received injections, and follow-up information was available for 251 (94.4 %). The mean age of the patients was 80.3 years, the mean baseline visual acuity was 20/184, and 175 (69.7 %) had inadequate response to alternate methods of treatment. At the 1-month follow-up (data available for 244 patients), the mean visual acuity was 20/137 (p < 0.001 as compared with baseline), and 74 (30.3 %) of patients had improvement in visual acuity as defined by a halving of the visual angle. At the 2-month follow-up (data available for 222 patients), the mean visual acuity was 20/122 (p < 0.001), and 78 (31.1 %) of patients had visual improvement. At the 3-month follow-up (data available for 141 patients), the mean visual acuity was 20/109 (p < 0.001), and 54 (38.3 %) of patients had visual acuity improvement. The mean central macular thickness at baseline was 340 microm and decreased to a mean of 247 microm at month 1 (p <
0.001) and 213 microm at month 3 (p < 0.001). At 1 month, two patients had mild vitritis, as did one patient at 2 months, who had a history of recurrent uveitis. No endophthalmitis, increased intraocular pressure, retinal tear, or retinal detachment occurred. The risk for thromboembolic disorders did not seem to be different than reported previously in studies concerning macular degeneration. There were no apparent short-term safety concerns for intra-vitreal bevacizumab injection for CNV. Treated eyes had a significant decrease in macular thickness and improvement in visual acuity. The results of this study are in agreement with those of Inturralde et al (2006, 16 eyes/15 patients), Bashshur et al (2006, 17 eyes/17 patients), Rich et al (2006, 53 eyes/50 patients), and Avery et al (2006, 81 eyes/79 patients).

A German review on new treatments for neovascular AMD (authors not listed, 2006) stated that therapeutic options include laser photoocoagulation, PDT with verteporfin, triamcinolone and its possible combination with PDT, anecortave acetate, pegaptanib and ranibizumab. It noted that extra-foveal classic CNV should be treated with thermal laser coagulation. For sub-foveal lesions with predominantly classic CNV, or occult forms with non-classic CNV, a lesion size less than or equal to 4 macular photoocoagulation study (MPS) disc areas (DA) and recent disease progression, PDT with verteporfin is a safe and effective therapy. For the remaining subtypes, VEGF inhibitors (e.g., pegaptanib, ranibizumab, bevacizumab) for intra-vitreal use are now available as therapeutic alternatives. The review stated that the results of the phase III studies for pegaptanib and ranibizumab, however, are not comparable, in particular with reference to the outcomes in the control groups. Since bevacizumab (Avastin) and ranibizumab are comparable in their pharmacological profile, bevacizumab may be an alternative in the off-label treatment of neovascular AMD. The switch to alternative treatment modalities should be considered in particular when the first line treatment is ineffective. The recommendations from this review provided evidence-based guidance for non-surgical therapies in the management of neovascular AMD.

In an editorial on the use of intra-vitreal Avastin as the low cost alternative to Lucentis published in the American Journal of Ophthalmology, Rosenfeld (2006) stated that "[c]urrently, there appears to be a global consensus that the treatment strategy using intravitreal Avastin is logical, the potential risks to our patients are minimal, and the cost-effectiveness is so obvious that the treatment should not be withheld".

On March 20, 2006, a survey by the American Society of Retinal Specialists of its membership was completed. It found that 92 % of 289 respondents felt intra-vitreal bevacizumab was "somewhat better" or "much better" than other FDA-approved or covered therapies. Only 4 % of respondents had seen any thromboembolic complications thought to be related to the intra-vitreal bevacizumab, and 96 % thought intra-vitreal bevacizumab was the same or better in terms of overall safety compared to other FDA-approved or covered therapies.

On April 20, 2006, the American Academy of Ophthalmology (AAO) wrote to the Centers for Medicare and Medicaid Services (CMS) supporting the reimbursement for treating AMD with intra-vitreal injections of bevacizumab, to meet the medical needs of patients who have not responded to therapy with PDT with verteporfin or intra-vitreal pegaptanib. The AAO's support for reimbursement is limited to "such patients who are deemed by their treating physician to have failed FDA-approved therapies, or in the judgment of their treating physician, based on his/her experience, are likely to have greater benefit from the use of intra-vitreal bevacizumab".
On October 5, 2006, the National Institutes of Health's National Eye Institute said it will fund a multi-center clinical trial to compare Lucentis with Avastin in the treatment of AMD (NIH, 2006).

Astam and colleagues (2009) evaluated the short-term effectiveness of intra-vitreal bevacizumab injection for the management of macular edema due to diabetic retinopathy and retinal vein occlusion. Standardized ophthalmic evaluation, ETDRS visual acuity measurement, and central macular thickness were performed at baseline and 1 month intervals after injection. There were 23 eyes of 21 patients with macular edema due to diabetic retinopathy (14 eyes of 12 patients), and retinal vein occlusion (9 eyes of 9 patients). The mean baseline logMAR visual acuity and central macular thickness were 0.82 +/- 0.27 and 604.71 +/- 123.62 mum, respectively, in patients with diabetic retinopathy. There was no statistically significant difference between the mean logMAR visual acuity (p = 0.22) and central retinal thickness (p = 0.16) measurements at baseline and 3 months follow-up. The mean baseline logMAR visual acuity and central macular thickness were 0.94 +/- 0.48 and 557 +/- 113.9 mum, respectively, in patients with retinal vein occlusion. There was a statistically significant difference between the mean logMAR visual acuity and central retinal thickness measurements at baseline and 3 months follow-up (p < 0.01). Almost all of the eyes (88.8 %) regained normal foveal configuration. The authors concluded that although the follow-up period was short and the number of patients were limited to provide specific treatment recommendations, intra-vitreal bevacizumab seems to be more effective for macular edema due to retinal vein occlusion than diabetic macular edema. The favorable short-term findings suggested that further study is needed. This is in agreement with the observations of Badala (2008) as well as Wu et al (2008).

Badala (2008) noted that intra-vitreal bevacizumab appears to be a safe and effective treatment for macular edema associated with branch retinal vein occlusion, at least in the short-term. However, further randomized, controlled studies are needed to evaluate long-term safety and effectiveness of this approach. Wu et al (2008) stated that longer studies are needed to ascertain what role, if any, intra-vitreal injection of bevacizumab may play in the long-term treatment of macular edema secondary to branch retinal vein occlusion. Furthermore, Fraser-Bell et al (2008) noted that there remains no proven intervention that consistently prevents or reverses visual loss from diabetic macular edema in all patients. A variety of promising new medical and surgical therapies including intra-vitreal bevacizumab are under investigation, but further research is needed to determine their role alone or in combination.

An evidence review by Scanlon and Stratton (2008) for the National Library of Health stated that bevacizumab and other vascular endothelial growth factor inhibitors have not been studied in diabetic eye disease and that there are only early reports of their use. A recent systematic evidence review found insufficient evidence for the use of bevacizumab or other anti-VEGFs in diabetic eye disease (Mohamed et al, 2007). An ongoing randomized controlled clinical trial sponsored by the National Eye Institute is comparing the effects of laser treatment, intravitreal bevacizumab, and combined intravitreal bevacizumab and laser or sham injection on diabetic macular edema (National Eye Institute, 2008).

