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Bevacizumab for Non-Ocular Indications

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

Number: 0685

Policy

Note: REQUIRES PRECERTIFICATION

Precertification of bevacizumab (Avastin), bevacizumab-awwb (Mvasi), and bevacizumab-bvzr (Zirabev) is required of all Aetna participating providers and members in applicable plan designs. For precertification, call (866) 752-7021 (Commercial), (866) 503-0857 (Medicare), or fax (866) 267-3277.

Aetna considers bevacizumab (Avastin), bevacizumab – awwb (Mvasi), and bevacizumab-bvzr (Zirabev) medically necessary for the following non-ocular indications:

- AIDS-related Kaposi's sarcoma
- Angiosarcoma - single agent therapy
- Breast cancer
- Central Nervous System cancers (including low-grade infiltrative supratentorial astrocytoma/oligodendroglioma, anaplastic gliomas, glioblastoma, intracranial and spinal ependymoma [excludes subependymoma],medulloblastoma, primary CNS

Policy History

Last Review

07/01/2020

Effective: 05/14/2004

Next Review: 02/11/2021

Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes

lymphoma, meningioma, brain metastases, leptomeningeal metastases, and metastatic spine tumors)
- Cervical cancer - for persistent, recurrent, or metastatic disease
- Colorectal cancer, including small bowel adenocarcinoma, appendiceal carcinoma, and anal adenocarcinoma
- Epithelial Ovarian cancer/Fallopian tube cancer/Primary peritoneal cancer:

    - Epithelial ovarian cancer, including:

        - Carcinosarcoma (malignant mixed Müllerian tumors)
        - Clear cell carcinoma
        - Mucinous carcinoma
        - Grade 1 endometrioid carcinoma
        - Low-grade serous carcinoma
        - Borderline epithelial tumors (low malignant potential) with invasive implants
        - Malignant sex cord-stromal tumors

    - Fallopian tube cancer
    - Primary peritoneal cancer

- Hepatocellular carcinoma, in combination with atezolizumab.
- Malignant pleural mesothelioma - in combination with pemetrexed and either cisplatin or carboplatin, followed by single-agent maintenance therapy
- Non-small cell lung cancer - for recurrent, advanced, or metastatic non-squamous disease
- Kidney cancer (renal cell carcinoma)- for relapse or metastatic disease
- Peritoneal mesothelioma
- Pericardial mesothelioma
- Solitary fibrous tumors or hemangiopericytoma - in combination with temozolomide
- Tunica vaginalis testis mesothelioma
- Uterine or Endometrial cancer - for progressive, advanced, or recurrent disease
- Vaginal cancer - for persistent, recurrent, or metastatic disease

- Vulvar cancer - for unresectable locally advanced, recurrent, or metastatic disesase
- 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 (../700_799/0701.html)

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Aetna considers continued therapy with bevacizumab (Avastin), bevacizumab – awwb (Mvasi), and bevacizumab-bvzr (Zirabev) medically necessary for members who are experiencing a clinical benefit to therapy or who have not experienced an unacceptable toxicity.

Aetna considers bevacizumab (Avastin), bevacizumab – awwb (Mvasi), and bevacizumab-bvzr (Zirabev) experimental and investigational for the treatment of the following non-ocular indications (not an all-inclusive list) as its effectiveness for these indications has not been established.

- Acoustic neuroma
- Adrenocortical carcinoma
- Apocrine adenocarcinoma
- Bladder cancer
- Brain arterio-venous malformations (AVMs)
- Cancer of unknown origin (primary occult)
- Carcinoid tumors
- Cholangiocarcinoma
- Coat's disease
- Desmoid tumor (e.g., fibromatosis and fibrosarcoma)
- Desmoplastic small round blue cell tumor
- Diffuse leptomeningeal glio-neuronal tumor
- Esophageal cancer
- Gallbladder cancer
- Gastric cancer
- Gastroesopheal junction adenocarcinoma
- Gastrointestinal stromal tumors
- Hemangioblastoma (including retinal capillary hemangioblastoma)
- Hereditary hemorrhagic telangiectasia (HHT) and HHT-related epistaxis
- Hydatidiform mole

- Islet cell cancer
- Laryngeal papillomatosis
- Melanoma
- Meningeal melanoma metastases
- Mucoepidermoid carcinoma of the salivary gland
- Multiple myeloma
- Neuroendocrine tumors
- Neurofibromatosis
- Olfactory neuroblastoma (esthesioneuroblastoma)
- Pancreatic cancer
- Pelvic bone cancer
- Pineal gland malignancy
- Prostate cancer
- Pseudomyxoma peritonei
- Radiation-induced myelopathy
- Sarcomas (e.g., Ewing sarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, and osteosarcoma) other than AIDS-related Kaposi's sarcoma, angiosarcoma, solitary fibrous tumors, and hemangiopericytoma
- Squamous cell carcinoma of the head and neck
- Small cell carcinoma of the lung
- Squamous cell carcinoma of the lung
- Urachal carcinoma
- Urothelial carcinoma
- Vogt-Koyanagi-Harada syndrome
- von Hippel Lindau disease.

Aetna considers bevacizumab in combination with cetuximab (Erbitux) or panitumumab (Vectibix) experimental and investigational because the effectiveness and safety of these combinations has not been established.

For bevacizumab for ocular indications, see CPB 0701 - Vascular Endothelial Growth Factor Inhibitors for Ocular Indications (../700_799/0701.html)

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See also CPB 0371 - Brachytherapy (../300_399/0371.html), CPB 0375 - Photodynamic Therapy (../300_399/0375.html),

CPB 0516 - Colorectal Cancer Screening, (../500_599/0516.html)
CPB 0535 - Virtual Gastrointestinal Endoscopy (../500_599/0535.html),
CPB 0683 - Oxaliplatin (Eloxatin) (0683.html), and
CPB 0684 - Cetuximab (Erbitux) (0684.html).

Dosing Recommendations

Avastin

Bevacizumab is available as Avastin in an Intravenous Solution: 25 MG/ML (100mg and 400mg vials).

Metastatic colorectal cancer is:

- 5 mg/kg IV every 2 weeks with bolus-IFL
- 10 mg/kg IV every 2 weeks with FOLFOX4
- 5 mg/kg IV every 2 weeks or 7.5 mg/kg IV every 3 weeks with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy after progression on a first-line Avastin containing regimen.

Non-squamous non-small cell lung cancer: 15 mg/kg IV every 3 weeks with carboplatin/paclitaxel.

Glioblastoma: is 10 mg/kg IV every 2 weeks.

Metastatic renal cell carcinoma (mRCC): 10 mg/kg IV every 2 weeks with interferon alfa.

Persistent, recurrent, or metastatic cervical cancer: 15 mg/kg IV every 3 weeks with paclitaxel/cisplatin or paclitaxel/topotecan.

Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer:

- 10 mg/kg IV every 2 weeks with paclitaxel, pegylated liposomal doxorubicin or weekly topotecan

- 15 mg/kg IV every 3 weeks with topotecan given every 3 weeks.

Stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer following initial surgical resection: 15 mg/kg every 3 weeks with carboplatin and paclitaxel for up to 6 cycles, followed by 15 mg/kg every 3 weeks as a single agent, for a total of up to 22 cycles

Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer:

- 15 mg/kg every 3 weeks with carboplatin and paclitaxel for 6-8 cycles, followed by 15 mg/kg every 3 weeks as a single agent
- 15 mg/kg every 3 weeks with carboplatin and gemcitabine for 6-10 cycles, followed by 15 mg/kg every 3 weeks as a single agent

Administer as an intravenous infusion

Please consult the Full Prescribing Information for complete details for recommended dose adjustments

Source: Genentech, 2019

Mvasi and Zirabev

Bevacizumab is available as Mvasi or as Zirabev as single-dose vials in the following strengths: 100 mg/4 mL and 400 mg/16 mL. Do not administer MVASI for 28 days following major surgery and until surgical wound is fully healed.

Metastatic colorectal cancer

- 5 mg/kg every 2 weeks with bolus-IFL
- 10 mg/kg every 2 weeks with FOLFOX4
- 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy after progression on a first-line bevacizumab product-containing regimen

First-line non-squamous non-small cell lung cancer

- 15 mg/kg every 3 weeks with carboplatin and paclitaxel

Recurrent glioblastoma

- 10 mg/kg every 2 weeks

Metastatic renal cell carcinoma

- 10 mg/kg every 2 weeks with interferon-alfa

Persistent, recurrent, or metastatic cervical cancer

- 15 mg/kg every 3 weeks with paclitaxel and cisplatin or paclitaxel and topotecan

Administer as an intravenous infusion

Please consult the Full Prescribing Information for complete details for recommended dose adjustments.

Source: Amgen, Inc., 2019; Pfizer Inc., 2019.

Background

Avastin (bevacizumab) is a recombinant humanized monoclonal IgG1 antibody. Bevacizumab binds to vascular endothelial growth factor (VEGF) and inhibits the interaction of VEGF to Flt1 and KDR receptors on the surface of endothelial cells. In the process, it prevents the proliferation of endothelial cells and formation of new blood vessels. Vascular endothelial growth factor (VEGF) is an important signaling protein involved in angiogenesis (the growth of blood vessels from pre-existing vasculature). As its name implies, VEGF activity has been mostly studied on cells of the vascular endothelium, although it does have effects on a number of other cell types (e.g. stimulation monocyte/macrophage migration, neurons, cancer cells, kidney epithelial cells).

Avastin (bevacizumab) has been approved by the U.S. Food and Drug Administration (FDA) for: (i) metastatic colorectal cancer in combination with 5-fluorouracil-based chemotherapy as first-line or second-line therapy, or in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy as second-line therapy in patients who have progressed on a first-line bevacizumab-containing regimen; (ii) non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease; (iii) glioblastoma, as a single agent for patients with progressive disease following prior therapy (Effectiveness based on improvement in objective response rate. No data available demonstrating improvement in disease-related symptoms or survival with bevacizumab); (iv) metastatic renal cell carcinoma, in combination with interferon alfa; (v) cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease; and (vi) platinum-resistant recurrent epithelial ovarian cancer, fallopian tube or primary peritoneal cancer, (a) in combination with carboplatin and paclitaxel, followed by bevacizumab as a single agent, for stage III or IV disease following initial surgical resection (b) in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens (c) in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by bevacizumab as a single agent, for platinum-sensitive recurrent disease. On September 14, 2017, the U.S. Food and Drug Administration (FDA) approved Mvasi (bevacizumab-awwb), a biosimilar to Avastin (bevacizumab). Mvasi is the first oncology therapeutic biosimilar approved by the U.S. Food and Drug Administration (FDA). Mvasi is a recombinant humanized monoclonal IgG1 antibody that binds vascular endothelial growth factor (VEGF) and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease

progression. Mvasi was proven to be highly similar to, and to have no clinically meaningful differences in terms of safety and effectiveness from Avastin, based on a totality of evidence, which included comparative analytical, clinical safety and efficacy data.

Subsequently, on June 28, 2019, the FDA approved Zirabev (bevacizumab-bvzr), another biosimilar to Avastin (bevacizumab), for the treatment of five types of cancer: metastatic colorectal cancer; unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer (NSCLC); recurrent glioblastoma; metastatic renal cell carcinoma (RCC); and persistent, recurrent or metastatic cervical cancer. Like Mvasi, Zirabev is also a recombinant humanized monoclonal IgG1 antibody VEGF inhibitor. The FDA approval was based on review of a comprehensive data package which demonstrated biosimilarity of Zirabev to the reference product. This includes results from the REFLECTIONS B7391003 clinical comparative study, which showed clinical equivalence and found no clinically meaningful differences between Zirabev and the reference product in patients with advanced non-squamous NSCLC.

Mvasi and Zirabev are indicated for the following:

- Metastatic colorectal cancer, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment;
- Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab product-containing regimen;

    - Mvasi and Zirabev are not indicated for adjuvant treatment of colon cancer;

- Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment;
- Recurrent glioblastoma in adults;
- Metastatic renal cell carcinoma in combination with interferon alfa;

- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan.

Warnings

- *Gastrointestinal perforations:* Serious, and sometimes fatal, gastrointestinal perforation occurred at a higher incidence in patients receiving bevacizumab compared to patients receiving chemotherapy. The incidence ranged from 0.3% to 3% across clinical studies, with the highest incidence in patients with a history of prior pelvic radiation. Perforation can be complicated by intra-abdominal abscess, fistula formation, and the need for diverting ostomies. The majority of perforations occurred within 50 days of the first dose.

  Serious fistulae (including, tracheoesophageal, bronchopleural, biliary, vaginal, renal and bladder sites) occurred at a higher incidence in patients receiving bevacizumab compared to patients receiving chemotherapy. The incidence ranged from < 1% to 1.8% across clinical studies, with the highest incidence in patients with cervical cancer. The majority of fistulae occurred within 6 months of the first dose. Patients who develop a gastrointestinal vaginal fistula may also have a bowel obstruction and require surgical intervention, as well as a diverting ostomy.

  Avoid bevacizumab in patients with ovarian cancer who have evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction. Discontinue in patients who develop gastrointestinal perforation, tracheoesophageal fistula or any Grade 4 fistula. Discontinue in patients with fistula formation involving any internal organ.

- *Wound Healing Complications:* Bevacizumab administration can result in the development of wound dehiscence, in some instances resulting in fatality. Bevacizumab therapy should be permanently discontinued in patients with wound healing complications requiring medical intervention. Bevacizumab should be discontinued at least 28 days prior to elective surgery. Do not

administer for at least 28 days following surgery and until the wound is fully healed.
Necrotizing fasciitis including fatal cases, has been reported in patients receiving Avastin, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Discontinue Avastin in patients who develop necrotizing fasciitis.

- *Hemorrhage:* Fatal pulmonary hemorrhage can occur in patients with NSCLC treated with chemotherapy and bevacizumab. The incidence of severe or fatal hemoptysis was 31% in patients with squamous histology and 4% in patients with NSCLC excluding predominant squamous histology. Patients with recent hemoptysis (1/2 teaspoonful or more of red blood) should not receive bevacizumab. Discontinue in patients who develop a Grades 3-4 hemorrhage.

- *Arterial Thromboembolic Events (ATE):* Discontinue for severe ATE.

- *Venous Thromboembolic Events (VTE):* Discontinue for Grade 4 VTE.

- *Hypertension:* Monitor blood pressure and treat hypertension. Withhold if not medically controlled; resume once controlled. Discontinue for hypertensive crisis or hypertensive encephalopathy.

- *Posterior Reversible Encephalopathy Syndrome (PRES):* Discontinue.

- *Renal Injury and Proteinuria:* Monitor urine protein. Discontinue for nephrotic syndrome. Withhold until less than 2 grams of protein in urine.

- *Infusion-Related Reactions:* Decrease rate for infusion-related reactions. Discontinue for severe infusion-related reactions and administer medical therapy.

- *Embryo-Fetal Toxicity:* May cause fetal harm. Advise females of potential risk to fetus and need for use of effective contraception.

- *Ovarian Failure:* Advise females of the potential risk.

- *Congestive Heart Failure (CHF):* Discontinue Avastin in patients who develop CHF.

Risk versus benefit must be discussed with patients that are pregnant or breast feeding.

Colorectal Cancer

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 cross-over, 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 endpoint was progression-free survival (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 pre-clinical 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 mitomicin 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). 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.

Non-Small Cell Lung Cancer

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 in 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.