In an interventional, retrospective, multi-center study, Arevalo et al (2009a) determined the feasibility, safety, and clinical effect of intra-vitreal (IVT) bevacizumab in patients with refractory cystoid macular edema (CME) following cataract surgery. A total of 36 eyes of 31 patients with refractory CME after cataract surgery and with a mean age of 68.2 years
(range of 67 to 87 years) were included in this study. Patients were treated with at least 1 IVT injection of 1.25 or 2.5 mg bevacizumab. Patients were followed-up for 12 months. Main outcome measures included best-corrected visual acuity (BCVA) and central macular thickness (CMT) by optical coherence tomography (OCT). Twenty-six eyes (72.2 %) showed improvement of BCVA (greater than or equal to 2 Early Treatment Diabetic Retinopathy Study [ETDRS] lines), and no eye experienced worsening of visual acuity (greater than or equal to 2 ETDRS lines). Mean baseline BCVA was 20/200 (0.96 logarithm of the minimum angle of resolution [logMAR] units), and the mean 12-month BCVA was 20/80 (0.62 logMAR units; p < 0.0001). Optical coherence tomography demonstrated that mean CMT at baseline was 499.9 microm (range of 298 to 784 microm) and decreased to a mean of 286.1 microm (range of 168 to 499 microm) at 12 months (p < 0.0001). Four (11 %) eyes received 2 injections, 10 (27.8 %) eyes received 3 injections, 10 (27.8 %) eyes received 4 injections, 1 (2.8 %) eye received 5 injections, and 1 (2.8 %) eye received 6 injections. The mean number of injections was 2.7 (range of 1 to 6), and the mean interval between injections was 15.1 weeks (range of 4 to 45 weeks). No ocular or systemic adverse events were observed. The authors concluded that short-term results suggest that IVT bevacizumab is well-tolerated in patients with refractory pseudophakic CME. Treated eyes had a significant improvement in BCVA and decrease in macular thickness by OCT at 12 months. They stated that these results are promising and suggested the need for further evaluation with longer follow-up and a larger series of patients.

In a retrospective, multi-center, interventional, comparative case series, Arevalo et al (2009b) reported the 24-month anatomic and ETDRS BCVA response following primary intra-vitreal bevacizumab ([IVB] 1.25 or 2.5 mg) in patients with diffuse diabetic macular edema (DDME). In addition, a comparison of the 2 different doses of IVB used was presented. The clinical records of 115 consecutive patients (139 eyes) with DDME at 11 centers from 8 countries were reviewed. Patients were treated with at least 1 IVT injection of 1.25 or 2.5 mg of bevacizumab. All patients were followed-up for 24 months. Patients underwent ETDRS BCVA testing, ophthalmoscopic examination, OCT, and fluorescein angiography (FA) at the baseline, 1-, 3-, 6-, 12-, and 24-month visits. Main outcome measures included changes in BCVA and OCT results. The mean age of the patients was 59.4 +/- 11.1 years. The mean number of IVB injections per eye was 5.8 (range of 1 to 15 injections). In the 1.25-mg group at 1 month, BCVA improved from 20/150 (0.88 logarithm of the minimum angle of resolution [logMAR] units) to 20/107, 0.76 logMAR units (p < 0.0001). The mean BCVA at 24 months was 20/75 (0.57 logMAR units; p < 0.0001). Similar BCVA changes were observed in the 2.5-mg group: at 1 month, BCVA improved from 20/168 (0.92 logMAR units) to 20/118 (0.78 logMAR units; p = 0.02). The mean BCVA at 24 months was 20/114 (0.76 logMAR units; p < 0.0001). In the 1.25-mg group, the mean CMT decreased from 466.5 +/- 145.2 microm at baseline to 332.2 +/- 129.6 microm at 1 month and 286.6 +/- 81.5 microm at 24 months (p < 0.0001). Similar results were obtained in the 2.5-mg group. The authors concluded that primary IVB at doses of 1.25 to 2.5 mg seem to provide stability or improvement in BCVA, OCT, and FA in DDME at 24 months. The results show no evident difference between IVB at doses of 1.25 or 2.5 mg. Moreover, they stated that the results are promising and suggested the need for further investigation especially randomized controlled trials comparing IVB and focal or grid photocoagulation.

In a Cochrane review on anti-angiogenic therapy with anti-VEGF modalities for diabetic macular edema, Parravano and colleagues (2009) concluded that there is insufficient high quality evidence from large RCTs supporting the use of either single or multiple anti-VEGF
intra-vitreal injections to treat diabetic macular edema. Results from ongoing studies on several compounds should assess not only treatment efficacy but also, if a benefit is found, the number of injections needed for maintenance and long-term safety. Furthermore, the Spanish Retina and Vitreous Society's guidelines on management of diabetic retinopathy and macular oedema (Pareja-Ríos et al, 2009) stated that the role of anti-angiogenics is not yet sufficiently defined.

In a randomized 3-arm clinical trial, Soheilian et al (2009) compared the results of IVB injection alone or in combination with intra-vitreal triamcinolone acetonide (IVTA) versus macular laser photocoagulation (MPC) as a primary treatment of DME. A total of 150 eyes of 129 patients with clinically significant DME and no previous treatment were included in this study. The eyes were randomly assigned to 1 of the 3 study arms: (i) the IVB group, patients who received 1.25 mg IVB (50 eyes); (ii) the IVB/IVTA group, patients who received 1.25 mg of IVB and 2 mg of IVTA (50 eyes); and (iii) the MPC group, patients who underwent focal or modified grid laser (50 eyes). Re-treatment was performed at 12-week intervals whenever indicated. Subjects were followed at 12 week intervals through 36 weeks. Outcome measures included changes from baseline in BCVA and CMT. Overall, re-treatment was required for 27 eyes up to 36 weeks (14 in the IVB group, 10 in the IVB/IVTA group, and 3 in the MPC group). In regards to reduction of CMT, the authors found that there was no meaningful superiority of the IVB and IVB/IVTA groups over the MPC group. The IVB/IVTA group showed an initial significant improvement in visual acuity over the MPC group; however, no statistically significant difference in visual improvement was seen at weeks 24 and 36. The IVB group showed a significant improvement in visual acuity over the MPC group, but by 36 weeks, this difference was of marginal statistical significance. The authors found no adjunctive effect of IVTA. The authors stated that larger studies with long-term follow-up evaluating the therapeutic effects of bevacizumab focusing on different features of DME are recommended.

In a prospective, randomized, masked cohort study, Takamura et al (2009) determined the feasibility and clinical effectiveness of IVB combined with cataract surgery for management of the post-operative increase of retinal thickness in patients with diabetic maculopathy. A total of 42 eyes with DME of 42 patients with type 2 diabetes mellitus were included in this analysis. Patients were randomly assigned to receive either cataract surgery only (control; 21 eyes) or combined with IVT injection of 1.25 mg bevacizumab (21 eyes). Efficacy measures included BCVA testing, OCT, and ophthalmoscopic examination. Retinal thickness (RT) on OCT and BCVA were measured at baseline and 1 and 3 months after surgery. There were no significant differences in RT, BCVA, severity of cataract, or systemic condition between the control and bevacizumab groups at the baseline. One and 3 months after surgery, the control group showed a significant increase in RT, whereas the bevacizumab group showed a significant decrease. Although post-operatively the eyes in both groups showed a significant improvement of BCVA, bevacizumab-treated eyes showed significantly better results (mean logarithm of the minimum angle of resolution, 0.38) than the control group (0.51) at month 3. There was a significant relationship between RT and VA post-operatively in the control (p = 0.0001) and bevacizumab (p = 0.0141) groups. No systemic or ocular adverse events were observed. The authors concluded that short-term results suggested that IVT bevacizumab has the potential not only to prevent the increase in RT, but also reduce the RT of eyes with DME following cataract surgery. Moreover, they stated that these results seem promising and further investigation with a longer follow-up and a larger series of patients may be needed.
In a retrospective, consecutive, interventional case series, Wakabayashi et al (2008) assessed the effectiveness of intravitreal bevacizumab (IVB) for iris neovascularization (INV) or neovascular glaucoma (NVG) in patients with ischemic retinal disorders. A total of 30 patients (41 eyes) with INV or NVG secondary to ischemic retinal disorders were included in this study. Patients received IVB (1 mg) as the initial treatment for INV or NVG and were followed-up for at least 6 months. Ophthalmic evaluations included measurement of visual acuity and intra-ocular pressure (IOP), a complete ophthalmic examination, and fluorescein angiography. Patients were divided into 3 subgroups: (i) INV without elevated IOP (INV group), (ii) NVG with an open angle (O-NVG group), and (iii) NVG with angle closure (C-NVG group) for outcomes analysis. Main outcome measures included the controllability of IOP by IVB, incidence of recurrence, and requirement for surgery to treat NVG. No significant ocular or systemic adverse events developed during follow-up (range of 6 to 22 months; mean of 13.3 months). The mean IOP levels were 14.7, 31.2, and 44.9 mmHg at baseline in the INV, O-NVG, and C-NVG groups, respectively. In the INV group (9 eyes), the INV regressed or resolved after 1 injection. Iris neovascularization recurred in 4 eyes by 6 months and stabilized after repeated injections without IOP elevation. In the O-NVG group (17 eyes), rapid neovascular regression with successful IOP normalization (less than or equal to 21 mmHg) occurred in 12 eyes (71 %) within 1 week after 1 injection. Five (29 %) of the 17 eyes required surgery by 6 months despite repeated IVB injections, and a total of 7 eyes (41 %) underwent surgery during follow-up. In the C-NVG group (15 eyes), IVB caused INV resolution but failed to lower the IOP. Fourteen (93 %) of 15 eyes required surgery by 2 months after initial IVB and achieved IOP stabilization. The mean interval between IVB and surgery was significantly shorter in the C-NVG group than in the O-NVG group (p < 0.001). The authors concluded that intra-vitreal bevacizumab is well-tolerated, effectively stabilized INV activity, and controlled IOP in patients with INV alone and early-stage NVG without angle closure. In advanced NVG, IVB cannot control IOP but may be used adjunctively to improve subsequent surgical results. They stated that further evaluation in controlled randomized studies (with long-term results) is needed to elucidate the appropriate use of bevacizumab in the management of neovascular glaucoma.

Schaal and associates (2009) evaluated the short-term safety and efficacy of intra-vitreal bevacizumab for the treatment of intra-retinal or sub-retinal fluid accumulation secondary to chronic central serous chorioretinopathy (CSC). A total of 12 patients were treated with intra-vitreal injections of 2.5 mg bevacizumab at 6- to 8-week intervals until intra-retinal or sub-retinal fluid resolved. Observation procedures were Early Treatment Diabetic Retinopathy Study BCVA, ophthalmic examination, and OCT, performed at 6- to 8-week intervals. Fluorescein angiography was performed at baseline visit and thereafter depending on clinical and OCT findings. Multi-variate analysis of variance with repeated measures was used to calculate a statistical significance of change in BCVA and mean central retinal thickness, which were the main outcome measures. Patients received 2 +/- 1 intra-vitreal injections of bevacizumab on average during a follow-up of 24 +/- 14 weeks. Mean BCVA increased by 2 +/- 2 lines; the change in BCVA (logMAR) was significant (p < 0.02). Mean central retinal thickness decreased significantly over follow-up (p < 0.05), with 6 patients (50 %) showing complete resolution of sub-retinal fluid. The authors concluded that anatomical and functional improvement following intra-vitreal bevacizumab injections suggest that VEGF may be involved in fluid leakage in patients with chronic CSC. The results suggested a possible role for anti-VEGF agents in the treatment of chronic CSC. They stated that further evaluation of intra-vitreal bevacizumab for chronic CSC in controlled randomized studies is warranted.
In a prospective, controlled clinical study, Artunay et al (2010) examined the effect of IVB in treatment of persistent CSC. A total of 30 eyes of 30 patients with persistent, symptomatic CSC of 3 months’ duration or more were included in this study. Fifteen eyes of 15 patients were treated with intra-vitreal injections of 2.5 mg (0.1 ml) bevacizumab (treatment group). Fifteen eyes of 15 patients with the same characteristics who declined treatment were an acceptable control group. The visual and anatomical responses were observed with BCVA and central foveal thickness measured by OCT at baseline, 1, 3, and 6 months after treatment. Twelve (80 %) eyes in the IVB group compared with 8 (53.3 %) eyes in the control group showed morphological restitution at 6 months (p < 0.01). All 15 (100 %) treated eyes had stable or improved vision, compared with 10 (66.6 %) eyes in the control group (p < 0.01). At 6 months, the mean +/- SD central foveal thickness for the treatment group remained significantly lower compared to the control group, with 174 +/- 68 microm and 297 +/- 172 microm, respectively (p < 0.001). Injection-related complications were not encountered. The authors concluded that these findings indicate that intra-vitreal bevacizumab injection may be a new, promising treatment option for select patients with idiopathic persistent CSC. They stated that continued studies with IVB in this population will help to establish its long-term efficacy.

Teng and co-workers (2009) examined the effect of sub-conjunctival bevacizumab on primary pterygium. A patient with an inflamed nasal primary pterygium refractory to artificial tears and naphazoline was enrolled in this study. After pre-treatment with topical proparacaine and moxifloxacin, 0.05 ml bevacizumab (1.25 mg/0.05 ml) was injected sub-conjunctivally at the limbus. Clinical signs of irritation, redness, and vascularization were monitored over 7 weeks. At 1 week post-injection, irritation and hyperemia showed near-total regression. At week 2, the pterygium maintained this appearance. By week 7, the degree of vascularity and symptoms of irritation had regressed to its pre-injection state. The authors concluded that treatment of primary pterygium with sub-conjunctival bevacizumab results in a short-term decrease in vascularization and irritation. They stated that further long-term studies should investigate the efficacy of bevacizumab as an adjunct to surgical excision or combined topical treatment targeting other growth factors involved in pterygium pathogenesis.