Zhang and associates (2016) stated that bevacizumab and erlotinib inhibit different tumor growth pathways, and both exhibit beneficial effects in the treatment of NSCLC. However, the efficacy of bevacizumab in

combination with erlotinib remains controversial. These researchers carried out a meta-analysis to compare combination treatment with bevacizumab and erlotinib to bevacizumab or erlotinib monotherapy in the treatment of NSCLC; RCTs published in PubMed, Web of Science and EMBASE were systematically reviewed. The main outcome measures included OS, PFS, overall response rate (ORR) and adverse events (AEs). Results were expressed as HRs or RRs with 95 % CIs. A total of 5 RCTs involving a total of 1,736 patients were included in this meta-analysis. The combination of bevacizumab and erlotinib significantly improved PFS (HR = 0.63, 95 % CI: 0.53 to 0.75; p = 0.000) and the ORR (RR = 1.91, 95 % CI: 1.19 to 3.06; p = 0.007) in the 2nd-line treatment of NSCLC compared with bevacizumab or erlotinib alone. However, no significant difference in OS was observed between the combination and monotherapy groups (HR = 0.96, 95 % CI: 0.83 to 1.11; p = 0.573). A subgroup analysis has shown that the greatest PFS benefit was associated with an age of less than 65 years (HR = 0.74, 95 % CI: 0.57 to 0.96; p = 0.026), Asian/Pacific Islander ethnicity (HR = 0.23, 95 % CI: 0.10 to 0.54; p = 0.001), Eastern Cooperative Oncology Group performance status (ECOG PS) 1 (HR = 0.82, 95 % CI: 0.68 to 0.98; p = 0.033), stage IIIB or IV disease (HR = 0.68, 95 % CI: 0.57 to 0.82; p = 0.000) and no history of smoking (HR = 0.48, 95 % CI: 0.32 to 0.71; p = 0.000). The incidence of grade 3/4 AEs such as rash and diarrhea was higher in the combination group than in the monotherapy group. The authors concluded that the addition of bevacizumab to erlotinib can significantly improve PFS and the ORR in the 2nd-line treatment of NSCLC with an acceptable and manageable risk of rash and diarrhea. Moreover, these researchers stated that further well-conducted, large-scale trials are needed to verify their findings and examine the efficacy of the combined therapy in patients with non-squamous NSCLC with EGFR mutations.

The authors stated that this meta-analysis had several drawbacks. First, this study included only 5 RCTs, and some of these trials had relatively small sample sizes. Although all of these studies were high-quality, well-performed trials, the conclusions of this meta-analysis should be interpreted with caution because smaller trials were more likely to result in over-estimation of the treatment effect than larger trials. Second, the examination of the effect of Bev in combination with Erl in patients with NSCLC with EGFR mutations was insufficient because of sparse

reporting among the included studies. Finally, it should be noted that all of these trials were partly funded by the pharmaceutical industry, and their results might have been affected by the inherent conflict of interest and possible bias. However, these trials were all high-quality studies that were conducted well, and they were the only eligible studies that evaluated the efficacy of the combination treatment.

Zhao and colleagues (2018) noted that a role for erlotinib and bevacizumab as single agents has been established in the treatment of NSCLC. However, the safety and efficacy of erlotinib in combination with bevacizumab compared with single agents remain unclear. In a meta-analysis, these investigators examined the status of this combined strategy in NSCLC. They systematically searched relevant databases for RCTs on the use of erlotinib plus bevacizumab in NSCLC. The main outcomes analysis reported OS, PFS, ORR, and AEs. Random-effects models were used to estimate pooled HR and RR. A total of 10 studies with 2,802 participants were eligible for meta-analysis, the results of which suggested that erlotinib plus bevacizumab failed to significantly enhance either OS (95 % CI: 0.87 to 1.12; p = 0.825) or ORR (95 % CI: 0.69 to 1.67; p = 0.758). Although PFS was modestly improved, there was no statistical significance (5.55 months versus 4.67 months, 95 % CI: 0.63 to 1.15; p = 0.297). Incidence of rash or diarrhea was higher in the combination group than in the single-agent group. Subgroup analysis showed encouraging OS (95 % CI: 0.29 to 0.69; p < 0.001) in EGFR-mutant patients treated with combination therapy, no such benefits were found in groups restricting on KRAS status. The authors concluded that erlotinib plus bevacizumab enhanced OS for EGFR-mutant patients, with rash and diarrhea common but acceptable adverse effects; combination treatment can be recommended as the preferable option for EGFR-mutant patients. Moreover, these researchers stated that further large-scale, well-designed RCTs are needed to confirm their validation.

In a systematic review and meta-analysis, Shan and colleagues (2018) examined the effect of combination maintenance therapy of pemetrexed plus bevacizumab for patients with advanced NSCLC. These researchers identified relevant studies by electronic search (Embase, PubMed, Cochrane, and Web of Science from January 1, 1960 to October 29, 2016) and manual search. The primary outcome of interest was PFS and secondary end-point included OS and toxicities. Data were

pooled for quantitative analysis and the final effect size was reported as HR for survival outcomes and RR for safety outcomes, both with a random-effects model. A total of 3 RCTs enrolling 1,302 patients with advanced NSCLC were included in this meta-analysis. An evident PFS improvement (HR = 0.73, 95 % CI: 0.63 to 0.83, p < 0.01) was observed in patients with pemetrexed and bevacizumab combination maintenance therapy compared with single-agent maintenance therapy, yet it did not subsequently lead to a significant improvement in OS (HR = 0.97, 95 % CI: 0.84 to 1.10, p = 0.66). This analysis also showed statistically increased risks for provoking grade 3 to 4 AEs in patients managed using pemetrexed plus bevacizumab combination (RR = 1.59, 95 % CI: 1.07 to 2.36, p = 0.022). The authors concluded that pemetrexed plus bevacizumab combination maintenance therapy led to significant improvement in PFS but not in OS for patients with advanced NSCLC, which also increased the risks of grade 3 to 4 AE. These researchers stated that because of the limitation of existing studies and this meta-analysis, there is insufficient evidence to support routine use of pemetrexed-bevacizumab combination as maintenance therapy.

The authors stated that this study had several drawbacks. First, the data extracted were merely from previous publication, whereas original data and individual patient data were unavailable, which make these researchers unable to perform more detailed analysis and obtain more comprehensive results. Second, this analysis was limited by substantial heterogeneity across included trials, which was possibly attributed to the variation in trial design, inclusion and exclusion criteria, and treatment regimen involving induction modalities and agents' dosage. Third, even though most of the included trials were published in journals with high impact factor, open-label design and pharmaceutical industry funding as potential risks of bias still exist. Finally, this meta-analysis was limited by lack of available studies. Thus, these results should be interpreted with caution.

Renal Cell Carcinoma

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 can not 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.

Breast Cancer

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 human epidermal growth factor receptor 2 (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).

In a multi-center, randomized, open-label, phase III clinical trial, Martin et al (2015) examined if combining bevacizumab with endocrine therapy (ET) could potentially delay the emergence of resistance to ET in patients with breast cancer. This bi-national (Spain and Germany) study added bevacizumab (15 mg/kg every 3 weeks) to ET (ET-B; letrozole or fulvestrant) as first-line therapy in post-menopausal patients with HER2-negative and hormone receptor-positive advanced breast cancer. These researchers compared PFS, OS, ORR, response duration (RD), time to treatment failure (TTF), clinical benefit rate (CBR), and safety. From 380 patients recruited (2007 to 2011), 374 were analyzed by intent to-treat (184 patients on ET and 190 patients on ET-B). Median age was 65 years, 270 patients (72 %) had ECOG performance status of 0, 178 patients (48 %) had visceral metastases, and 171 patients (46 %) and 195 patients (52 %) had received prior chemotherapy or ET, respectively. Median PFS was 14.4 months in the ET arm and 19.3 months in the ET-B arm (HR, 0.83; 95 % CI: 0.65 to 1.06; p = 0.126); ORR, CBR, and RD with ET versus ET-B were 22 % versus 41 % (p < 0.001), 67 % versus 77 % (p = 0.041), and 13.3 months versus 17.6 months (p = 0.434), respectively; TTF and OS were comparable in both arms. Grade 3 to 4 hypertension, aminotransferase elevation, and proteinuria were significantly higher in the ET-B arm; 8 patients (4.2 %) receiving ET-B died during study or within 30 days of end of treatment. The authors concluded that the addition of bevacizumab to ET in first-line treatment failed to produce a statistically significant increase in PFS or OS in

women with HER2-negative/hormone receptor-positive advanced breast cancer. They stated that ET-B should not be recommended in the treatment of advanced hormone receptor-positive/HER2-negative breast cancer.

Epithelial Ovarian Cancer and Primary Peritoneal Cancer

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).

Gliomas

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.

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, thrombo-embolic 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.

Mansour et al (2014) stated that glioblastoma multiforme (GBM) is the most aggressive subtype of malignant gliomas. Current standard treatment for GBM involves a combination of cyto-reduction through surgical resection, followed by radiation with concomitant and adjuvant chemotherapy (temozolomide). Despite aggressive treatment, these

tumors remain undoubtedly fatal, especially in the elderly. Furthermore, tumors present in the pineal gland are extremely rare, accounting for only 0.1 to 0.4 % of all adult brain tumors, with this location adding to the complexity of treatment. These researchers presented a case of GBM, at the rare location of pineal gland, in an elderly patient who was refractory to initial standard of care treatment with radiation and concomitant and adjuvant temozolomide, but who developed a significant response to anti-angiogenic therapy using bevacizumab.

Pineal Gland Malignancy

An UpToDate review on "Pineal gland masses" (Moschovi and Chrousos, 2015) does not mention bevacizumab as a therapeutic option. Furthermore, according to National Comprehensive Cancer Network's Drugs & Biologics Compendium (2015), pineal gland tumor is not a recommended indication of bevacizumab.

Cervical Cancer

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.

Ependymomas

Guidelines from the NCCN (2010) indicated bevacizumab as a single agent for disease progression after radiation therapy for spine or brain ependymoma recurrence.

Pancreatic Cancer

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.

Gastric Cancer

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.

Cancer of Unknown Primary

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 subset 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.

Endometrial Cancer

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.

Hepatocellular Carcinoma

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.

Neurofibromatosis

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 shrank 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.

Plotkin and colleagues (2019) stated that bevacizumab treatment at 7.5 mg/kg every 3 weeks resulted in improved hearing in approximately 35 % to 40 % of patients with neurofibromatosis type 2 (NF2) and progressive vestibular schwannomas (VSs). However, the optimal dose is unknown. In a multi-center, phase-II clinical trial, these researchers examined the safety and efficacy of high-dose bevacizumab in pediatric and adult patients with NF2 with progressive VS. Bevacizumab was given for 6 months at 10 mg/kg every 2 weeks, followed by 18 months at 5 mg/kg every 3 weeks. The primary end-point was hearing response defined by word recognition score (WRS) at 6 months. Secondary end-points included toxicity, radiographic response, QOL, and plasma biomarkers. A total of 22 subjects with NF2 (median age of 23 years) with progressive hearing loss in the target ear (median baseline WRS, 53 %) were enrolled; 9 (41 %) of 22 subjects achieved a hearing response at 6 months (1 of 7 children and 8 of 15 adults; p = 0.08). Radiographic

response was observed in 7 (32 %) of 22 patients with VS at 6 months (7 of 15 adults and 0 of 7 children; p = 0.05). Common mild-to-moderate AEs included hypertension, fatigue, headache, and irregular menstruation. Improvement in NF2-related QOL and reduction in tinnitus-related distress were reported in 30 % and 60 % of subject, respectively. Paradoxically, high-dose bevacizumab treatment was not associated with a significant decrease in free VEGF but was associated with increased carbonic anhydrase IX, hepatocyte growth factor, placental growth factor, stromal cell-derived factor 1α, and basic fibroblast growth factor concentrations in plasma. The authors concluded that high-dose bevacizumab appeared to be no more effective than standard-dose bevacizumab for treatment of patients with NF2 with hearing loss. In contrast to adults, pediatric subjects did not experience tumor shrinkage. However, adult and pediatric subjects reported similar improvement in QOL during induction. These researchers stated that novel approaches using bevacizumab should be considered for children with NF2.

Adrenocortical Carcinoma

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/m(2) 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 can not be recommended as a salvage therapy.

Respiratory Papillomatosis

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.

Melanoma

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.

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.

Neuroendocrine Tumors

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 multi-center, phase II trial, Hobday and colleagues (2015) evaluated the effectiveness of combination therapy of temsirolimus and bevacizumab in patients with pancreatic neuroendocrine tumors (PNET). These investigators conducted a 2-stage single-arm phase II trial of the mammalian target of rapamycin (mTOR) inhibitor temsirolimus 25 mg intravenously (IV) once-weekly and bevacizumab 10 mg/kg IV once every 2 weeks in patients with well or moderately differentiated PNETs and progressive disease by Response Evaluation Criteria in Solid Tumors (RECIST) within 7 months of study entry. Co-primary end-points were tumor response rate and 6-month PFS. A total of 58 patients were enrolled, and 56 patients were eligible for response assessment. Confirmed response rate (RR) was 41 % (23 of 56 patients); PFS at 6 months was 79 % (44 of 56). Median PFS was 13.2 months (95 % CI: 11.2 to 16.6). Median OS was 34 months (95 % CI: 27.1 to "not reached"). For evaluable patients, the most common grade 3 to 4 AEs attributed to therapy were hypertension (21 %), fatigue (16 %), lymphopenia (14 %), and hyperglycemia (14 %). The authors concluded that the combination of temsirolimus and bevacizumab had substantial activity and reasonable tolerability in a multi-center phase II trial, with RR of 41 %, well in excess of single targeted agents in patients with progressive PNETs. Six-month PFS was a notable 79 % in a population of patients with disease progression by RECIST criteria within 7 months of study entry. They stated that on the basis of this trial, continued evaluation of combination mTOR and VEGF pathway inhibitors is warranted.

Head and Neck Cancer

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/m(2) 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.

Hereditary Hemorrhagic Telangiectasia (HHT) / HHT-Related Epistaxis

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/m(2) (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 mal-formations 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.

Stokes and Rimmer (2018) performed a systematic review of the efficacy of bevacizumab in local treatment of epistaxis in patients with HHT based on epistaxis duration, frequency, severity and impact on QOL. A systematic search was performed using the PubMed, Medline and Embase databases. The Preferred Items for Systematic Reviews and Meta-Analyses guidelines were followed. Studies that measured the efficacy of intranasal bevacizumab treatment of epistaxis in patients with HHT were included for qualitative analysis. A total of 13 studies (4 RCTs, 3 prospective studies, 3 retrospective studies, 1 case-series study and 2 case reports) with a total of 357 patients were included. Local administration (either by submucosal injection or topically) did not have a significant impact on epistaxis duration, frequency, severity or QOL

compared to placebo or other local treatments. The authors concluded that the available evidence suggested that intra-nasal bevacizumab treatment did not have a significant effect on epistaxis in patients with HHT. There are several limitations that require further investigation to confidently rule out local bevacizumab as an effective therapy in HHT related epistaxis.

Halderman and colleagues (2018) stated that bevacizumab has been used in several forms to treat epistaxis in HHT; however thus far, evidence-based recommendations are limited. These investigators performed a systematic review with evidence-based recommendations. A systematic review of the literature following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines was performed using Embase, Medline, Medline In-Process/Epub, and Cochrane databases. English language abstracts were reviewed for relevance. Results Eleven manuscripts met inclusion criteria and were analyzed. Submucosal injection, submucosal injection plus laser coagulation, intravenous (IV), and topical formulations of bevacizumab were evaluated for their therapeutic impact on epistaxis in patients with HHT. A total of 3 RCTs failed to show topical bevacizumab to be more effective in controlling epistaxis than saline or other moisturizers. The authors concluded that the use of submucosal and IV bevacizumab shows promise, but further study is needed to determine the true efficacy in the treatment of epistaxis as only grade C level of evidence exists currently. Based on the available literature, the use of topical bevacizumab is not recommended (grade B).

Guilhem et al (2017) noted that bevacizumab has recently emerged as a new option for severe forms of hereditary hemorrhagic telangiectasia (HHT). Its utilization in this orphan disease has rapidly spread despite the lack of randomized trials and international guidelines. These researchers reported the main clinical data (baseline characteristics, dose schedule, efficacy, adverse events [AEs] and deaths) of HHT patients treated by intravenous (IV) bevacizumab in France. This was a retrospective, observational study of HHT patients treated with bevacizumab for a severe form of the disease in the 14 centers of the French HHT network. A total of 46 patients (median age of 68 years) were treated between March 2009 and May 2015; 10 patients were treated for high-output cardiac failure, 20 patients for severe hemorrhages, and 16 for both indications. The standard protocol (6 infusions of 5 mg/kg every 2 weeks)

was initially used in 89 % of the cases; but diverse strategies were subsequently applied. A clinical improvement was noted by the referent physician for 74 % of the patients with a median effect's duration of 6 months. Wound healing complications led to 2 amputations. Arthralgia/arthritis and arterial hypertension occurred in 5 patients each; 1/3 of the patients were dead at the time of the final update, coherently with age and the poor prognosis of these highly symptomatic patients. The authors concluded that IV bevacizumab appeared to provide a clinical benefice in severe HHT patients. Moreover, they stated that precautions concerning wound healing and vascular pathologies must be respected; prospective, double-blinded versus placebo trials are needed.

The authors stated that this study suffered from drawbacks inherent to its retrospective, non-interventional and open design. The retrospective data collection and the diversity of participating centers did not allowed these investigators to obtain standardized objective parameters for the efficacy assessment. Nevertheless, they thought that these data honestly reflected the daily practice and provided valuable information to apprehend the risk/benefit ratio of this new drug. It constituted a preliminary step to conducting a large, prospective, and randomized versus placebo trial, which is deeply needed. The lack of consensual modalities of bevacizumab use, especially for long-term treatments, was another concern. It has generated a high level of heterogeneity in these researchers' data. Most of physicians had initially followed the "standard protocol" of 6 injections of 5 mg/kg, by analogy with the oncological use and the prospective trial. Other protocols with lower doses had also been proposed and could be more appropriate in some cases, notably for frail patients. Concerning the subsequent treatment (maintenance or re-treatment), a pharmacological study based on a mathematical model suggested a systematic monthly injection. A re-treatment strategy individually adapted to the clinical needs has been applied for 24 % of the cohort. This strategy could be pertinent but requires to be sustained by further clinical and biopharmaceutical investigations.

Iyer et al (2018) presented a multi-year clinical experience with IV bevacizumab for the management of severe gastro-intestinal (GI) bleeding and/or epistaxis in patients with HHT. All patients treated with IV bevacizumab for severe HHT-related bleeding from June 1, 2013, through January 31, 2017, were included in this report. Severity of epistaxis

(determined using the Epistaxis Severity Score questionnaire); hemoglobin (Hb), iron, and ferritin levels; and quality of life (QOL) data were collected serially in all patients. Intravenous bevacizumab was administered to 34 patients using a standardized treatment protocol. Anemia was primarily related to severe epistaxis (n = 15, 44 %), severe GI bleeding (n = 4, 12 %), or both (n = 15, 44 %), with a median baseline Hb level of 9.1 g/dL (range of 8.3 to 10.5 gm/dL; to convert to mmol/L, multiply by 0.62). Red blood cell (RBC) transfusions had been administered to 28 patients (82 %). Of these, 16 patients (47 %) were RBC transfusion-dependent and had received a median of 75 RBC transfusions (range of 4 to greater than 500 RBC units) before initiation of bevacizumab. The median length of follow-up was 17.6 months from the beginning of bevacizumab treatment (range of 3 to 42.5 months). There was a significant reduction in epistaxis severity scores ($p < 0.001$) and RBC transfusion requirements ($p = 0.007$) after completion of the initial bevacizumab treatment cycle. New-onset or worsened hypertension was noted in 4 patients, with 1 patient experiencing hypertensive urgency with a temporary decline in renal function. The authors concluded that IV bevacizumab was an effective therapeutic option for patients with severe anemia related to epistaxis and/or GI bleeding. Moreover, these researchers stated that further studies are needed to establish a dose-response relationship as well as clinical, genetic, and biomarker predictors of response.

In what appeared to be an accompanying editorial, Gossage (2018) stated that "The study by Iyer et al is a semi-prospective study that finds a remarkable improvement in ESS score, quality of life, and transfusion need. Although one can attribute changes in ESS score or quality of life to the placebo effect, it is much harder to attribute so dramatic a change in transfusion need to placebo. It is still desirable to have a randomized placebo controlled trial. However, until we have those data in hand, I agree with Iyer et al that "systemic bevacizumab should be considered as a first-line therapy for the treatment of refractory bleeding in patients with HHT". At this point, the bulk of the literature suggests that the initial course of treatment should be 4 to 6 infusions of 5 mg/kg bevacizumab every 2 to 3 weeks. Some have reported success with doses as low as 0.125 mg/kg, but most of the literature and informal polling of North American HHT Center Directors (James R. Gossage, MD, oral communication, 2015-2017) favor a dose of 5 mg/kg for most patients. In

terms of maintenance therapy, the literature is less clear. Some have advocated a routine infusion every 1 to 6 months, whereas others have based additional infusions on recurrence of symptoms. Finally, although this therapy seems to be well tolerated by patients with HHT, serious adverse effects have been reported in patients with HHT, and therefore careful patient selection along with close monitoring of blood pressure, blood chemistry, and urine protein is advised".

Al-Samkari et al (2019) stated that HHT is a rare hereditary multi-system vascular disorder causing visceral arterio-venous malformations (AVMs) and mucocutaneous bleeding. Chronic GI bleeding and epistaxis often produce profound anemia refractory to conventional treatment. Bevacizumab may be effective in treatment of bleeding in HHT. All HHT patients treated with systemic bevacizumab for chronic bleeding were selected for retrospective analysis. Data collected included demographics, baseline HHT characteristics, epistaxis grade, surgical interventions, bevacizumab dosing, AEs, Hb, RBC transfusions, intravenous iron infusions, and other anemia and/or bleeding-directed therapies. A total of 13 HHT patients were treated with bevacizumab for a median of 13.9 (range of 4.9 to 30.1) months. Compared with pre-treatment values, bevacizumab treatment increased the mean Hb by 4.0 g/dL (95 % CI: 2.6 to 5.3 g/dL) [mean (95 % CI: hemoglobin 8.5 (7.8 to 9.9) g/dL versus 12.5 (11.2 to 13.7) g/dL, $p < 0.001$)], reduced RBC units transfused by 92 % [median of 6 (range of 0 to 59) units versus 0 (range of 0 to 15) units, $p = 0.004$], and reduced quantity of iron infused by 73 % [mean (95 % CI: 462 (257 to 668) mg/month versus 126 (75 to 178) mg/month, $p = 0.002$]. Epistaxis control was achieved in 85 % with bevacizumab, versus 0 % before treatment ($p < 0.001$). No patient required nasal or GI procedures during the maintenance period; 2 patients (15 %) developed grade 3 hypertension requiring medical management. The authors concluded that systemic bevacizumab was highly effective to treat chronic bleeding in HHT. Moreover, they stated that further study is needed to confirm the magnitude of benefit and further define optimal dosing, treatment duration, and long-term safety.

An UpToDate review on "Management of hereditary hemorrhagic telangiectasia" (Shovlin, 2019) states that "Epistaxis affects over 95 % of individuals with hereditary hemorrhagic telangiectasia (HHT). A number of topical, systemic, and surgical treatments are available. As a general

rule, we try to use local preventive therapies (e.g., nasal humidification, ointments) and other modifications such as dietary changes in order to avoid potential toxicities of systemic therapy; however, management is individualized. Some individuals with bleeding from localized vascular lesions may require subspecialist management, and some may require medical systemic therapies such as tamoxifen, tranexamic acid, or bevacizumab if epistaxis is recurrent or localized interventions are insufficient. Systemic agents should be used with caution if there is a propensity to venous or arterial thromboemboli … Hepatic AVMs are almost always asymptomatic. In our experience, a major risk is of misdiagnoses as metastases and clinician education is required. In less than 10 % of patients, symptoms may develop, attributable to portal hypertension, biliary disease, and/or high-output heart failure. For individuals with symptomatic liver involvement, treatment is generally supportive and directed at optimizing cardiac status and iron stores. If medical management fails, liver transplantation is the treatment of choice. The angiogenesis inhibitor bevacizumab may also be helpful, but data are too preliminary to support routine use in this setting".

Stokes and Rimmer (2018) HHT remains a difficult disease for the ear, nose, and throat (ENT) specialist to manage. Affected patients often report recurrent epistaxis as the most debilitating symptom. The pathogenesis of the disease is due to genetic mutations affecting angiogenesis. For this reason, the anti-angiogenic therapy bevacizumab has gained popularity in the local treatment of epistaxis in patients with HHT. These investigators carried out a systematic review of the efficacy of bevacizumab in local treatment of epistaxis in patients with HHT based on epistaxis duration, frequency, severity and impact on QOL. A systematic search was performed using the PubMed, Medline and Embase databases. The Preferred Items for Systematic Reviews and Meta-Analyses guidelines were followed. Studies that measured the efficacy of intra-nasal bevacizumab treatment of epistaxis in patients with HHT were included for qualitative analysis. A total of 13 studies (4 RCTs, 3 prospective studies, 3 retrospective studies, 1 case series and 2 case reports) with a total of 357 patients were included. Local administration (either by submucosal injection or topically) did not have a significant impact on epistaxis duration, frequency, severity or QOL compared to placebo or other local treatments. The authors concluded that available evidence suggested that intra-nasal bevacizumab treatment did not have

a significant effect on epistaxis in patients with HHT. These researchers noted that there were several limitations that need further investigation to confidently rule out local bevacizumab as an effective therapy in HHT-related epistaxis.

Halderman and co-workers (2018) stated that epistaxis is a primary complaint in 90 % to 96 % of patients with HHT. Numerous surgical and medical treatments aim to decrease the frequency and severity of epistaxis in this patient population. Bevacizumab has been used in several forms to treat epistaxis in HHT but thus far, evidence-based recommendations are limited. These investigators performed a systematic review of the literature following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines using Embase, Medline, Medline In-Process/Epub, and Cochrane databases. English language abstracts were reviewed for relevance. A total of 11 manuscripts met inclusion criteria and were analyzed. Submucosal injection, submucosal injection plus laser coagulation, intravenous (IV), and topical formulations of bevacizumab were evaluated for their therapeutic impact on epistaxis in patients with HHT; 3 RCTs failed to show topical bevacizumab to be more effective in controlling epistaxis than saline or other moisturizers. The authors concluded that the use of submucosal and IV bevacizumab showed promise, however, further study is needed to determine the true efficacy in the treatment of epistaxis as only grade C level exists currently. These researchers stated that based on the available literature, the use of topical bevacizumab is not recommended (grade B).

Kini and associates (2019) reviewed the current literature regarding the use of bevacizumab for the treatment of epistaxis in patients with HHT and provided guidance on its usage for this indication. These investigators carried out a narrative literature review to analyze various methods and dosages of bevacizumab administration for the treatment of HHT-related epistaxis, along with a review of current treatment modalities and their drawbacks. The current standard of care for HHT-related epistaxis consists of treatments that are largely ineffective or invasive with significant potential complications. Submucosal bevacizumab has demonstrated efficacy in reducing frequency, duration, and severity of epistaxis in those with HHT. The authors concluded that given the inadequacies and potential drawbacks of current treatments for epistaxis

in HHT, there is a need for new therapeutic options. Submucosal bevacizumab has been effective with a limited risk profile in a number of studies and should now be considered as a therapeutic option for refractory epistaxis. Moreover, these researchers stated that controlled studies are recommended to quantify optimal dosing, treatment schedule, and specific sub-populations that will respond best to this treatment.

Multiple Myeloma

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.

Vaginal Cancer

According to information from the National Cancer Institute (NCI, 2015), no established anticancer drugs can be considered of proven clinical benefit in vaginal cancer, although patients are often treated with regimens used to treat cervical cancer.

Mesothelioma: Peritoneal, Pleural, Pericardium, and Tunica Vaginalis Testes

Malignant mesothelioma is a highly lethal malignancy of the serosal membranes of the pleura, peritoneum, pericardium, or tunica vaginalis testes. This is a rare disease, with the pleural variant being the most common, followed by peritoneal mesothelioma (Alexander 2019; UpToDate).Pericardial mesothelioma is a rare form of mesothelioma that develops in the pericardium. Symptoms include chest pain and difficulty breathing. Pericardial mesothelioma is rare, accounting for less than 1% of mesothelioma cases. Although a causal relationship between asbestos exposure and pleural mesotheliomas is well established, the relationship between asbestos exposure and pericardial mesothelioma is less certain. Mesotheliomas arising in the pericardium produce tamponade and constriction. Resection is the treatment of choice for mesothelioma, but the prognosis with malignant pericardial mesotheliomas is very poor. The addition of radiation and/or chemotherapy has been attempted but has not been shown to be of value (Gaasch and Vander Salm 2019; UpToDate).

Chekol and Sun (2012) stated malignant mesothelioma of the tunica vaginalis testis is an extremely rare tumor representing 0.3% to 5% of all malignant mesotheliomas. Gross examination of testicular mesotheliomas typically reveals tumor nodules studding the thickened tunica vaginalis and, in some cases, infiltrating the testicular parenchyma, leading to diagnostic challenges. Microscopically, the tumor is characterized by epithelioid cells arising from the tunica vaginalis with papillary, tubulopapillary, or solid architectural patterns. The papillae are usually lined by a single layer of cells with relatively bland cytologic features. An epithelial cell phenotype admixed with a sarcomatoid pattern has also been described in a few cases. Immunohistochemically, the tumor is usually positive for calretinin, Wilms tumor-1, epithelial membrane antigen, D2-40, thrombomodulin, cytokeratin 7, and cytokeratin 5/6. Electron microscopic studies reveal epithelial cells joined by tight junctions, forming lumina, and displaying long microvilli with length to width ratios often greater than 10. The most important differential diagnostic considerations include florid mesothelial hyperplasia, adenomatoid tumor, carcinoma of the rete testis, and serous papillary tumors. In addition, the various types of testicular germ cell tumors should be considered, including seminomas, embryonal carcinomas, and intratubular germ cell tumors, particularly in tumors with testicular parenchymal involvement. Pleomorphic sarcomas should also be

considered, particularly when dealing with the biphasic variant. The prognosis for this entity is grave, with a median survival of 23 months. Aggressive therapy with radical orchiectomy remains the mainstay of treatment.

The addition of bevacizumab to the pemetrexed-cisplatin regimen improved both progression-free and overall survival compared with pemetrexed plus cisplatin without bevacizumab in the large phase III MAPS trial conducted exclusively in patients with malignant pleural mesothelioma. It is reasonable to extrapolate this experience to patients with malignant peritoneal mesothelioma, although care should be taken in patient selection for bevacizumab (i.e., patients should have no poorly controlled hypertension, deep venous thrombosis, recent surgery, or viscus perforation, and they must have a good performance status) (Alexander and Kindler 2019; UpToDate).