Razeghinejad and associates (2010) assessed the effectiveness of sub-conjunctival bevacizumab as an adjunctive therapy for primary pterygium surgery. This randomized prospective clinical study was conducted on 30 eyes of 30 patients. After pterygium excision and accomplishing a rotational conjunctival flap, 15 patients (case group) received 1.25 mg (0.1 ml) bevacizumab, and 15 other patients (control group) received 0.1 ml balanced salt solution subconjunctivally. The main outcome measures were recurrence of pterygia, horizontal length of the corneal epithelial defect, conjunctival erythema, lacrimation and photophobia during the first post-operative week. There were no statistically significant differences regarding age, sex or recurrence risk factors between the 2 groups (p > 0.05). The pterygia resolved in 13 (86.6 %) of 15 eyes in both groups, with a recurrence rate of 13.4 % during a mean follow-up period of 8 +/- 1.4 months in the case group and 7.4 +/- 1.5 months in the control group (p = 0.2). There were no statistically significant differences regarding reduction in refractive astigmatism, improvement in visual acuity, corneal epithelial defects, conjunctival erythema, lacrimation or photophobia between the case and control groups (p > 0.05). The authors concluded that a single intra-operative subconjunctival bevacizumab injection had no effect on recurrence rate or early post-operative conjunctival erythema, lacrimation, photophobia or healing of corneal epithelial defects following pterygium excision.
In a case series study, Ghanem and associates (2009) evaluated the effect of intra-vitreal injection of bevacizumab (2.5 mg) in cases of neovascular glaucoma. A total of 16 eyes of 16 patients with rubeosis iridis (RI) and secondary glaucoma were included in this study. The patients were followed for 2 months. These researchers noted partial or complete regression of iris neovascularization 1 week after injection of bevacizumab. Re-proliferation of new vessels was detected in 25% of the cases after 2 months. The mean IOP before injection was 28 +/- 9.3 mm Hg under topical SS-blocker and systemic acetazolamide. One week after injection, the IOP decreased to 21.7 +/- 11.5 mm Hg (5 cases without anti-glaucoma drugs, 6 cases with topical SS-blocker, and 5 cases with both topical SS-blocker and systemic acetazolamide). The authors concluded that intra-vitreal bevacizumab injection leads to regression of iris neovascularization with subsequent drop of IOP in eyes with neovascular glaucoma. This was a small study with short-term follow-up; its finding was also confounded by the concomitant use of anti-glaucoma drugs in some cases. These findings need to be validated by well-designed studies.

Batman and Ozdamar (2010) reported the outcomes of the use of intra-cameral bevacizumab for iris neovascularization occurring after silicone oil (SO) removal in eyes undergoing vitre-oretinal surgery (VRS). This study included 12 eyes that had iris neovascularization after SO removal. There were 8 men and 4 women with an average age of 41.6 +/- 12.7 years. All eyes had VRS for various vitreo-retinal diseases. After the mean follow-up period of 9.7 +/- 5.3 months, SO removal was performed. Then, patients were followed for more than 2 months and detailed retinal examinations and IOP were normal during this period, but RI developed. Rubeosis iridis was treated with 1 dose of 1.25 mg bevacizumab into the anterior chamber. After a mean follow-up period of 4.8 +/- 2.2 months, the regression of iris neovascularization was detected and IOP was below 21 mmHg in all eyes. The authors concluded that anterior segment neovascularization (ASNV) may develop through various mechanisms in patients with VRS after SO removal, and anterior chamber injection of bevacizumab may lead to regression of ASNV. Again, this was a small study with short-term follow-up; its findings need to be validated by well-designed studies.

In a retrospective review, Maturo and Hartnick (2010) described their initial experience with intra-lesional bevacizumab treatment for children with severe, recurrent respiratory papilloma (RRP). A total of 3 children, aged 3 to 6 years, with severe RRP requiring more than 4 operative interventions in 1 year whose parents (or legal guardians) consented to adjuvant treatment with intra-lesional bevacizumab. All 3 children were treated as follows: surgical debridement with a micro-debrider, pulsed KTP laser treatments, and adjuvant intra-lesional injections with bevacizumab (1.25 mg total). Main outcome measures were time interval between operative interventions, Derkay severity scale for RRP, and pediatric voice-related quality of life (PVRQOL) scores. All 3 children demonstrated increased time between operative interventions. Two children had a substantial decrease in their Derkay score and improved PVRQOL scores. One child, although time between operative interventions improved, did not have any change in Derkay score and required further adjuvant therapy. The authors concluded that injectable bevacizumab appears to show some efficacy in prolonging the time between treatments and therefore reducing the number of treatments per year in children with severe RRP. However, before any meaningful conclusions can be drawn, further studies must be conducted in the form of head-to-head trials looking specifically at the issues of time between treatment intervals, efficacy of one adjunct over another, vocal outcomes, and whether several adjunctive treatments confer advantage over 1 treatment.
In a review on diabetic retinopathy (DR), Cheung et al (2010) noted that although anti-VEGF therapy has promising clinical applications for the management of DR, its long-term safety in patients with diabetes has not yet been established. Local adverse events of IVB include cataract formation, infection, retinal detachment, vitreous hemorrhage, as well as potential loss of neural retinal cells. Furthermore, a significant portion of anti-VEGF agents injected into the eye could pass into the systemic circulation. Thus, systemic inhibition of angiogenesis is a potential risk. Also, although clinical trials on the use of intra-vitreal anti-VEGF therapy for the treatment of AMD generally show low (0.6 to 1.2 %) rates of stroke, this risk could be increased in patients with DR because of pre-existing diabetes-related vascular disease.

Nicholson and Schachat (2010) stated that many observational and pre-clinical studies have implicated VEGF in the pathogenesis of DR, and recent successes with anti-VEGF therapy for age-related macular degeneration have prompted research into the application of anti-VEGF drugs to DR. These investigators reviewed the numerous early studies that suggest an important potential role for anti-VEGF agents in the management of DR. The authors concluded that for diabetic macular edema, phase II trials of intra-vitreal pegaptanib and intra-vitreal ranibizumab have shown short-term benefit in visual acuity. Intra-vitreal bevacizumab also has been shown to have beneficial short-term effects on both visual acuity and retinal thickness. For proliferative diabetic retinopathy (PDR), early studies suggest that IVB temporarily decreases leakage from diabetic neovascular lesions, but this treatment may be associated with tractional retinal detachment. Furthermore, several studies indicate that bevacizumab is likely to prove a helpful adjunct to diabetic pars plana vitrectomy for tractional retinal detachment. Finally, 3 small series suggest a potential beneficial effect of a single dose of bevacizumab to prevent worsening of DME after cataract surgery. The authors noted that use of anti-VEGF medications for any of these indications is off-label. Despite promising early reports on the safety of these medications, the results of large, controlled trials to substantiate the safety and efficacy of anti-VEGF drugs for diabetic retinopathy are eagerly awaited.

In a pilot study, Guenterberg and associates (2011) hypothesized that administration of bevacizumab in combination with high-dose interferon-alpha2b (IFN-α2b) would have clinical activity in patients with metastatic ocular melanoma. Patients with metastatic ocular melanoma received bevacizumab (15 mg/kg intravenously every 2 weeks) plus IFN-α2b (5 MU/m subcutaneously 3 times weekly for 2 weeks followed by a dose of 10 MU/m subcutaneously thereafter). Patients exhibiting a clinical response or stabilization of disease were treated until disease progression. A total of 5 patients were treated (3 men and 2 women) with a mean age of 63.8 years (range of 53 to 71 years). Overall, the regimen was well-tolerated. The following adverse events were noted: grade 3 dyspnea (n = 2), grade 3 and 4 fatigue (n = 2), grade 3 muscle weakness (n = 1), grade 3 anorexia (n = 1), grade 1 and 2 proteinuria (n = 2), and grade 3 diarrhea (n = 1). All adverse events resolved with a treatment holiday or dose reduction. One patient had reduction in tumor burden of 23 % by Response Evaluation Criteria in Solid Tumors criteria and 2 patients had stabilization of disease lasting 28 and 36 weeks, respectively. Two patients failed to respond and progressed after 6 and 7 weeks of therapy. The authors concluded that bevacizumab and IFN-α2b were well-tolerated in this patient population, and clinical activity was observed. They stated that further study of high-dose IFN-α2b in combination with bevacizumab in this setting is warranted.
The NET Task Force of the National Cancer Institute GI Steering Committee (Kulke et al., 2011) convened a clinical trials planning meeting to identify key unmet needs, develop appropriate study end points, standardize clinical trial inclusion criteria, and formulate priorities for future neuroendocrine tumor (NET) studies for the United States cooperative group program. Emphasis was placed on the development of well-designed clinical trials with clearly defined efficacy criteria. Key recommendations include the evaluation of pancreatic NET separately from NETs of other sites and the exclusion of patients with poorly differentiated histologies from trials focused on low-grade histologies. Specific recommendations for ongoing and future studies on carcinoid tumors and pancreatic NETs are: (i) successful completion of the ongoing phase III study of bevacizumab and IFN in patients with advanced carcinoid tumors may define the role of bevacizumab in these patients, and (ii) everolimus is active in patients with advanced pancreatic NETs. A randomized phase II study comparing everolimus alone with combination of everolimus plus bevacizumab in patients with pancreatic NET will build on the recent observation of activity with everolimus alone, and may help define the potential additive activity of bevacizumab in this setting.

In a phase II clinical trial, Argiris et al. (2011) hypothesized that bevacizumab will potentiate the activity of pemetrexed in squamous cell carcinoma of the head and neck (SCCHN). Patients with previously untreated, recurrent, or metastatic SCCHN were treated with pemetrexed 500 mg/m² and bevacizumab 15 mg/kg given intravenously every 21 days with folic acid and B-12 supplementation until disease progression. Primary end point was time-to-progression (TTP). DNA was isolated from whole blood samples for the detection of polymorphisms in thymidylate synthase, methylenetetrahydrofolate reductase (MTHFR), and VEGF. A total of 40 patients were enrolled. The median TTP was 5 months, and the median OS was 11.3 months. In 37 evaluable patients, the overall response rate was 30 %, including a complete response rate of 5 %, and the disease control rate was 86 %. Grade 3 to 5 bleeding events occurred in 6 patients (15 %): 4 were grade 3, and 2 were fatal. Other serious toxicities in 10 % or more of patients included neutropenia (10 %) and infection (12.5 %). One patient died of sepsis after receiving 8 cycles of therapy. For the MTHFR A1298C (rs1801131) single nucleotide polymorphisms, homozygote patients with AA had worse OS (p = 0.034). The authors concluded that the addition of bevacizumab to pemetrexed resulted in promising efficacy outcomes in SCCHN. Bleeding events were frequent but some may have been due to natural history of disease. Polymorphisms in MTHFR may offer potential for treatment individualization. They stated that bevacizumab-containing regimens should be further investigated in SCCHN.

In a prospective, randomized, clinical trial, Ahn et al. (2011) evaluated the effects of pre-operative and IVB injection on the incidence of post-operative vitreous hemorrhage (VH) after vitrectomy for PDR. A total of 107 eyes of 91 patients undergoing pars plana vitrectomy (PPV) for the management of PDR-related complications were enrolled. A total of 107 cases were assigned randomly to either group 1 (intra-vitreal 1.25 mg/0.05 ml bevacizumab injection 1 to 14 days before PPV), group 2 (intra-vitreal 1.25 mg/0.05 ml bevacizumab injection at the end of PPV), or group 3 (no IVB injection). The primary outcome was the incidence of early (less than or equal to 4 weeks) and late (greater than 4 weeks) recurrent VH. Secondary outcome measures were the initial time of vitreous clearing (ITVC) and BCVA at 6 months after surgery. The incidences of early recurrent VH were 22.2 %, 10.8 %, and 32.4 % in groups 1, 2, and 3, respectively (p = 0.087). A subgroup pair-wise analysis showed significantly decreased early VH incidence in group 2 compared with that of group 3 (p = 0.026). The incidences of late recurrent VH were 11.1
\%\, 16.2 \%, and 14.7 \% in groups 1, 2, and 3, respectively (p = 0.813). The ITVC in groups 1, 2, and 3 were 26.4 +/- 42.5 days, 10.3 +/- 8.2 days, and 25.2 +/- 26.1 days, respectively. The ITVC was significantly shorter in group 2 compared with that in groups 1 and 3 (p = 0.045 and p = 0.015, respectively). The BCVA at 6 months after surgery did not differ significantly among the 3 groups (p = 0.418). The authors concluded that this study found no substantial evidence to support the adjunctive use of pre-operative IVB to reduce post-operative recurrence of VH in vitrectomy for PDR. For select cases in which adjunctive IVB use is considered, intra-operative administration seems to be the better option for reducing post-operative VH.

Farahvash et al (2011) evaluated the effect of pre-operative IVB on surgery and on the early post-operative course in diabetic patients undergoing vitrectomy for dense VH. A total of 35 patients with dense diabetic VH were randomly assigned to a group that received 1.25 mg of IVB 1 week before vitrectomy (18 patients) or the control group (17 patients). To compare the complexity of 2 groups, intra-operative complexity score and proliferative diabetic vitre-oretinopathy stage were recorded. Intra-operative bleeding, break formation, number of endodiathermy applications, BCVA, anatomical outcome at month 3 and at final follow-up, and post-operative complications were evaluated. Mean complexity scores and proliferative diabetic vitreo-retinopathy stages of both groups were similar. The mean score of bleeding was 1.05 in the IVB group versus 1.76 in the control group (p = 0.35); endodiathermy applications and break formations were 0.44 versus 0.52 (p = 0.68) and 0.22 versus 0.29 (p = 0.60) in the IVB and control groups, respectively. Anatomical outcome and visual acuity at month 3 and at the final follow-up were similar. The authors concluded that these findings suggested that IVB before vitrectomy for dense diabetic VH has no significant effect on facilitation of surgery or on the early post-operative course.

In a Cochrane review, Smith and Steel (2011) assessed the effect of peri-operative anti-VEGF in reducing the incidence of post-operative vitreous cavity hemorrhage (POVCH). These investigators searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2011, Issue 2), MEDLINE (January 1950 to March 2011), PubMed (10 March 2011), EMBASE (January 1980 to March 2011), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to March 2011), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com) and ClinicalTrials.gov (www.clinicaltrial.gov). There were no date or language restrictions in the electronic searches for trials. The electronic databases were last searched on March 10, 2011. These researchers included all RCTs that looked at the use of anti-VEGFs and the incidence of POVCH in people undergoing vitrectomy for PDR. Both review authors independently assessed and extracted the data using a standardized form based on the CONSORT statement. They included 4 studies (202 eyes of 198 participants) in this review. The 4 RCTs met the inclusion criteria, but the authors were unable to conduct a meta-analysis due to methodological issues in 3 of the trials. They have provided a summary of the effects of the interventions; and have also provided a summary of the current literature addressing each primary and secondary outcome. The authors concluded that results from 1 of the included studies support the use of pre-operative IVB to reduce the incidence of early POVCH. There are currently no other high-quality RCTs that support the use of anti-VEGF agents peri-operatively to reduce the incidence of early or late POVCH. The remaining studies identified by the search suggested that the pre-operative use of bevacizumab may reduce the incidence of early POVCH, but it should be recognized that there are a number of significant methodological
issues in these studies that lead us to be cautious when interpreting their findings and make any definitive conclusions unwarranted.