NCCN guidelines (2015) added the first-line combination chemotherapy regimen of pemetrexed/cisplatin/bevacizumab followed by maintenance bevacizumab as a treatment option for patients with unresectable malignant pleural mesothelioma (MPM). This is a category 2A recommendation, based upon a study by Zalcman, et al. (2015; 2016). Zalcman et al (2016) stated malignant pleural mesothelioma is an aggressive cancer with poor prognosis, linked to occupational asbestos exposure. Vascular endothelial growth factor is a key mitogen for malignant pleural mesothelioma cells, therefore targeting of vascular endothelial growth factor might prove effective. The authors aimed to assess the effect on survival of bevacizumab when added to the present standard of care, cisplatin plus pemetrexed, as first-line treatment of advanced malignant pleural mesothelioma. This randomised, controlled, open-label, phase 3 trial recruited patients aged 18-75 years with unresectable malignant pleural mesothelioma who had not received previous chemotherapy, had an Eastern Cooperative Oncology Group performance status of 0-2, had no substantial cardiovascular comorbidity, were not amenable to curative surgery, had at least one evaluable (pleural effusion) or measurable (pleural tumour solid thickening) lesion with CT, and a life expectancy of >12 weeks from 73 hospitals in France. Exclusion criteria were presence of central nervous system metastases, use of antiaggregant treatments (aspirin ≥325 mg per day, clopidogrel, ticlopidine, or dipyridamole), anti-vitamin K drugs at a

curative dose, treatment with low-molecular-weight heparin at a curative dose, and treatment with non-steroidal anti-inflammatory drugs. The authors randomly allocated patients (1:1; minimization method used [random factor of 0·8]; patients stratified by histology [epithelioid vs sarcomatoid or mixed histology subtypes], performance status score [0-1 vs 2], study centre, or smoking status [never smokers vs smokers]) to receive intravenously 500 mg/m(2) pemetrexed plus 75 mg/m(2) cisplatin with (PCB) or without (PC) 15 mg/kg bevacizumab in 21 day cycles for up to six cycles, until progression or toxic effects. The primary outcome was overall survival (OS) in the intention-to treat population. Treatment was open label. From Feb 13, 2008, to Jan 5, 2014, the authors randomly assigned 448 patients to treatment (223 [50%] to PCB and 225 [50%] to PC). OS was significantly longer with PCB (median 18·8 months [95% CI 15·9-22·6]) than with PC (16·1 months [14·0-17·9]; hazard ratio 0·77 [0·62-0·95]; p=0·0167). Overall, 158 (71%) of 222 patients given PCB and 139 (62%) of 224 patients given PC had grade 3-4 adverse events. The authors noted more grade 3 or higher hypertension (51 [23%] of 222 vs 0) and thrombotic events (13 [6%] of 222 vs 2 [1%] of 224) with PCB than with PC. The authors concluded that the addition of bevacizumab to pemetrexed plus cisplatin significantly improved OS in malignant pleural mesothelioma at the cost of expected manageable toxic effects, therefore it should be considered as a suitable treatment for the disease (MAPS Trial; NCT00651456) (MAPS Trial; NCT00651456).).

Leiomyosarcoma

In a phase III, double-blind, placebo-controlled trial, Hensley et al (2015) examined if the addition of bevacizumab to gemcitabine-docetaxel increases PFS in patients with uterine leiomyosarcoma (uLMS). Patients with chemotherapy-naive, metastatic, unresectable uLMS were randomly assigned to gemcitabine-docetaxel plus bevacizumab or gemcitabine-docetaxel plus placebo. Progression-free survival, OS, and ORRs were compared to determine superiority. Target accrual was 130 patients to detect an increase in median PFS from 4 months (gemcitabine-docetaxel plus placebo) to 6.7 months (gemcitabine-docetaxel plus bevacizumab). Treatment effects on PFS and OS were described by HRs, median times to event, and 95 % CIs. In all, 107 patients were accrued: gemcitabine-docetaxel plus placebo (n = 54) and gemcitabine-docetaxel plus bevacizumab (n = 53). Accrual was stopped early for futility. No

statistically significant differences in grade 3 to 4 toxicities were observed. Median PFS was 6.2 months for gemcitabine-docetaxel plus placebo versus 4.2 months for gemcitabine-docetaxel plus bevacizumab (HR, 1.12; p = 0.58). Median OS was 26.9 months for gemcitabine-docetaxel plus placebo and 23.3 months for gemcitabine-docetaxel plus bevacizumab (HR, 1.07; p = 0.81). Objective responses were observed in 17 (31.5 %) of 54 patients randomly assigned to gemcitabine-docetaxel plus placebo and 19 (35.8 %) of 53 patients randomly assigned to gemcitabine-docetaxel plus bevacizumab. Mean duration of response was 8.6 months for gemcitabine-docetaxel plus placebo versus 8.8 months for gemcitabine-docetaxel plus bevacizumab. The authors concluded that the addition of bevacizumab to gemcitabine-docetaxel for first-line treatment of metastatic uLMS failed to improve PFS, OS, or ORR. Gemcitabine-docetaxel remains a standard first-line treatment for uLMS.

Desmoplastic Small Round Cell Tumor

Desmoplastic small round cell tumor (DSRCT), a rare malignant cancer, is a soft tissue sarcoma that usually affects young boys and men and is found most often in the abdomen. Its name means that it is formed by small, round cancer cells surrounded by scar-like tissue. The most common symptoms include abdominal pain, abdominal mass and symptoms of gastro-intestinal obstruction. Patients with DSRCTs are treated first with chemotherapy, then with surgery to remove the tumor, if possible. Radiation therapy is sometimes given, depending on the tumor. In addition, some patients with DSRCT are candidates for bone marrow transplantation. There is insufficient evidence regarding the clinical value of bevacizumab for the treatment of DSRCT.

de Araujo and Araujo (2014) presented 2 case reports of patients with DSRCT and discussed 2 therapeutic options for this sarcoma. This report focused on men aged 22 and 37 years, respectively. The first patient presented with an abdomino-pelvic mass that was not suitable for surgery. He underwent chemotherapy (adriblastina and cisplatin) with a brief partial remission and survival time of 13 months. The second patient presented with an abdominal mass and underwent partial resection. He received chemotherapy and bevacizumab, resulting in a partial remission and a survival time of 34 months. The extent of surgery and monoclonal

antibody use probably had a positive impact on survival. The authors concluded that it is necessary to include specific targeted therapies in an attempt to improve survival.

Urothelial Carcinoma

In a phase II clinical trial, Hahn and colleagues (2011) evaluated the effectiveness and toxicity of bevacizumab in combination with cisplatin and gemcitabine (CGB) as first-line treatment for patients with metastatic urothelial cancer (UC). Chemotherapy-naive patients with metastatic or unresectable UC received cisplatin 70 mg/m(2) on day 1, gemcitabine 1,000 to 1,250 mg/m(2) on days 1 and 8, and bevacizumab 15 mg/kg on day 1, every 21 days. A total of 43 patients with performance status of 0 (n = 26) or 1 (n = 17) and median age of 66 years were evaluable for toxicity and response. Grade 3 to 4 hematologic toxicity included neutropenia (35 %), thrombocytopenia (12 %), anemia (12 %), and neutropenic fever (2 %). Grade 3 to 5 non-hematologic toxicity included deep vein thrombosis/pulmonary embolism (21 %), hemorrhage (7 %), cardiac (7 %), hypertension (5 %), and proteinuria (2 %). Three treatment-related deaths (central nervous system [CNS] hemorrhage, sudden cardiac death, and aortic dissection) were observed. Best response by RECIST was CR in 8 patients (19 %) and PR in 23 patients (53 %), for an ORR of 72 %. Stable disease lasting greater than or equal to 12 weeks occurred in 4 patients (9 %), and progressive disease occurred in 6 patients (14 %). With a median follow-up of 27.2 months (range of 3.5 to 40.9 months), median PFS was 8.2 months (95 % CI: 6.8 to 10.3 months) with a median OS time of 19.1 months (95 % CI: 12.4 to 22.7 months). The study-defined goal of 50 % improvement in PFS was not met. The authors concluded that CGB demonstrated promising OS and anti-angiogenic treatment-related toxicities in the phase II setting of metastatic UC. They stated that the full risk/benefit profile of CGB in patients with metastatic UC will be determined by an ongoing phase III inter-group trial.

Kurtoglu et al (2015) stated that despite recent advances in the identification of genomic alterations that lead to urothelial oncogenesis in-vitro, patients with advanced urothelial carcinomas continue to have poor clinical outcomes. These researchers focused on targeted therapies that have yielded the most promising results alone or combined with

traditional chemotherapy, including the anti-angiogenesis agent bevacizumab, the human epidermal growth factor receptor 2 antibody trastuzumab, and the tyrosine kinase inhibitor cabozantinib. They also described ongoing and developing clinical trials that use innovative approaches, including dose-dense scheduling of singular chemotherapy combinations, prospective screening of tumor tissues for mutational targets and biomarkers to predict chemo-sensitivity before the determination of the therapeutic regimen, and novel agents that target proteins in the immune checkpoint regulation pathway (programmed cell death protein 1 [PD-1] and anti-PD-ligand 1) that have shown significant potential in pre-clinical models and early clinical trials. New agents and targeted therapies, alone or combined with traditional chemotherapy, will only be validated through accrual to developing clinical trials that aim to translate these therapies into individualized treatments and improved survival rates in urothelial carcinoma.

Furthermore, the National Cancer Institute's PDQ on "Bladder cancer treatment – for health professionals" (2015) and the NCCN's clinical practice guideline on "Bladder cancer" (Version 2.2015) do not mention bevacizumab as a therapeutic option.

Brain Metastases

Lin and DeAngelis (2015) noted that brain metastases (BMs) occur in 10 % to 20 % of adult patients with cancer, and with increased surveillance and improved systemic control, the incidence is likely to grow. Despite multi-modal treatment, prognosis remains poor. Current evidence supports use of whole-brain radiation therapy (WBRT) when patients present with multiple BMs. However, its associated cognitive impairment is a major deterrent in patients likely to live longer than 6 months. In patients with oligometastases (1 to 3 metastases) and even some with multiple lesions less than 3 to 4 cm, especially if the primary tumor is considered radiotherapy resistant, stereotactic radiosurgery is recommended; if the BMs are greater than 4 cm, surgical resection with or without post-operative WBRT should be considered. There is increasing evidence that systemic therapy, including targeted therapy and immunotherapy, is effective against BM and may be an early choice, especially in patients with sensitive primary tumors. In patients with progressive systemic disease, limited therapeutic options, and poor

performance status, best supportive care may be appropriate. These investigators stated that small prospective studies of bevacizumab, in combination with other systemic agents, demonstrated activity against BM from heavily pre-treated HER2-positive breast cancer, NSCLC, melanoma, and SCLC. Currently, there is an ongoing phase III trial examining the effectiveness of bevacizumab, in addition to cisplatin and pemetrexed, in patients with NSCLC with asymptomatic BM (NCT02162537). Phase II trials of bevacizumab in BM from breast cancer (NCT02185352), melanoma (NCT02065466), and any solid tumor (NCT01898130) are also under way.

Olfactory Neuroblastoma (Esthesioneuroblastoma)

Dunbar et al (2012) stated that olfactory neuroblastomas (ONBs) are rare malignant tumors that arise from olfactory epithelium and typically present with symptoms attributable to locally invasive disease. Kadish radiographic staging and Hyams' histopathologic grading are prognostic. Overall survival rates, averaging 60 to 70 % at 5 years, remain limited by high rates of delayed loco-regional and distant progression. At initial presentation, the available evidence supports the use of multi-modality therapy, historically surgery and radiation, to improve disease-free and overall survival. At recurrence/progression, the available evidence supports the use of therapy to improve disease control and symptoms (palliation), but patient heterogeneity dictates individualization of modalities. Although the ideal use of chemotherapy as a modality remains undefined, the available evidence supports its use, historically platinum-based, for palliation. However, recent insights into the molecular-genetic aberrations of ONBs, coupled with the emergence chemotherapeutic agents capable of targeting such aberrations, suggest an expanded role. The authors reported a case of a 60-year old man, heavily pre-treated for metastatic ONB, presenting with profound central nervous system as well as head-and-neck symptoms. He experienced unexpectedly durable palliation with bevacizumab. Additionally, he experienced localized palliation with an Ommaya reservoir. The authors reviewed the literature regarding historical and emerging therapies for ONB to emphasize the needs for individualization and translational clinical studies.

An UpToDate review on "Olfactory neuroblastoma (esthesioneuroblastoma)" (Synderman et al, 2017) does not list bevacizumab as a therapeutic option.

Furthermore, National Comprehensive Cancer Network's Drugs & Biologics Compendium (2017) does not list esthesioneuroblastoma/olfactory neuroblastoma as a recommended indication of bevacizumab.

Radiation-Induced Myelopathy

In a retrospective, case-series study, Psimaras and colleagues (2016) examined the effectiveness of bevacizumab for treatment of late-onset radiation-induced myelopathy. These investigators studied all patients diagnosed with radiation-induced myelopathy presenting to 2 neuro-oncology centers between 2008 and 2012. All patients were treated with bevacizumab, after no clinical or radiologic improvement was achieved with conventional (in particular steroid) treatment. This study included 4 patients (2 women) with late-onset radiation-induced myelopathy who were each treated with 4 cycles of bevacizumab. The median delay from radiotherapy to myelopathy was 19 months (range of 14 to 22 months). Initial treatment with steroids was unsuccessful in all 4 patients. Bevacizumab was introduced after a median of 4.8 months (range of 4 to 5 months) from the onset of the neurologic symptoms. These researchers observed stabilization of clinical outcome in 3 patients; radiologic findings improved in all 4 patients. The authors concluded that the use of bevacizumab resulted in radiologic improvement, but had only a modest effect on clinical outcome. The authors also noted that the discrepancy between the clinical and radiologic outcome called into question the effectiveness of the treatment and may suggest that the bevacizumab mechanism of action targeted the edema but did not treat the demyelination or the axonal loss. Nevertheless, the lack of clinical improvement in this study might be due to a number of factors, such as (i) late initiation of bevacizumab treatment, when the neurologic deficit was no longer reversible; (ii) the severity of the cases reported here, with 3 patients already bedridden; and (iii) more detailed assessment of disability and QOL assessment, which was not assessed here, may have revealed subtle clinical improvements. The authors stated that these findings suggested that the use of bevacizumab in late-onset

radiation-induced myelopathy deserves further study with a particular focus on the optimal timing of treatment. This study provided Class IV evidence that for patients with late radiation-induced myelopathy unresponsive to steroids, bevacizumab improved radiologic but not clinical outcomes.

Radiation Necrosis

Delishaj and colleagues (2017) stated that RN of brain tissue is a serious late complication of brain irradiation and recently bevacizumab has been suggested as therapeutic option of RN. There is a lack of data in the literature regarding the effectiveness of bevacizumab for the treatment of RN. These investigators performed a comprehensive analysis of all reported cases using bevacizumab for the treatment of brain RN. In September 2016, these researchers performed a comprehensive literature search of the following electronic databases: PubMed, Web of Science, Scopus and Cochrane Library. The research for the review was conducted using a combination of the keywords "radiation necrosis", "radiotherapy" and "bevacizumab" alongside the fields comprising article title, abstract and keywords. Randomized trials, non-randomized trials, prospective studies, retrospective studies and single-case reports were included in the review. The research generated 21 studies and 125 cases where bevacizumab had been used for the treatment of RN. The median follow-up was 8 months and the most frequent bevacizumab dose used was 7.5 mg/kg for 2 weeks with a median of 4 cycles. Low-dose bevacizumab resulted in effectiveness with improvement in both clinical and radiographic response. The median decrease in T1 contrast enhancement and in T2/FLAIR signal abnormality was 64 % and 6 0%, respectively. A reduction in steroidal therapy was observed in majority of patients treated. The authors concluded that based on the data of this review, bevacizumab appeared to be a promising agent for the treatment of brain RN. Moreover, they stated that future prospective studies are needed to evaluate the role of bevacizumab in RN and to define the optimal scheduling, dosage and duration of therapy.