In a prospective, interventional case series, Goel et al (2011) evaluated the role of IVB in the treatment of Coats' disease diagnosed in adulthood. A total of 3 patients with Coats' disease diagnosed in adulthood were managed with a single intravitreal injection of bevacizumab (1.25 mg) with peripheral laser photocoagulation 3 weeks later. All 3 patients had exudation at the macula (Stage 2B) along with peripheral retinal telangiectasia and aneurysms. They were followed-up for 9 months. An appreciable reduction in the exudation at the macula and macular edema was observed in all cases following IVB therapy. In all patients, the visual acuity improved, and no signs of recurrence were observed at the final follow-up at 9 months. The authors concluded that IVB may be effective as an adjunctive treatment for adult-onset Coats' disease with foveal exudation along with laser photocoagulation to the peripheral retinal vascular abnormalities.

Ramasubramanian et al (2012) evaluated the effect of supplemental IVB for management of Coats' disease. Retrospective analysis of 8 patients with Coats' disease manifesting total or partial exudative retinal detachment where the retinal telangiectasia was treated with standard laser photocoagulation and/or cryotherapy plus additional IVB (1.25 mg/0.05 ml). The mean patient age was 88 (range of 7 to 240) months and 63 % were male. Coats' disease was classified as stage 2 (n = 1, 12 %), 3a (n = 3, 38 %) and 3b (n = 4, 50 %). Features included retinal detachment (n = 8, 100 % with mean detachment extent involving 8 clock hours), telangiectasia (n = 8, 100 % with mean extent of 8 clock hours), peripheral retinal ischemia on fluorescein angiography (n = 7, 88 %) and no evidence of neovascularisation. Treatment consisted of cryotherapy (n = 8, 100 %), laser photocoagulation (n = 4, 50 %) and IVB (n = 8) with median number of 1 injection per eye (mean of 1.75, and range of 1 to 4 injections). After a mean follow-up of 8.5 months, resolution of retinopathy (n = 8, 100 %), Coats'-related subretinal fluid (n = 8, 100 %) and retinal exudation (n = 6, 75 %) was noted. However, vitreous fibrosis developed (n = 4, 50 %) at a mean of 5 months following a mean of 1.75 bevacizumab injections with 3 (38 %) evolving into traction retinal detachment. The authors concluded that Coats' disease treated with IVB in addition to standard therapy can develop to vitreo-retinal fibrosis and potentially traction retinal detachment. These tractional features are not often found in Coats' disease treated with standard measures without bevacizumab. Thus, caution is advised in the use of bevacizumab for patients with Coats' disease.

In a single-center, phase 2 clinical trial, Dupuis-Girod et al (2012) examined the effectiveness of bevacizumab in reducing high cardiac output (CO) in severe hepatic forms of hereditary hemorrhagic telangiectasia (HHT) and evaluated improvement in epistaxis duration and quality of life. Patients were 18 to 70 years old and had confirmed HHT, severe liver involvement, and a high cardiac index related to HHT. Bevacizumab, 5 mg/kg of body weight, every 14 days for a total of 6 injections. The total duration of the treatment was 2.5 months; patients were followed-up for 6 months after the beginning of the treatment. Main outcome measure was decrease in CO at 3 months after the first injection, evaluated by echocardiography. A total of 25 patients were included between March 2009 and November 2010. Of the 24 patients who had echocardiograms available for re-read, there was a response in 20 of 24 patients with normalization of cardiac index (complete response [CR]) in 3 of 24, partial response (PR) in 17 of 24, and no response in 4 cases. Median cardiac index at beginning of the treatment was 5.05 L/min/m² (range of 4.1 to 6.2) and significantly decreased at 3 months after the beginning of the treatment.
with a median cardiac index of 4.2 L/min/m(2) (range of 2.9 to 5.2; p < 0.001). Median cardiac index at 6 months was significantly lower than before treatment (4.1 L/min/m(2); range of 3.0 to 5.1). Among 23 patients with available data at 6 months, these researchers observed CR in 5 cases, PR in 15 cases, and no response in 3 cases. Mean duration of epistaxis, which was 221 mins/month (range of 0 to 947) at inclusion, had significantly decreased at 3 months (134 mins; range of 0 to 656) and 6 months (43 mins; range of 0 to 310) (p = 0.008). Quality of life had significantly improved. The most severe adverse events were 2 cases of grade 3 systemic hypertension, which were successfully treated. The authors concluded that in this preliminary study of patients with HHT associated with severe hepatic vascular malformations and high CO, administration of bevacizumab was associated with a decrease in CO and reduced duration and number of episodes of epistaxis. Drawbacks of this study included small sample size and lack of a control group. The authors stated that it is unclear if this treatment could be definitive or a bridging therapy while patients are waiting for a liver transplant. They noted that longer follow-up studies are needed to determine the duration of HHT efficacy and whether maintenance therapy is needed.

In a phase II clinical trial, White and colleagues (2013) compared bevacizumab and bortezomib versus bortezomib in relapsed or refractory multiple myeloma (MM). Patients with relapsed or refractory MM were randomized to receive bortezomib (1.3 mg/m(2) on days 1, 4, 8, and 11 of each 21-day cycle) and either placebo or bevacizumab (15 mg/kg on day 1 of each cycle) for up to 8 cycles. At completion, patients in the bortezomib-plus-bevacizumab arm could continue bevacizumab until they developed progressive disease or unacceptable toxicity. The primary endpoint was PFS. The stratified hazard ratio of PFS for the bevacizumab-containing arm (n = 49) relative to the bortezomib monotherapy arm (n = 53) was 0.743 (95 % CI: 0.43 to 1.28; p = 0.2804); the median PFS was 6.2 months (95 % CI: 4.4 to 8.5 months) and 5.1 months (95 % CI: 4.2 to 7.2 months), respectively; the overall response rates were 51 % and 43.4 % (p = 0.4029), respectively; and the median response duration was 6.9 months (95 % CI: 4.73 to 11.83 months) and 6.0 months (95 % CI: 4.86 to 8.31 months), respectively. Frequent adverse events occurred at similar rates across treatment arms, but hypertension, fatigue, and neuralgia occurred more frequently in the bevacizumab-containing arm. The authors concluded that the addition of bevacizumab to bortezomib in unselected patients with pretreated MM did not result in significant improvements in efficacy outcomes.

In a randomized, double-blind, placebo-controlled trial, Gilbert et al (2014) treated adults who had centrally confirmed glioblastoma with radiotherapy (60 Gy) and daily temozolomide. Treatment with bevacizumab or placebo began during week 4 of radiotherapy and was continued for up to 12 cycles of maintenance chemotherapy. At disease progression, the assigned treatment was revealed, and bevacizumab therapy could be initiated or continued. The trial was designed to detect a 25 % reduction in the risk of death and a 30 % reduction in the risk of progression or death, the 2 co-primary end-points, with the addition of bevacizumab. A total of 978 patients were registered, and 637 underwent randomization. There was no significant difference in the duration of OS between the bevacizumab group and the placebo group (median of 15.7 and 16.1 months, respectively; HR for death in the bevacizumab group, 1.13). Progression-free survival was longer in the bevacizumab group (10.7 months versus 7.3 months; HR for progression or death, 0.79). There were modest increases in rates of hypertension, thromboembolic events, intestinal perforation, and neutropenia in the bevacizumab group. Over time, an increased symptom burden, a worse QOL, and a decline in neurocognitive function were more frequent in the bevacizumab group. The authors concluded that first-line use of
bevacizumab did not improve OS in patients with newly diagnosed glioblastoma; PFS was prolonged but did not reach the pre-specified improvement target.

In a phase III clinical trial, Chinot et al (2014) evaluated the effect of the addition of bevacizumab to radiotherapy-temozolomide for the treatment of newly diagnosed glioblastoma. These researchers randomly assigned patients with supratentorial glioblastoma to receive intravenous bevacizumab (10 mg/kg of body weight every 2 weeks) or placebo, plus radiotherapy (2 Gy 5 days a week; maximum of 60 Gy) and oral temozolomide (75 mg/square meter of body-surface area/day) for 6 weeks. After a 28-day treatment break, maintenance bevacizumab (10 mg/kg intravenously every 2 weeks) or placebo, plus temozolomide (150 to 200 mg/square meter/day for 5 days), was continued for six 4-week cycles, followed by bevacizumab monotherapy (15 mg/kg intravenously every 3 weeks) or placebo until the disease progressed or unacceptable toxic effects developed. The co-primary end-points were investigator-assessed PFS and OS. A total of 458 patients were assigned to the bevacizumab group, and 463 patients to the placebo group. The median PFS was longer in the bevacizumab group than in the placebo group (10.6 months versus 6.2 months; stratified HR for progression or death, 0.64; 95 % CI: 0.55 to 0.74; p < 0.001). The benefit with respect to PFS was observed across subgroups. Overall survival did not differ significantly between groups (stratified HR for death, 0.88; 95 % CI: 0.76 to 1.02; p = 0.10). The respective OS rates with bevacizumab and placebo were 72.4 % and 66.3 % at 1 year (p = 0.049) and 33.9 % and 30.1 % at 2 years (p = 0.24). Baseline health-related QOL and performance status were maintained longer in the bevacizumab group, and the glucocorticoid requirement was lower. More patients in the bevacizumab group than in the placebo group had grade 3 or higher adverse events (66.8 % versus 51.3 %) and grade 3 or higher adverse events often associated with bevacizumab (32.5 % versus 15.8 %). The authors concluded that the addition of bevacizumab to radiotherapy-temozolomide did not improve survival in patients with glioblastoma. Improved PFS and maintenance of baseline quality of life and performance status were observed with bevacizumab; however, the rate of adverse events was higher with bevacizumab than with placebo.

The American College of Radiology Expert Panel on Radiation Oncology-Gynecology’s Appropriateness Criteria® on “Advanced cervical cancer” (Gaffney et al, 2012) stated that “The combinations of cisplatin and topotecan have demonstrated an improvement in overall survival, and recently bevacizumab has shown promising activity in recurrent or metastatic cervix cancer”.

Vici and colleagues (2014) noted that cervical cancer is the 3rd most common cancer worldwide, and the development of new diagnosis, prognostic, and treatment strategies is a major interest for public health. Cisplatin, in combination with external beam irradiation for locally advanced disease, or as monotherapy for recurrent/metastatic disease, has been the cornerstone of treatment for more than 2 decades. Other investigated cytotoxic therapies include paclitaxel, ifosfamide and topotecan, as single agents or in combination, revealing unsatisfactory results. In recent years, much effort has been made towards evaluating new drugs and developing innovative therapies to treat cervical cancer. Among the most investigated molecular targets are EGFR and VEGF signaling pathways; both playing a critical role in the development of cervical cancer. Studies with bevacizumab or VEGF receptor tyrosine kinase have given encouraging results in terms of clinical efficacy, without adding significant toxicity.
Goey and Figg (2014) stated that the VEGF-A binding monoclonal antibody bevacizumab is a widely prescribed angiogenesis inhibitor and indicated for many types of cancer. As shown by 3 randomized phase III trials recently published in the New England Journal of Medicine, novel indications for this drug are still being explored. In the RTOG 0825 and AVAglio trials the effect of bevacizumab addition to standard therapy in newly diagnosed glioblastoma (radiotherapy plus temozolomide) was investigated, while in GOG 240 the combination of platinum-based chemotherapy plus bevacizumab was explored in advanced cervical cancer. In RTOG 0825, addition of bevacizumab to standard therapy did not result in survival benefit, and moreover, quality of life was more deteriorated in the bevacizumab arm. In AVAglio, however, PFS was significantly increased in the bevacizumab group and these patients also experienced a longer deterioration-free survival. These conflicting results do not fully support the incorporation of bevacizumab in the first-line treatment of glioblastoma. In contrast, in GOG 240 the bevacizumab group (including paclitaxel plus topotecan or paclitaxel) experienced a significant longer PFS and OS, and quality of life was not negatively affected in these patients. Thus, these results favor the use of bevacizumab in the treatment of advanced cervical cancer.

Tewari and colleagues (2014) evaluated the effectiveness of bevacizumab and non-platinum combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer. Using a 2-by-2 factorial design, these researchers randomly assigned 452 patients to chemotherapy with or without bevacizumab at a dose of 15 mg/kg of body weight. Chemotherapy consisted of cisplatin at a dose of 50 mg/m2 of body-surface area, plus paclitaxel at a dose of 135 or 175 mg/m2 or topotecan at a dose of 0.75 mg/m2 on days 1 to 3, plus paclitaxel at a dose of 175 mg/m2 on day 1. Cycles were repeated every 21 days until disease progression, the development of unacceptable toxic effects, or a CR was documented. The primary end-point was OS; a reduction of 30 % in the hazard ratio for death was considered clinically important. Groups were well-balanced with respect to age, histologic findings, performance status, previous use or non-use of a radio-sensitizing platinum agent, and disease status. Topotecan-paclitaxel was not superior to cisplatin-paclitaxel (HR for death, 1.20). With the data for the 2 chemotherapy regimens combined, the addition of bevacizumab to chemotherapy was associated with increased OS (17.0 months versus 13.3 months; HR for death, 0.71; 98 % CI: 0.54 to 0.95; p = 0.004 in a 1-sided test) and higher response rates (48 % versus 36 %, p = 0.008). Bevacizumab, as compared with chemotherapy alone, was associated with an increased incidence of hypertension of grade 2 or higher (25 % versus 2 %), thrombo-embolic events of grade 3 or higher (8 % versus 1 %), and gastro-intestinal fistulas of grade 3 or higher (3 % versus 0 %). The authors concluded that the addition of bevacizumab to combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer was associated with an improvement of 3.7 months in median OS.