The authors stated that the inherent drawbacks of this study were due to the retrospective studies analyzed, the small number of patients reported in the studies, the patients having been treated for different conditions, different radiation doses, different radiation modalities and with limited

follow-up after bevacizumab therapy. Furthermore, the diagnosis of RN was made by radiologic evaluation in the majority of the studies analyzed in this review and the patients were treated in different institutions and countries. Furthermore, there was a publication bias present, because only patients who responded to bevacizumab were likely to be included in the published literature.

Furthermore, an UpToDate review on "Delayed complications of cranial irradiation" (Dietrich et al, 2018) states that "The optimal dose and duration of bevacizumab for treatment of radiation necrosis have not been established. In small series, symptomatic and/or radiographic relapse after discontinuation of bevacizumab has been described in 2 of 5 and 11 of 20 patients. Some of these patients may respond to retreatment with bevacizumab. While no serious adverse events were reported in the randomized trial, additional studies are needed to better determine the safety profile of bevacizumab in the management of radiation necrosis as well as the optimal dose and duration of treatment".

Leptomeningeal Metastases

Burger et al (2016) stated that leptomeningeal dissemination of a primary brain tumor is a condition which is challenging to treat, as it often occurs in rather late disease stages in highly pre-treated patients. Its prognosis is dismal and there is still no accepted standard of care. These researchers reported here a good clinical effect with a partial response (PR) in 3 out of 9 patients and a stable disease(SD) with improvement on symptoms in 2 more patients following systemic anti-angiogenic treatment with bevacizumab (BEV) alone or in combination with chemo- and/or radiotherapy in a series of patients with leptomeningeal dissemination from primary brain tumors (diffuse astrocytoma WHO°II, anaplastic astrocytoma WHO°III, anaplastic oligodendroglioma WHO°III, primitive neuro-ectodermal tumor and glioblastoma, both WHO°IV). This translated into effective symptom control in 5 out of 9 patients, but only moderate progression-free survival (PFS) and overall survival (OS) times were reached; PRs as assessed by RANO criteria were observed in 3 patients (each 1 with anaplastic oligodendroglioma, primitive neuro-ectodermal tumor and glioblastoma). In these patients PFS intervals of 17, 10 and 20 weeks were achieved. In 3 patients (each with diffuse astrocytoma, anaplastic astrocytoma and primitive neuro-ectodermal

tumor) SD was observed with PFS of 13, 30 and 8 weeks. Another 3 patients (all with glioblastoma) were primary non-responders and deteriorated rapidly with PFS of 3 to 4 weeks. No severe AEs were seen. The authors concluded that these experiences suggested that the combination of BEV with more conventional therapy schemes with chemo- and/or radiotherapy may be a palliative therapeutic option for patients with leptomeningeal dissemination of brain tumors. (This was a small study; and its findings were confounded by the combinational use of bevacizumab with chemo- and/or radiotherapy).

Sakata et al (2016) noted that leptomeningeal metastasis is a severe complication of non-small cell lung cancer. Its prognosis is very poor and conventional treatments have limited efficacy. However, epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors have exhibited high response rates in EGFR mutation-positive lung cancer patients with central nervous system (CNS) metastases. It has been postulated that this could be due to the penetration of agents into the CNS and a high cerebro-spinal fluid (CSF) concentration is a key consideration in measuring treatment effect. Bevacizumab has also been used as an effective therapeutic agent in patients with CNS metastases. However, the efficacy of EGFR-tyrosine kinase inhibitor doublet therapy for leptomeningeal metastases and the CSF penetration of EGFR-tyrosine kinase inhibitors have yet to be determined. Moreover, the safety of this doublet regimen in patients with a poor general condition is not known. These researchers reported on a case treated with erlotinib plus bevacizumab for leptomeningeal metastases from EGFR mutation-positive non-small cell lung cancer. The patient's performance status significantly improved and the CSF penetration rate of erlotinib plus bevacizumab was equal to or greater than the past reports of erlotinib alone. (This was a single-case study; and its findings were confounded by the combinational use of bevacizumab and erlotinib).

Matsuda et al (2017) stated that although promising preliminary results have been widely observed with bevacizumab for recurrent malignant gliomas, many unanswered questions remain to be resolved to achieve an optimal outcome. No predictive biomarkers of a survival benefit from bevacizumab have been established, and no consensus exists about the response or survival benefit regarding the prior recurrence pattern or tumor location. These researchers retrospectively analyzed the clinical

benefit from bevacizumab for recurrent malignant gliomas in relation to the prior recurrence pattern or tumor location. A total of 31 consecutive patients with recurrent malignant gliomas who were treated with bevacizumab were investigated. The treatment response and survival benefit from bevacizumab were analyzed in association with age, sex, Karnofsky performance status (KPF), prior pathological diagnosis, prior recurrence pattern, primary location of tumor, recurrence status, and expression of angiogenic and hypoxic markers. The group with leptomeningeal dissemination had a significantly shorter median OS with bevacizumab (OSBev) (6.0 months, 95 % confidence interval (CI): 1.4 to 10.7) compared to those in the local/distant group (11.8 months, 95 % CI: 6.1 to 17.4). The median OSBev of the infra-tentorial tumor group and supra-tentorial tumor group were 9.2 months (95 % CI: 5.0 to 13.4) and 10.4 months (95 % CI: 6.6 to 14.3), respectively. With multi-variate analysis, the prior recurrence pattern was the only independent prognostic factor of OSBev. The authors concluded that patients with leptomeningeal dissemination of recurrent malignant glioma experienced minimal benefit from bevacizumab.

Hemangioblastoma

Riklin and colleagues (2012) stated that hemangioblastomas represent rare benign tumors of the CNS. In the case of metastatic spread and limited surgical options, systemic treatment may be considered. However there is no standard of care beyond surgery. These investigators reported the cases of 2 patients with progressive multi-locular hemangioblastomas, who showed clinical benefit and radiological stabilization of tumor growth after treatment with bevacizumab. The authors concluded the findings of these case reports suggested activity of bevacizumab in hemangioblastomas after failure of standard therapeutic options

Furthermore, an UpToDate review on "Hemangioblastoma" (Wong et al, 2018) does not mention bevacizumab as a therapeutic option.

AIDS-related Kaposi's sarcoma

Uldrick et al (2012) stated alternatives to cytotoxic agents are desirable for patients with HIV-associated Kaposi's sarcoma (KS). Vascular endothelial growth factor-A (VEGF-A) contributes to KS pathogenesis. We evaluated the humanized anti-VEGF-A monoclonal antibody, bevacizumab, in patients with HIV-KS. Patients with HIV-KS who either experienced progression while receiving highly active antiretroviral therapy (HAART) for at least 1 month or did not regress despite HAART for at least 4 months were administered bevacizumab 15 mg/kg intravenously on days 1 and 8 and then every 3 weeks. The primary objective was assessment of antitumor activity using modified AIDS Clinical Trial Group (ACTG) criteria for HIV-KS. HIV-uninfected patients were also eligible and observed separately. Seventeen HIV-infected patients were enrolled. Fourteen patients had been receiving effective HAART for at least 6 months (median, 1 year). Thirteen patients had advanced disease (ACTG T(1)), 13 patients had received prior chemotherapy for KS, and seven patients had CD4 count less than 200 cells/μL. Median number of cycles was 10 (range, 1 to 37 cycles); median follow-up was 8.3 months (range, 3 to 36 months). Of 16 assessable patients, best tumor responses observed were complete response (CR) in three patients (19%), partial response (PR) in two patients (12%), stable disease in nine patients (56%), and progressive disease in two patients (12%). Overall response rate (CR + PR) was 31% (95% CI, 11% to 58.7%). Four of five responders had received prior chemotherapy for KS. Over 202 cycles, grade 3 to 4 adverse events at least possibly attributed to therapy included hypertension (n = 7), neutropenia (n = 5), cellulitis (n = 3), and headache (n = 2). The authors concluded that bevacizumab is tolerated in patients with HIV-KS and has activity in a subset of patients.

Meningioma

In their review, Franke et al (2018) state meningiomas are the most prevalent primary tumor of the central nervous system (CNS), and although the majority of these neoplasms are classified as benign, nearly one fourth of the lesions display an aggressive profile characterized by pleomorphic histology, high recurrence rates, and overall resistance to standard treatment. Despite the ubiquitous nature of these tumors, no adjuvant therapeutic regimen has been identified which effectively controls disease recurrence and progression after surgery and radiation, leading to a dismal prognosis in this patient population. The primary focus

of this research study is, hence, to assess the recently emerging use of bevacizumab, an anti-angiogenic agent, in the treatment of meningiomas. This systematic literature review analyzes the efficacy and safety of therapeutic bevacizumab for treatment-refractory meningiomas. A systematic PubMed search was conducted according to PRISMA guidelines to identify all relevant reports investigating the anti-angiogenic agent bevacizumab in the treatment of intracranial meningiomas. The reported parameters from pertinent retrospective reviews, prospective studies, and case studies were volumetric reduction, radiographic response, clinical stability, overall survival (OS), and progression free survival (PFS) measured at 6 and 12 months post-initiation of treatment. Complications were cataloged based on the range and severity of the therapy-related toxicities. A total of 11 articles, 5 retrospective series, 2 prospective trials, and 4 case reports, reporting on a total of 92 patients, were included in this review. The use of bevacizumab therapy for intracranial meningiomas demonstrated median overall PFS of 16.8 months (range: 6.5-22 months) and PFS-6 of 73% (range: 44%-93%). The authors concluded that therapeutic bevacizumab, either alone or with combination chemotherapies, for select patient populations with recurrent or progressive meningiomas, offers a treatment option that confers improved overall progression-free survival. To assess OS parameters, larger randomized controlled trials assessing the use of anti-angiogenic agents for recurrent/progressive meningiomas are warranted.

Shih et al (2016) stated meningiomas that progress after standard therapies are challenging with limited effective chemotherapy options. This phase II trial evaluated the efficacy of everolimus plus bevacizumab in patients with recurrent, progressive meningioma after treatment with surgical resection and local radiotherapy when appropriate. Patients with recurrent meningioma (WHO grade I, II, or III) following standard treatments with surgical resection and radiotherapy received bevacizumab (10 mg/kg IV days 1 and 15) and everolimus (10 mg PO daily) each 28 day cycle. Evaluation of response occurred every 2 cycles. The primary endpoint was progression-free survival (PFS). Secondary endpoints included response rate, overall survival and safety. Seventeen patients with a median age of 59 years (29-84) received study treatment. WHO grades at study entry included: I, 5 (29 %); II, 7 (41 %); III, 4 (24 %); unknown, 1 (6 %). Patients received a median of 8 cycles (1-37); all patients are off study treatment. A best response of SD was observed in

15 patients (88 %), and 6 patients had SD for >12 months. Overall median PFS was 22 months (95 % CI 4.5-26.8) and was greater for patients with WHO grade II and III compared to grade I tumors (22.0 months vs 17.5 months). Four patients discontinued treatment due to toxicity (proteinuria, 2; colitis, 1, thrombocytopenia, 1). However, other grade 3 toxicity was uncommon, and no patient had grade 4 toxicity. The authors concluded that the combination of everolimus and bevacizumab was well-tolerated, and produced stable disease in 88 % of patients; the median duration of disease stabilization of 10 months (2-29). The median PFS from this prospective trial was similar to previous retrospective reports of bevacizumab in the treatment of recurrent meningioma.

Brain Arterio-Venous Malformations

Williams and colleagues (2012) presented a case of an arterio-venous malformation (AVM) of the central sulcus treated with Gamma Knife surgery. The patient developed perilesional edema 9 months after treatment and experienced severe headache and hemiparesis. Her symptoms were refractory to corticosteroid therapy and pain management. She was subsequently treated with bevacizumab with striking improvement in her symptoms and results of neuroimaging studies. The authors concluded that this was the 1st time that bevacizumab has been used to control severe refractory perilesional edema related to an intra-cranial AVM.

Quan and associates (2018) examined delayed complications in patients with brain AVM (BAVM) after Gamma Knife stereotactic radiosurgery (GKSR) and presented the salvage therapy experiences of patients with BAVM with radiation-induced changes (RICs) or intra-cranial hemorrhage (ICH). This cohort consisted of 44 patients with BAVM who underwent failed GKSR between 2000 and 2015. These patients were further divided into an RIC group (23 patients) and an ICH group (21 patients) based on their post-GKSR complications. Patients' characteristics, treatment strategies, and long-term outcomes were analyzed. The modified Rankin Scale (mRS) was used to assess the neurologic status of each patient. The marginal dose and radiosurgery-based AVM score were not significantly different between the 2 groups. Craniotomy was performed in 26 patients (9 patients with ICH and 17 patients with RICs), and histologic examination showed cavernous angioma changes in 6

patients. In addition, 6 patients underwent repeat radiosurgery in the ICH group, and 7 patients used bevacizumab in the RIC group. A total of 30 patients showed good outcomes at the last follow-up (mRS score of less than 3). The authors concluded that salvage therapy for patients with BAVM should be performed based on the latency period and lesion characteristics of each individual; prompt treatment and a longer follow-up are recommended to achieve good clinical outcomes.

Furthermore, an UpToDate review on "Brain arteriovenous malformations" (Singer et al, 2019) does not mention bevacizumab as a therapeutic option.

Bevacizumab plus Paclitaxel, Albumin-Bound (Abraxane) for the Treatment of Metastatic Trophoblastic Tumor

Worley et al (2018) reported on the case of a 36-year old woman with metastatic and refractory choriocarcinoma following single- and multi-agent chemotherapy and surgical metastectomy experienced a durable remission after receiving therapy with an anti-endoglin monoclonal antibody and bevacizumab.

Yang et al (2019) stated that epithelioid trophoblastic tumors (ETTs) are the rarest type of gestational trophoblastic neoplasia. These investigators examined the clinical features, treatments, outcomes, and prognostic factors in patients with ETT, and explored potential therapeutic targets. They retrospectively analyzed the clinical features, treatments, survival, and prognostic factors of 21 ETT patients treated at the authors' institution between January 2002 and December 2017. Expression levels of programmed cell death 1 (PD-1), PD-1 ligands (PD-L1and PD-L2), B7 family ligands (B7-H3, B7-H4, V-domain Ig suppressor of T cell activation [VISTA], and B7-H6), and CD105 expression were assessed by immunohistochemistry. A total of 14 patients with ETT (66.7 %) presented with irregular vaginal bleeding; 3 stage I patients (14.3 %) with normal β-human chorionic gonadotropin (β- hCG) levels underwent hysterectomy alone. Of the remaining 18 patients who had elevated β-hCG levels (85.7 %), 1 received chemotherapy and 17 underwent surgery and multi-agent chemotherapy. After treatment, 17 patients (81.0 %) achieved complete remission (CR; 2 of whom [11.8 %] later relapsed) and 4 (19.0 %) with stage IV died of their disease. On uni-variate and multi-

variate analyses, stage IV disease was an independent prognostic factor for overall survival (OS) and disease-free survival (DFS) ($p < 0.001$). PD-L1, B7-H3, and CD105 were detected in 100 % of samples, PD-L2 and VISTA in 82 %, B7-H6 in 18 %, and B7-H4 was undetectable in ETT cells. The authors concluded that hysterectomy and metastatic lesion resection are essential for controlling ETT. Surgery plus chemotherapy are recommended for patients with abnormal β-hCG levels and metastatic disease; PD-L1, PD-L2, B7-H3, VISTA and CD105 were potential therapeutic targets for metastatic ETT.

National Comprehensive Cancer Network's Drugs & Biologics Compendium (2019) does not list trophoblastic tumor as a recommended indication of paclitaxel, albumin-bound (Abraxane).

Furthermore, National Comprehensive Cancer Network's Drugs & Biologics Compendium (2019) does not list trophoblastic tumor as a recommended indication of bevacizumab (Avastin).

Pseudomyxoma Peritonei

Winer and Buckanovich (2009) stated that pseudomyxoma peritonei (PMP) is a rare tumor syndrome that can be diagnosed in association with mucinous ovarian tumors of low malignant potential. Surgical debulking is the primary treatment modality as chemotherapy has generally proven ineffective in this slowly progressive tumor. When patients with PMP are not surgical candidates, there is no effective treatment, and patients will die of progressive disease. These investigators reported 2 patients with PMP with associated mucinous ovarian tumor of low malignant potential treated with bevacizumab. Both patients demonstrated disease response to bevacizumab. One patient had a prolonged response while on therapy, remained stable for 6 months when treatment was held, and then after progressing responded to a 2nd course of therapy. The authors concluded that while this phase-II study was encouraging, further management strategies for PMP are clearly necessary; the majority of patients in this study did not receive a clinical benefit. The authors' experience with bevacizumab suggested a relatively non-toxic therapy with significant activity in ovarian PMP worthy of further study. Similar to the patients in the trial with mitomycin-C and capecitabine, the patients in this trial demonstrated tumor marker

response that correlated with disease response. Patient 1 demonstrated a clear reduction in her ascites as well as tumor. Patient 2 had a clinical and biomarker response to both single agent bevacizumab a s well as bevacizumab in combination with chemotherapy. These researchers stated that the finding of this study provided an initial rationale for the use of bevacizumab in clinical trials in PMP. Given the improved activity observed with bevacizumab in combination with chemotherapy in other solid tumors and the recent report of an active chemotherapeutic regimen for PMP, trials with bevacizumab as a single agent or in combination with chemotherapy for unresectable PMP may be warranted.

Sun et al (2009) noted that effective systemic therapy for advanced PMP is the focus of investigation. These researchers described a case of PMP arising from an adenoma of the appendix in a 58-year old man. First, the patient underwent explorative laparotomy with ileo-coecal resection, but without possibility of major tumor debulking due to adhesive gross tumor masses. Subsequently, 6 cycles of Folfox IV chemotherapy were administered, without response, but with severe side effects. Upon progressive disease, a combination of bevacizumab and capecitabine led to a long-term stabilization of disease and obvious improvement of performance status. The authors concluded that he findings of this case suggested that modulation of tumor micro-environment and angiogenesis by bevacizumab, potentially augmented by capecitabine, may be beneficial in borderline tumors such as PMP. These researchers stated that their observation may encourage studies using bevacizumab based therapies in advanced borderline tumors. With such therapy, remission of PMP is not the primary goal in an advanced situation, but stabilization of disease and clinical improvement.

Dohan et al (2014) stated that PMP is an uncommon peritoneal mucinous carcinomatosis confined to the peritoneal cavity. The rarity of PMP in humans makes evaluation of the disease biological features and new therapeutic strategies difficult. Accordingly, there is a need for animal models of PMP. Human PMP tissue was intraperitoneally grafted and grown into nude mice, then constituted into reliable and reproducible orthotopic models. Histological and immunostaining analysis was performed. Bevacizumab was injected twice-weekly either during tumor growth or after cytoreductive surgery. In-vivo imaging of tumor angiogenesis was performed using barium sulfate or isolectin

microangiography and Doppler ultrasonography (US) of the superior mesenteric artery. Tumor angiogenesis was confirmed by the presence of tortuous vascular networks with high levels of expression of CD31, vascular endothelial cadherin, and desmin. Doppler US of the superior mesenteric artery revealed a 2-fold increase in blood flow velocity compared with tumor-free mice ($p < 0.001$). Bevacizumab administration was correlated with the normalization of tumor vascularity when injected during tumor growth and with the stabilization of the histological and hemodynamic findings when injected after cyto-reductive surgery (CRS). The authors concluded that their PMP models mimicked human PMP; these findings confirmed the presence of tumor angiogenesis related to PMP growth; this murine model allowed researchers to actually bench test and evaluate, in pre-clinical studies, the efficacy of new therapeutic strategies and anti-angiogenic therapies.

Furthermore, National Comprehensive Cancer Network's Drugs & Biologics Compendium (2019) does not list pseudomyxoma peritonei adenocarcinoma as a recommended indication of bevacizumab.

Meningeal Melanoma Metastases

Simonsen and colleagues (2020) stated that melanoma patients with metastatic growth in the meninges have poor prognosis and few therapeutic options. Although treatment with BRAF inhibitors or immune checkpoint inhibitors has provided promising results, most patients with advanced melanoma are resistant to these treatments and develop severe side effects. Novel treatment strategies are needed for patients with meningeal melanoma metastases, and the potential of anti-angiogenic therapy was examined in this pre-clinical study. Two GFP-transfected melanoma models (A-07 and D-12) differing substantially in VEGF-A expression were included in the study, and the anti-VEGF-A antibody bevacizumab was used as therapeutic agent. Meningeal metastases were initiated in BALB/c nu/nu mice by intra-cranial inoculation of melanoma cells, and bevacizumab treatment was given twice-weekly in intra-peritoneal (i.p.) doses of 10 mg/kg until the mice became moribund. Therapeutic effects were evaluated by determining tumor host survival time, assessing tumor growth and angiogenic activity by quantitative analyses of histological preparations, and measuring the expression of angiogenesis-related genes by quantitative PCR.

Meningeal A-07 melanomas showed higher expression of VEGF-A than meningeal D-12 melanomas, whereas the expression of ANGPT2 and IL8, 2 important angiogenesis drivers in melanoma, was much higher in D-12 than in A-07 tumors. Bevacizumab treatment inhibited tumor angiogenesis and prolonged host survival in mice with A-07 tumors but not in mice with D-12 tumors. Meningeal A-07 tumors in bevacizumab-treated mice compensated for the reduced VEGF-A activity by up-regulating a large number of angiogenesis-related genes, including ANGPT2 and its receptors TIE1 and TIE2. Melanoma cells migrated from meningeal tumors into the cerebrum, where they initiated metastatic growth by vessel co-option. In the A-07 model, the density of cerebral micro-metastases was higher in bevacizumab-treated than in untreated mice, either because bevacizumab treatment increased mouse survival or induced increased tumor gene expression. The authors concluded that bevacizumab treatment inhibited tumor angiogenesis and prolonged tumor host survival in mice with meningeal A-07 tumors, but had no effect on the angiogenic activity of meningeal D-12 tumors. Meningeal A-07 tumors compensated for reduced VEGF-A-mediated angiogenic activity by up-regulating the expression of a large number of other angiogenesis-related genes, including genes governing the ANGPT/TIE pathway. Melanoma cells migrated from meningeal tumors into the cerebral parenchyma and formed micro-metastases vascularized by vessel co-option, and in the A-07 model, bevacizumab-treated mice developed more and larger cerebral micro-metastases than untreated mice. These discoveries suggest that anti-angiogenic therapy may have the potential to inhibit the growth of meningeal melanoma metastases, but emphasize the need to target multiple angiogenic pathways and to individualize the treatment based on the angiogenic signature of the tumor tissue. Furthermore, anti-angiogenic therapy cannot be expected to improve the outcome of meningeal melanoma metastases without being combined with therapeutic strategies for preventing tumor cell migration, vessel co-option, and metastatic growth in the cerebral parenchyma.

Appendix

National Comprehensive Cancer Network (NCCN) Recommendations

The NCCN Drugs & Biologics Compendium (NCCN, 2020) recommends bevacizumab for the following:

AIDS-Related Kaposi Sarcoma

- Subsequent systemic therapy given with antiretroviral therapy (ART) for relapsed/refractory advanced, cutaneous, oral, visceral, or nodal disease that has progressed on or not responded to first-line systemic therapy, and progressed on alternate first-line systemic therapy [2A]

Breast Cancer - Invasive Breast Cancer

- In combination with paclitaxel (useful in certain circumstances, in select patients with high tumor burden, rapidly progressing disease, and visceral crisis) for recurrent or stage IV (M1) human epidermal growth factor receptor 2 (HER2)-negative disease that is [2A]

    - hormone receptor-negative
    - hormone receptor-positive with visceral crisis or endocrine therapy refractory

Central Nervous System Cancers
Adult Medulloblastoma

- Consider short-course single agent therapy for management of symptoms driven by RT necrosis, poorly controlled vasogenic edema, or mass effect [2A]

Extensive Brain Metastases

- Consider short-course single agent therapy for management of symptoms driven by RT necrosis, poorly controlled vasogenic edema, or mass effect [2A]

Glioblastoma

- Treatment for recurrent disease [2B for combination with carboplatin; 2A for all others]

    - as a single agent (preferred)

- in combination with carmustine, lomustine, temozolomide, or carboplatin

- Consider short-course single agent therapy for management of symptoms driven by RT necrosis, poorly controlled vasogenic edema, or mass effect [2A]

Adult Low-Grade (WHO Grade II) Infiltrative Supratentorial Astrocytoma/Oligodendroglioma

- Consider short-course single agent therapy for management of symptoms driven by RT necrosis, poorly controlled vasogenic edema, or mass effect [2A]

Anaplastic Gliomas

- Consider short-course single agent therapy for management of symptoms driven by RT necrosis, poorly controlled vasogenic edema, or mass effect [2A]
- Treatment for recurrent disease [2A for all others; 2B for combination with carboplatin]

  - as a single agent (preferred)
  - in combination with carmustine, lomustine, temozolomide, or carboplatin

Metastatic Spine Tumors

- Consider short-course single agent therapy for management of symptoms driven by RT necrosis, poorly controlled vasogenic edema, or mass effect [2A]

Adult Intracranial and Spinal Ependymoma (Excluding Subependymoma)

- Consider as single-agent treatment for progression or recurrent disease, if received prior RT and any of the following [2A]

  - gross total or subtotal resection
  - localized recurrence
  - evidence of metastasis (brain, spine, or CSF)

- Consider short-course single agent therapy for management of symptoms driven by RT necrosis, poorly controlled vasogenic edema, or mass effect [2A]

Leptomeningeal Metastases

- Consider short-course single agent therapy for management of symptoms driven by RT necrosis, poorly controlled vasogenic edema, or mass effect [2A]

Limited Brain Metastases

- Consider short-course single agent therapy for management of symptoms driven by RT necrosis, poorly controlled vasogenic edema, or mass effect [2A]

Meningiomas

- Treatment as single agent or in combination with everolimus for surgically inaccessible recurrent or progressive disease when radiation is not possible. [2B in combination with everolimus; 2A for single agent therapy]
- Consider short-course single agent therapy for management of symptoms driven by RT necrosis, poorly controlled vasogenic edema, or mass effect [2A]

Primary CNS Lymphoma

- Consider short-course single agent therapy for management of symptoms driven by RT necrosis, poorly controlled vasogenic edema, or mass effect [2A]

Cervical Cancer

- First-line therapy, or second-line therapy as clinically appropriate (if not used previously as first-line) in combination with paclitaxel and cisplatin, carboplatin, or topotecan (preferred regimens), or second-line therapy as a single agent for [1 for combination with cisplatin and paclitaxel, or topotecan and paclitaxel; 2B as single agent; 2A for combination with carboplatin and paclitaxel]

- local/regional recurrence
- Stage IVB or distant metastases

Colon Cancer

- Preferred anti-angiogenic therapy as primary treatment for patients with unresectable metachronous metastases and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months [2A]

  - in combination with irinotecan
  - in combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen

- Subsequent therapy for progression of unresectable advanced or metastatic disease [2A]

  - as the preferred anti-angiogenic agent in combination with irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen if previously treated with oxaliplatin-based therapy without irinotecan
  - in combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) regimen if previously treated with irinotecan-based therapy without oxaliplatin
  - as the preferred anti-angiogenic agent in combination with irinotecan or FOLFIRI if previously treated with fluoropyrimidine therapy without irinotecan or oxaliplatin
  - in combination with FOLFOX, CapeOX, or irinotecan and oxaliplatin if previously treated with fluoropyrimidine therapy without irinotecan or oxaliplatin

- Therapy in combination with capecitabine or with FOLFOX (fluorouracil, leucovorin, and oxaliplatin), FOLFIRI (fluorouracil, leucovorin, and irinotecan), CapeOX (capecitabine and oxaliplatin), FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan), or 5-FU/leucovorin (fluorouracil and leucovorin) regimen [2A]

- as primary treatment for locally unresectable or medically inoperable disease
- for unresectable synchronous liver and/or lung metastases that remain unresectable after primary systemic therapy
- as primary treatment for synchronous abdominal/peritoneal metastases that are nonobstructing, or following local therapy for patients with existing or imminent obstruction
- for synchronous unresectable metastases of other sites
- as primary treatment for unresectable metachronous metastases in patients who have not received previous adjuvant FOLFOX or CapeOX within the past 12 months, who have received previous fluorouracil/leucovorin (5-FU/LV) or capecitabine therapy, or who have not received any previous chemotherapy
- for unresectable metachronous metastases that remain unresectable after primary treatment

- Primary treatment for unresectable synchronous liver and/or lung metastases in combination with [2A]

  - FOLFOX (fluorouracil, leucovorin, and oxaliplatin) regimen
  - FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen
  - FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin and irinotecan) regimen
  - CapeOX (capecitabine and oxaliplatin) regimen

- Therapy in combination with capecitabine or with FOLFOX (fluorouracil, leucovorin, and oxaliplatin), FOLFIRI (fluorouracil, leucovorin and irinotecan), CapeOX (capecitabine and oxaliplatin), FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin and irinotecan) or 5-FU/leucovorin (fluorouracil and leucovorin) regimen [2B]

  - as adjuvant treatment following synchronized or staged resection for synchronous liver and/or lung metastases that converted from unresectable to resectable disease after primary treatment
  - as adjuvant treatment (following resection and/or local therapy) for resectable metachronous metastases in patients

who have received previous chemotherapy or had growth on neoadjuvant chemotherapy
- as adjuvant treatment for unresectable metachronous metastases that converted to resectable disease after primary treatment

Hepatocellular Carcinoma

- Preferred first-line treatment in combination with atezolizumab for patients (Child-Pugh Class A only) who [2A]

  - have unresectable disease and are not a transplant candidate
  - are inoperable by performance status or comorbidity, or have local disease or local disease with minimal extrahepatic disease only
  - have metastatic disease or extensive liver tumor burden

Kidney Cancer

- Therapy for relapse or stage IV disease [2A for non-clear cell histology; 2B for subsequent therapy for clear cell histology]

  - as single-agent subsequent therapy for clear cell histology (useful under certain circumstances)
  - as single-agent systemic therapy for non-clear cell histology (useful under certain circumstances)
  - in combination with erlotinib for non-clear cell histology in selected patients with advanced papillary renal cell carcinoma including hereditary leiomyomatosis and renal cell cancer (HLRCC) (useful under certain circumstances)
  - in combination with everolimus as systemic therapy for non-clear cell histology (useful under certain circumstances)

Malignant Pleural Mesothelioma

- Used in combination with pemetrexed* and either cisplatin or carboplatin followed by single-agent maintenance bevacizumab as treatment of [2A for all others; 1 for combination with pemetrexed

and cisplatin]