On August 14, 2014, the FDA approved Avastin (bevacizumab) to treat patients with persistent, recurrent or late-stage (metastatic) cervical cancer. The FDA reviewed Avastin for treatment of patients with cervical cancer under its priority review program because the drug demonstrated the potential to be a significant improvement in safety or effectiveness over available therapy in the treatment of a serious condition. Priority review provides an expedited review of a drug’s application. The safety and effectiveness of bevacizumab for treatment of patients with cervical cancer was evaluated in a clinical study involving 452 patients with persistent, recurrent, or late-stage disease. Subjects were randomly assigned to receive paclitaxel and cisplatin with or without Avastin or paclitaxel and topotecan with or without Avastin. Results showed an increase in OS to 16.8 months in
participants who received chemotherapy in combination with Avastin as compared to 12.9 months for those receiving chemotherapy alone.

Furthermore, NCCN's clinical practice guideline on “Cervical cancer” (Version 1.2015) lists cisplatin/paclitaxel/bevacizumab (category 1) and topotecan/paclitaxel/bevacizumab (category 2B) as 1st-line combinational therapy; as well as bevacizumab (category 2B) as 2nd-line single-agent therapy.

CPT Codes / HCPCS Codes / ICD-9 Codes

Other CPT codes related to the CPB:

67028
96401 - 96450

HCPCS codes covered if selection criteria are met:

J9035  Injection, bevacizumab, 10 mg [for neovascular (wet) age related macular degeneration see C9257]

C9257  Injection, bevacizumab, 0.25 mg [covered for neovascular (wet) age related macular degeneration]

Other HCPCS codes related to the CPB:

Q0083 - Q0085  Chemotherapy administration

J9190  Injection, fluorouracil, 500 mg

ICD-9 codes covered if selection criteria are met [See CPB 701 for ocular indications]:

115.02  Infections by Histoplasma capsulatum, retinitis
115.12  Infections by Histoplasma duboisi, retinitis
115.92  Histoplasmosis, unspecified , retinitis
152.0 - 152.9  Malignant neoplasm of small intestine, including duodenum
153.0 - 154.8  Malignant neoplasm of colon, rectum, rectosigmoid junction and anus
158.0 - 158.9  Malignant neoplasm of retroperitoneum and peritoneum
162.2 - 162.9  Malignant neoplasm of the bronchus and lung [non-squamous, non-small cell]
171.0 - 171.9  Malignant neoplasm of connective and other soft tissue, [angiosarcoma][hemangiopericytoma]
174.0 - 175.9  Malignant neoplasm of breast
180.0 - 180.9  Malignant neoplasm of cervix uteri
182.0  Malignant neoplasm of corpus uteri, except isthmus [recurrent, metastatic endometrial cancer in members who have progressed on prior cytotoxic chemotherapy]
183.0  Malignant neoplasm of ovary [epithelial]
183.2  Malignant neoplasm of fallopian tube
189.0  Malignant neoplasm of kidney, except pelvis [renal cell carcinoma]
191.0 - 191.9  Malignant neoplasm of brain
360.21  Progressive high (degenerative) myopia
362.07  Diabetic macular edema
362.13  Retinal vascular changes; changes in vascular appearance
362.14  Retinal microaneurysms NOS
362.16  Retinal neovascularization NOS
362.17  Other intraretinal microvascular abnormalities
362.18  Retinal vasculitis
362.20 - 362.29  Retinopathy of prematurity
362.35  Central retinal vein occlusion
362.36  Venous tributary(brand) occlusion
362.52  Exudative senile macular degeneration
362.70 - 362.77  Hereditary retinal dystrophies
363.00 - 363.08  Focal chorioretinitis and focal retinochoroiditis
363.10 - 363.15  Disseminated chorioretinitis and disseminated retinochoroiditis
363.20  Chorioretinitis, unspecified
363.43  Angioid streaks of choroid
363.50 - 363.57  Hereditary choroidal dystrophies
365.63  Glaucoma associated with vascular disorders
757.39  Other specified anomalies of skin [pseudoxanthoma elasticum]
V10.05  Personal history of malignant neoplasm of large intestine
V10.06  Personal history of malignant neoplasm of rectum, rectosigmoid junction, and anus
V10.3  Personal history of malignant neoplasm of breast
V10.43 Personal history of malignant neoplasm of ovary [epithelial]
V10.52 Personal history of malignant neoplasm of kidney [renal cell]

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

017.30  Tuberculosis of eye
078.5  Cytomegalovirus disease (retinitis)
091.51  Syphilitic chorioretinitis (secondary)
130.2  Chorioretinitis due to toxoplasmosis
140.0 - 151.9, Malignant neoplasms [except those specifically listed as covered]
155.0 - 157.9,
159.1 - 162.0,
163.0 - 170.9,
172.0 - 173.9,
176.0 - 179,
181, 182.1 -
182.8, 183.3 -
188.9, 189.2 -
190.5, 190.7 -
190.9, 192.0 -
209.79
212.1  Benign neoplasm of larynx [laryngeal papillomatosis]
215.5  Other benign neoplasm of connective and soft tissue of abdomen [stromal tumor]
225.1  Benign neoplasm of cranial nerves [acoustic neuroma]
225.2  Benign neoplasm of meninges [meningioma]
237.70 - 237.72 Neurofibromatosis
238.1  Neoplasm of uncertain behavior of connective and soft tissue [gastrointestinal stromal tumors]
239.2  Neoplasm of unspecified nature of bone, soft tissue, and skin [desmoid tumor]
277.87 Disorders of mitochondrial metabolism [NARP syndrome]
348.5  Cerebral edema [radiation-induced]
360.00 - 360.21 Disorders of globe
360.23 - 360.9  Other disorders of globe
361.00 - 361.9  Retinal detachments and defects
362.01 - 362.06 Diabetic retinopathy
362.11 - 362.12 Hypertensive and exudative retinopathy [Coat's disease]
362.15 Retinal telangiectasia
362.37 - 362.43 Venous engorgement and separation of retinal layers
362.50 - 362.51 Degeneration of macula and posterior pole other than exudative
362.53, 362.66 senile macular degeneration and peripheral retinal degenerations.
362.81 - 362.9 Other retinal disorders
363.21 - 363.42 Pars planitis, Harada's disease, chorioretinal scars and
degenerations except angioid streaks
363.61 - 363.9 Choroidal hemorrhage, detachment, and other disorders
365.00 - 365.62 Glaucoma
365.64 - 365.9

448.0 Hereditary hemorrhagic telangiectasia
630 Hydatidiform mole
759.6 Other hamartoses, not elsewhere classified [von Hippel Lindau
disease]
990 Effects of radiation, unspecified [radiation necrosis]

ICD-9 codes related to the CPB:
V58.11 - Encounter for antineoplastic chemotherapy and immunotherapy
V58.12

The above policy is based on the following references:

1. Figg WD, Kruger EA, Price DK, et al. Inhibition of angiogenesis: Treatment options
2. Ferrara N. Role of vascular endothelial growth factor in physiologic and pathologic
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4. Fernando NH, Hurwitz HI. Inhibition of vascular endothelial growth factor in the
5. Coutinho AK, Rocha Lima CM. Metastatic colorectal cancer: Systemic treatment in
7. O'Neil BH, Goldberg RM. Novel chemotherapeutic and targeted agents in
   metastatic colorectal cancer: The time has arrived. Expert Opin Investig Drugs.


98. Soheilian M, Ramezani A, Obudi A, et al. Randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular...


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