- unresectable clinical stage I-IIIA disease and tumors of epithelial histology or sarcomatoid or mixed histology
- clinical stage IIIB or IV disease or medically inoperable tumors in patients with performance status (PS) 0-2

*Pemetrexed-based chemotherapy may also be used for malignant peritoneal mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma

Non-Small Cell Lung Cancer

- Continuation maintenance therapy as a single agent or in combination with atezolizumab for recurrent, advanced or metastatic disease for PD-L1 expression positive (≥1%) tumors that are EGFR, ALK negative or unknown and no contraindications to the addition of pembrolizumab or atezolizumab in patients with performance status 0-2 who achieve a response or stable disease following first-line therapy with atezolizumab/carboplatin/paclitaxel/bevacizumab for nonsquamous cell histology [1 for all others; 2B for locoregional recurrence or symptomatic disease (excluding mediastinal lymph node recurrence with prior radiation therapy) with no evidence of disseminated disease]
- Treatment for recurrent, advanced, or metastatic disease as first-line therapy for PD-L1 expression positive (≥1%) tumors that are EGFR, ALK negative or unknown and no contraindications to the addition of pembrolizumab or atezolizumab and performance status 0-2 in combination with atezolizumab, carboplatin and paclitaxel for nonsquamous cell histology [1 for all others; 2B for locoregional recurrence or symptomatic local disease (excluding mediastinal lymph node recurrence with prior radiation therapy) with no evidence of disseminated disease]
- Treatment in combination with carboplatin and either paclitaxel or pemetrexed (if contraindications to the addition of pembrolizumab or atezolizumab), or in combination with cisplatin and pemetrexed (if contraindications to the addition of pembrolizumab or atezolizumab), or in combination with

atezolizumab, carboplatin and paclitaxel (if no contraindications to the addition of pembrolizumab or atezolizumab) for recurrent, advanced or metastatic disease in patients with performance status 0-1, tumors of nonsquamous cell histology, and no history of recent hemoptysis as [2A for all others; 1 for combination with carboplatin and paclitaxel with or without atezolizumab; 2B for locoregional recurrence or symptomatic local disease (excluding mediastinal lymph node recurrence with prior radiation therapy) with no evidence of disseminated disease]

- initial systemic therapy for EGFR, ALK, ROS1, BRAF negative or unknown, and PD-L1 <1% or unknown
- first-line or subsequent therapy for BRAF V600E-mutation positive tumors
- subsequent therapy for sensitizing EGFR mutation-positive tumors and prior erlotinib, afatinib, gefitinib, osimertinib, or dacomitinib therapy
- subsequent therapy for ALK rearrangement-positive tumors and prior crizotinib, ceritinib, alectinib, or brigatinib therapy
- subsequent therapy for ROS1 rearrangement-positive tumors and prior crizotinib or ceritinib therapy
- subsequent therapy for PD-L1 expression-positive (≥1%) tumors and EGFR, ALK negative or unknown and no prior platinum-doublet chemotherapy

- Continuation maintenance therapy for recurrent, advanced or metastatic disease in patients with performance status 0-2, tumors of nonsquamous cell histology, and no history of recent hemoptysis who achieve tumor response or stable disease following initial systemic therapy

  - as a single agent [2A for all others; 1 as a single agent or in combination with atezolizumab; 2B for locoregional recurrence or symptomatic local disease (excluding mediastinal lymph node recurrence with prior radiation therapy) with no evidence of disseminated disease]
  - in combination with pemetrexed if previously used with a first-line pemetrexed/platinum chemotherapy regimen

- in combination with atezolizumab if previously used first-line as part of an atezolizumab/carboplatin/paclitaxel/bevacizumab regimen

Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer

Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer

- Used in combination with paclitaxel and carboplatin as [2A]
  - primary treatment for patients with incomplete previous surgery and/or staging with stage II-IV and suspected unresectable residual disease
  - primary adjuvant therapy for pathologic stage II-IV disease
- Preferred therapy for platinum-resistant persistent disease or recurrence [2B for immediate treatment of biochemical relapse; 2A for clinical relapse]
  - in combination with oral cyclophosphamide, liposomal doxorubicin, weekly paclitaxel, or topotecan
  - as a single agent
- Used in combination with paclitaxel and carboplatin for patients who are poor surgical candidates or have low likelihood of optimal cytoreduction as [2A as continued treatment for stable disease following neoadjuvant therapy; 1 as neoadjuvant therapy]
  - neoadjuvant therapy
  - continued treatment for stable disease following neoadjuvant therapy

Bevacizumab-containing regimens should be used with caution and withheld for at least 6 weeks prior to interval debulking surgery due to potential interference with postoperative healing.

- Preferred therapy for platinum-sensitive persistent disease or recurrence [1 for first recurrence ≥6 months after completing prior chemotherapy; 2B for immediate treatment of biochemical

relapse; 2A for all others]

- in combination with carboplatin and gemcitabine
- in combination with carboplatin and paclitaxel
- in combination with carboplatin and liposomal doxorubicin

- Maintenance therapy as a single agent if used previously as part of a combination therapy [2A]

  - for patients with partial or complete remission or stable disease following primary therapy for stage II-IV disease
  - useful in certain circumstances, for patients with partial or complete response following recurrence therapy with bevacizumab for platinum-sensitive disease

- In combination with paclitaxel and carboplatin for rising CA-125 levels or clinical relapse in patients who have received no prior chemotherapy [2A]

Low-Grade Serous Carcinoma/Ovarian Borderline Epithelial Tumors (Low Malignant Potential) with invasive implants

- Adjuvant treatment in combination with carboplatin and paclitaxel for pathologic stage II-IV low-grade serous carcinoma or borderline epithelial tumors with invasive implants [2A]

Malignant Sex Cord-Stromal Tumors

- Single agent for clinical relapse in patients with stage II-IV disease [2A]

Carcinosarcoma (Malignant Mixed Müllerian Tumors)

- Preferred adjuvant treatment in combination with carboplatin and paclitaxel for pathologic stage I-IV disease [2A]

Mucinous Carcinoma

- Adjuvant treatment for pathologic stage II-IV disease in combination with [2A for combination with carboplatin and

paclitaxel; 2B for all others]

- carboplatin and paclitaxel
- fluorouracil, leucovorin, and oxaliplatin
- capecitabine and oxaliplatin

- Therapy for persistent disease or recurrence in combination with [2B]

  - fluorouracil, leucovorin, and oxaliplatin
  - capecitabine and oxaliplatin

Grade 1 Endometrioid Carcinoma

- Adjuvant treatment in combination with carboplatin and paclitaxel for pathologic stage II-IV, grade 1 endometrioid carcinoma [2A]

Clear Cell Carcinoma

- Adjuvant treatment in combination with carboplatin and paclitaxel for pathologic stage II-IV disease [2A]

Rectal Cancer

- Subsequent therapy for progression of unresectable advanced or metastatic disease [2A]

  - as the preferred anti-angiogenic agent in combination with irinotecan or FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen if previously treated with oxaliplatin-based therapy without irinotecan
  - in combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) regimen if previously treated with irinotecan-based therapy without oxaliplatin
  - as the preferred anti-angiogenic agent in combination with irinotecan or FOLFIRI if previously treated with fluoropyrimidine therapy without irinotecan or oxaliplatin
  - in combination with FOLFOX, CapeOX, or irinotecan and oxaliplatin if previously treated with fluoropyrimidine therapy

without irinotecan or oxaliplatin

- Preferred anti-angiogenic therapy as primary treatment for patients with unresectable metachronous metastases and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months [2A]

  - in combination with irinotecan
  - in combination with FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen

- Primary treatment for synchronous liver only and/or lung only metastases that are unresectable or medically inoperable in combination with [2A]

  - FOLFIRI (fluorouracil, leucovorin, and irinotecan) regimen
  - FOLFOX (fluorouracil, leucovorin, and oxaliplatin) regimen
  - CapeOX (capecitabine and oxaliplatin) regimen
  - FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan) regimen

- Therapy in combination with capecitabine or with FOLFOX (fluorouracil, leucovorin, and oxaliplatin), FOLFIRI (fluorouracil, leucovorin, and irinotecan), CapeOX (capecitabine and oxaliplatin), FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan), or 5-FU/leucovorin (fluorouracil and leucovorin) regimen [2A]

  - as primary treatment for T3, N Any; T1-2, N1-2; T4, N Any; or locally unresectable or medically inoperable disease if resection is contraindicated following neoadjuvant therapy
  - for synchronous liver only and/or lung only metastases that are unresectable or medically inoperable and remain unresectable (with no progression of primary tumor) after primary systemic therapy
  - following short-course radiation therapy (RT) or chemo/RT for synchronous liver only and/or lung only metastases that are unresectable or medically inoperable and remain unresectable

(with progression of primary tumor) after primary systemic therapy
- as primary treatment for synchronous abdominal/peritoneal metastases that are nonobstructing, or following local therapy for patients with existing or imminent obstruction
- as primary treatment for synchronous unresectable metastases of other sites
- as primary treatment for unresectable metachronous metastases in patients who have not received previous adjuvant FOLFOX or CapeOX within the past 12 months, who have received previous fluorouracil/leucovorin (5-FU/LV) or capecitabine therapy, or who have not received any previous chemotherapy
- for unresectable metachronous metastases that remain unresectable after primary treatment

- Therapy in combination with capecitabine or with FOLFOX (fluorouracil, leucovorin, and oxaliplatin), FOLFIRI (fluorouracil, leucovorin, and irinotecan), CapeOX (capecitabine and oxaliplatin), FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan), or 5-FU/leucovorin (fluorouracil and leucovorin) regimen [2B]

  - as adjuvant treatment (following resection and/or local therapy) for resectable metachronous metastases in patients who have received previous chemotherapy or had growth on neoadjuvant chemotherapy
  - as adjuvant treatment for unresectable metachronous metastases that converted to resectable disease after primary treatment

Small Bowel Adenocarcinoma

- Initial therapy in combination with capecitabine or 5-FU/leucovorin (fluorouracil and leucovorin) regimen for advanced or metastatic disease in patients not appropriate for intensive therapy [2A]
- Initial therapy in combination with FOLFOX (fluorouracil, leucovorin, and oxaliplatin), CapeOX (capecitabine and oxaliplatin), or FOLFOXIRI (fluorouracil, leucovorin, oxaliplatin, and irinotecan)

regimen for advanced or metastatic disease in patients appropriate for intensive therapy [2A]

Soft Tissue Sarcoma

Solitary Fibrous Tumor/Hemangiopericytoma

- In combination with temozolomide for the treatment of solitary fibrous tumor and hemangiopericytoma [2A]

Angiosarcoma

- Single agent therapy for angiosarcoma [2A]

Uterine Neoplasms

Endometrial Carcinoma

- Used in combination with carboplatin and paclitaxel for advanced and recurrent disease [2A]
- Single-agent therapy for disease that has progressed on prior cytotoxic chemotherapy [2A]

Vulvar Cancer

Squamous Cell Carcinoma

- In combination with cisplatin and paclitaxel (preferred regimen) or carboplatin and paclitaxel [2B for combination with carboplatin and paclitaxel; 2A for combination with cisplatin and paclitaxel]

    - as additional treatment for unresectable locally advanced disease clinically positive for residual tumor at the primary site and/or nodes
    - as additional treatment for locally advanced disease with positive margins following resection
    - as primary treatment for metastatic disease beyond the pelvis
    - for isolated groin/pelvic recurrence if prior external beam radiation therapy (EBRT)
    - for clinical nodal or distant recurrence with multiple pelvic nodes, distant metastasis, or prior pelvic EBRT

Note: Vaginal cancer should be treated according to guidelines for cervical cancer, and small bowel adenocarcinoma, anal adenocarcinoma and appendiceal carcinoma should be treated according to the guidelines for colorectal cancer.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":

Code	Code Description
Other CPT codes related to the CPB:	
67028	Intravitreal injection of a pharmacologic agent (separate procedure)
96401 - 96450	Chemotherapy administration
HCPCS codes covered if selection criteria are met:	
C9257	Injection, bevacizumab, 0.25 mg [covered for neovascular (wet) age related macular degeneration]
J9035	Injection, bevacizumab, 10 mg [for neovascular (wet) age related macular degeneration see C9257]
Q5107	Injection, bevacizumab-awwb, biosimilar, (mvasi), 10 mg
Q5118	Injection, bevacizumab-bvzr, biosimilar, (Zirabev), 10 mg
Other HCPCS codes related to the CPB:	
J8700	Temozolomide, oral, 5 mg
J9022	Injection, atezolizumab, 10 mg
J9035	Injection, pemetrexed, 10 mg
J9045	Injection, carboplatin, 50 mg
J9050	Injection, carmustine, 100 mg
J9060	Injection, cisplatin, powder or solution, 10 mg
J9190	Injection, fluorouracil, 500 mg
J9206	Injection, irinotecan, 20 mg
J9214	Injection, interferon, alfa-2b, recombinant, 1 million units
J9267	Injection, paclitaxel, 1 mg
J9328	Injection, temozolomide, 1 mg

Code	Code Description
Q0083 - Q0085	Chemotherapy administration
S0178	Lomustine, oral, 10mg
ICD-10 codes covered if selection criteria are met [See CPB 701 for ocular indications]:	
B39.4 [H32 also required]	Histoplasmosis capsulati, retinitis
B39.5 [H32 also required]	Histoplasmosis duboisli, retinitis
B39.9 [H32 also required]	Histoplasmosis, unspecified, retinitis
C17.0 - C17.9	Malignant neoplasm of small intestine, including duodenum
C18.0 - C21.8	Malignant neoplasm of colon, rectum, rectosigmoid junction and anus
C22.0	Liver cell carcinoma
C22.3	Angiosarcoma of liver
C26.0	Malignant neoplasm of intestinal tract, part unspecified
C34.00 - C34.92	Malignant neoplasm of the bronchus and lung [non-squamous, non-small cell] [covered for non- small cell lung cancer and non -squamous cell lung cancer]
C38.4	Malignant neoplasm of pleura [solitary fibrous tumors]
C45.0	Mesothelioma of pleura
C45.1	Mesothelioma of peritoneum
C45.2	Mesothelioma of pericardium
C45.7	Mesothelioma of other sites [tunica vaginalis testes mesothelioma]
C46.0 - C46.9	Kaposi's sarcoma [AIDS-related Kaposi's sarcoma]
C48.0 - C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C49.0 - C49.9	Malignant neoplasm of other connective and soft tissue, [angiosarcoma][hemangiopericytoma] [not covered for desmoplastic small round blue cell tumor]
C50.011 - C50.929	Malignant neoplasm of breast

Code	Code Description
C51.0 - C51.9	Malignant neoplasm of vulva
C52	Malignant neoplasm of vagina
C53.0 - C53.9	Malignant neoplasm of cervix uteri
C54.0, C54.1 - C54.3, C54.8, C54.9	Malignant neoplasm of corpus uteri, except isthmus [recurrent, metastatic endometrial cancer in members who have progressed on prior cytotoxic chemotherapy]
C56.1 - C56.9	Malignant neoplasm of ovary [epithelial and mucinous]
C57.00 - C57.02	Malignant neoplasm of fallopian tube
C64.1 - C64.9	Malignant neoplasm of kidney [renal cell carcinoma]
C71.0 - C71.9	Malignant neoplasm of brain [not covered for diffuse leptomeningeal glio-neuronal tumor]
C72.0 - C72.9	Malignant neoplasm of spinal cord, cranial nerves and other parts of central nervous system [not covered for diffuse leptomeningeal glio-neuronal tumor]
D32.0 - D32.9	Benign neoplasm of meninges [treatment for surgically inaccessible recurrent or progressive disease when radiation is not possible]
E08.311, E08.3211 - E08.3219, E08.3311 - E08.3319, E08.3411 - E08.3419, E08.3511 - E08.3559, E09.311, E09.3211 - E09.3219, E09.3311 - E09.3319, E09.3411 - E09.3419, E09.3511 -	Diabetic macular edema

Code	Code Description
E09.3559, E10.311, E10.3211 - E10.3219, E10.3311 - E10.3319, E10.3411 - E10.3419, E10.3511 - E10.3559, E11.311, E11.3211 - E11.3219, E11.3311 - E11.3319, E11.3411 - E11.3419, E11.3511 - E11.3559, E13.311, E13.3211 - E13.3219, E13.3311 - E13.3319, E13.3411 - E13.3419, E13.3511 - E13.3559	
G93.6	Cerebral edema
H30.001 - H30.049	Focal chorioretinal inflammaton
H30.101 - H30.149	Disseminated chorioretinal inflammation
H30.891 - H30.93	Other and unspecified chorioretinal inflammation

Code	Code Description
H31.20 - H31.29	Hereditary choroidal dystrophies
H32 [use with B39.4, B39.5, B39.9]	Chorioretinal disorders in diseases classified elsewhere
H34.8110 - H34.8192	Central retinal vein occlusion
H34.8310 - H34.8392	Venous tributary(branch) occlusion
H35.011 - H35.019	Changes in retinal vascular appearance
H35.041 - H35.049	Retinal microaneurysms unspecified
H35.051 - H35.059	Retinal neovascularization unspecified
H35.061 - H35.069	Retinal vasculitis
H35.09	Other intraretinal microvascular abnormalities
H35.101 - H35.23	Retinopathy of prematurity and other non-diabetic proliferative retinopathy
H35.3110 - H35.3293	Age-related macular degeneration
H35.33	Angioid streaks of macula
H35.50 - H35.54	Hereditary retinal dystrophies
H40.50x0 - H40.53x4	Glaucoma secondary to other eye disorders
H44.20 - H44.23	Degenerative myopia
H44.2A1 - H44.2E9	Degenerative myopia with choroidal neovascularization, macular hole, retinal detachment foveoschisis or other maculopathy

Code	Code Description
Q82.8	Other specified congenital malformations of skin [pseudoxanthoma elasticum]
T66.xxxA - T66.xxxS	Radiation sickness, unspecified [radiation therapy necrosis]
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
A18.50 - A18.59	Tuberculosis of eye
A51.43	Secondary syphilitic oculopathy
B25.9	Cytomegaloviral disease, unspecified (retinitis)
B58.01	Toxoplasma chorioretinitis
C08.0 - C08.9	Malignant neoplasm of other and unspecified major salivary glands [Mucoepidermoid carcinoma of the salivary gland]
C15.3 - C15.9	Malignant neoplasm of esophageal
C16.0 - C16.9	Malignant neoplasm of stomach
C22.1	Intrahepatic bile duct carcinoma
C23	Malignant neoplasm of gallbladder
C25.0 - C25.9	Malignant neoplasm of pancreas
C30.0	Malignant neoplasm of nasal cavity [olfactory neuroblastoma (esthesioneuroblastoma)]
C41.0 - C41.9	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C43.0 - C43.9	Malignant melanoma of skin
C44.42	Squamous cell carcinoma of scalp and neck
C44.99	Other specified malignant neoplasm of skin, unspecified [apocrine adenocarcinoma]
C46.0 - C46.9	Kaposi's sarcoma
C49.0 - C49.9	Malignant neoplasm of other connective and soft tissue
C49.A0 - C49.A9	Gastrointestinal stromal tumor
C61	Malignant melanoma of prostate
C67.1 - C67.9	Malignant neoplasm of bladder

Code	Code Description
C70.1	Malignant neoplasm of spinal meninges [diffuse leptomeningeal glio-neuronal tumor] [meningeal melanoma metastases]
C74.0	Malignant neoplasm of adrenal gland
C75.3	Malignant neoplasm of pineal gland
C7A.01 - C7A.8	Malignant neuroendocrine tumors
C7B.00 - C7B.8	Secondary neuroendocrine tumors
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum [pseudomyxoma peritonei]
C80.1	Malignant (primary) neoplasm, unspecified [cancer of unknown origin (primary occult)]
C90.00 - C90.02	Multiple myeloma
D3a.00 - D3a.8	Benign neuroendocrine tumors
D14.1	Benign neoplasm of larynx [laryngeal papillomatosis]
D18.00 - D18.09	Hemangioma [hemangioblastoma]
D21.4	Benign neoplasm of connective and other soft tissue of abdomen [stromal tumor]
D32.0	Benign neoplasm of cerebral meninges [meningioma]
D33.3	Benign neoplasm of cranial nerves [acoustic neuroma]
D48.1 - D48.2	Neoplasm of uncertain behavior of connective and other soft tissue [gastrointestinal stromal tumors]
D49.2	Neoplasm of unspecified behavior of bone, soft tissue, and skin [desmoid tumor]

Code	Code Description
E08.311 - E08.359 E09.311 - E09.359 E10.311 - E10.359 E11.311 - E11.359 E13.311 - E13.359	Diabetic retinopathy
E88.49	Other mitochondrial metabolism disorders [NARP syndrome]
G45.3	Amaurosis fugax
G93.6	Cerebral edema [radiation-induced]
G95.89	Other specified diseases of spinal cord
H16.241 - H16.249 H21.331 - H21.339 H44.001 - H44.9	Disorders of globe
H30.20 - H30.819 H31.001 - H31.129	Pars planitis, Harada's disease, chorioretinal scars and degenerations except angioid streaks
H31.301 - H31.9	Choroidal hemorrhage, detachment, and other disorders
H33.001 - H33.8	Retinal detachments and defects
H34.821 - H34.829 H35.70 - H35.739	Venous engorgement and separation of retinal layers
H35.021 - H35.029	Exudative retinopathy [Coat's disease]

Code	Code Description
H35.071 - H35.079	Retinal telangiectasis
H35.30 - H35.31 H35.351 - H35.359 H35.461 - H35.469	Degeneration of macula and posterior pole other than exudative senile macular degeneration and peripheral retinal degenerations.
H35.60 - H35.63 H35.81 - H35.9	Other retinal disorders
H40.001 - H42	Glaucoma
I78.0	Hereditary hemorrhagic telangiectasia
O01.0 - O01.9	Hydatidiform mole
Q15.0	Congenital glaucoma
Q28.2	Arteriovenous malformation of cerebral vessels
Q85.00 - Q85.02	Neurofibromatosis [nonmalignant]
Q85.8	Other phakomatoses, not elsewhere classified [von Hippel Lindau disease]
R04.0	Epistaxis [HHT-related epistaxis]
T66.xxx+	Radiation sickness, unspecified [radiation necrosis]

The above policy is based on the following references:

1. Abad A. New drugs in the treatment of gastric tumors. Clin Transl Oncol. 2008;10(5):256-261.
2. Abernethy AP, Coeytaux RR, Carson K, et al. Report on the evidence regarding off-label indications for targeted therapies used in cancer treatment. Technology Assessment Draft. Prepared for the Agency for Healthcare Research and Quality

(AHRQ) by the Duke Evidence-based Practice Center under Contract No. HHSA 290-02-0025. Rockville, MD: AHRQ; October 7, 2009.

3. Aghajanian C, Sill MW, Darcy KM, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: A Gynecologic Oncology Group study. J Clin Oncol. 2011;29(16):2259-2265.
4. Alexander HR. Malignant peritoneal mesothelioma: Epidemiology, risk factors, clinical presentation, diagnosis, and staging. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December 2019.
5. Alexander HR, Kindler HL. Malignant peritoneal mesothelioma: Treatment. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December 2019
6. Alsamarai S, Libutti SK, Saif MW. Updates in pancreatic neuroendocrine carcinoma. Highlights from the "2010 ASCO Annual Meeting". Chicago, IL, USA. June 4-8, 2010. JOP. 2010;11(4):336-340.
7. Al-Samkari H, Kritharis A, Rodriguez-Lopez JM, Kuter DJ. Systemic bevacizumab for the treatment of chronic bleeding in hereditary hemorrhagic telangiectasia. J Intern Med. 2019;285(2):223-231.
8. American Academy of Ophthalmology (AAO), Retinal/Vitreous Panel. Age-related macular degeneration. Preferred Practice Pattern. San Francisco, CA: AAO; 2015.
9. American Academy of Ophthalmology (AAO), Retinal/Vitreous Panel. Diabetic retinopathy. Preferred Practice Pattern. San Francisco, CA: AAO; 2017.
10. American Academy of Ophthalmology (AAO), Retinal/Vitreous Panel. Retinal vein occlusions. Preferred Practice Pattern. San Francisco, CA: AAO; 2015.
11. American Society of Health-System Pharmacists (ASHP). AHFS Drug Information [database online]. Hudson, OH: Lexi-Comp, Inc.; updated periodically. Available at; http://online.lexi.com/lco/action/index/dataset/complete_ashp [available with subscription]. Accessed January 17, 2019.
12. Amgen. Amgen and Allergan's MVASI™ (bevacizumab-awwb) and KANJINTI™ (trastuzumab-anns) now available in the United States. Press Release. Thousand Oaks, CA: Amgen; July 18, 2019.

13. Argiris A, Karamouzis MV, Gooding WE, et al. Phase II trial of pemetrexed and bevacizumab in patients with recurrent or metastatic head and neck cancer. J Clin Oncol. 2011;29(9):1140-1145.
14. Azzoli CG, Baker S Jr, Temin S, et al; American Society of Clinical Oncology. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol. 2009;27(36):6251-6266.
15. Blanck G, ed. Treating brain cancer by inhibiting formation of brain cancer blood vessels. USF's Health Headlines Explained. Tampa, FL: University of Southern Florida (USF); February 27, 2007.
16. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Off-label use of bevacizumab: Breast and lung cancer indications. TEC Assessment Program. Chicago, IL: BCBSA; October 2006;21(8).
17. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Off-label uses of bevacizumab: Renal cell carcinoma and other miscellaneous non-colorectal cancer indications. TEC Assessment Program. Chicago, IL: BCBSA; October 2006;21(9).
18. BlueCross BlueShield Association (BCBSA), Technology Evaluation Center (TEC). Off-label use of bevacizumab: Advanced adenocarcinoma of the pancreas. TEC Assessment Program. Chicago, IL: BCBSA; October 2009;24(4).
19. Boudreaux JP, Klimstra DS, Hassan MM, et al; North American Neuroendocrine Tumor Society (NANETS). The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: Well-differentiated neuroendocrine tumors of the Jejunum, Ileum, Appendix, and Cecum. Pancreas. 2010;39(6):753-66.
20. Burger MC, Zeiner PS, Jahnke K, et al. Addition of anti-angiogenetic therapy with bevacizumab to chemo- and radiotherapy for leptomeningeal metastases in primary brain tumors. PLoS One. 2016;11(6):e0155315.
21. Burger RA, Sill M, Monk BJ, et al. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: A GOG study. J Clin Oncol. 2005;23(16s): 457s.
22. CATT Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for neovascular age-related

macular degeneration. N Engl J Med. 2011;364(20):1897-1908.
23. Chan WM, Lai TY, Lui DT, et al. Intravitreal bevacizumab (Avastin) for myopic choroidal neovascularization: 1-year results of a prospective pilot study. Br J Ophthalmol.2009;93(2):150-154.
24. Chang YS, Kim JH, Kim KM, et al. Long-term outcomes of anti-vascular endothelial growth factor therapy for polypoidal choroidal vasculopathy. J Ocul Pharmacol Ther. 2016;32(4):219-224.
25. Chavan A, Schumann-Binarsch S, Luthe L, et al. Systemic therapy with bevacizumab in patients with hereditary hemorrhagic telangiectasia (HHT). Vasa. 2013;42(2):106-110.
26. Chekol SS, Sun CC. Malignant mesothelioma of the tunica vaginalis testis: diagnostic studies and differential diagnosis. Arch Pathol Lab Med. 2012;136(1):113-7.
27. Chen HX. Expanding the clinical development of bevacizumab. Oncologist. 2004;9(Suppl 1):27-35.
28. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med. 2014;370(8):709-722.
29. Cobleigh MA, Langmuir VK, Sledge GW, et al. A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. Semin Oncol. 2003;30(5 Suppl 16):117-124.
30. Coppin C, Le L, Porzsolt F, Wilt T. Targeted therapy for advanced renal cell carcinoma. Cochrane Database Syst Rev. 2008; (2):CD006017.
31. Coppin C, Porzsolt F, Awa A, et al. Immunotherapy for advanced renal cell cancer. Cochrane Database Systematic Rev. 2004; (3):CD001425.
32. Coutinho AK, Rocha Lima CM. Metastatic colorectal cancer: Systemic treatment in the new millennium. Cancer Control. 2003;10(3):224-238.
33. Crane CH, Winter K, Regine WF, et al. Phase II study of bevacizumab with concurrent capecitabine and radiation followed by maintenance gemcitabine and bevacizumab for locally advanced pancreatic cancer: Radiation Therapy Oncology Group RTOG 0411. J Clin Oncol. 2009;27(25):4096-4102.
34. Cunningham D, Stenning SP, Smyth EC, et al. Peri-operative chemotherapy with or without bevacizumab in operable oesophagogastric adenocarcinoma (UK Medical Research Council

ST03): Primary analysis results of a multicentre, open-label, randomised phase 2-3 trial. Lancet Oncol. 2017;18(3):357-370.

35. de Araujo RA, Araujo BJ. Desmoplastic small round cell tumor: Report of 2 cases treated with chemotherapy alone or in combination with bevacizumab. Case Rep Oncol. 2014;7(1):102-108.
36. Delishaj D, Ursino S, Pasqualetti F, et al. Bevacizumab for the treatment of radiation-induced cerebral necrosis: A systematic review of the literature. J Clin Med Res. 2017;9(4):273-280.
37. Desjardins A, Reardon DA, Herndon JE 2nd, et al. Bevacizumab plus irinotecan in recurrent WHO grade 3 malignant gliomas. Clin Cancer Res. 2008;14(21):7068-7073.
38. Diaz-Rubio E. New chemotherapeutic advances in pancreatic, colorectal, and gastric cancers. Oncologist. 2004;9(3):282-294.
39. Dietrich J, Gondi V, Mehta M. Delayed complications of cranial irradiation. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed May 2018.
40. Dohan A, Lousquy R, Eveno C, et al. Orthotopic animal model of pseudomyxoma peritonei: An in vivo model to test anti-angiogenic drug effects. Am J Pathol. 2014;184(7):1920-1929.
41. Dunbar EM, Pumphrey PK, Bidari S. Unexpectedly durable palliation of metastatic olfactory neuroblastoma using anti-angiogenic therapy with bevacizumab. Rare Tumors. 2012;4(2):e33.
42. Dupuis-Girod S, Ambrun A, Decullier E, et al. Effect of bevacizumab nasal spray on epistaxis duration in hereditary hemorrhagic telangectasia: A randomized clinical trial. JAMA. 2016;316(9):934-942.
43. Dupuis-Girod S, Ginon I, Saurin JC, et al. Bevacizumab in patients with hereditary hemorrhagic telangiectasia and severe hepatic vascular malformations and high cardiac output. JAMA. 2012;307(9):948-955.
44. Eriksson B. New drugs in neuroendocrine tumors: Rising of new therapeutic philosophies? Curr Opin Oncol. 2010;22(4):381-386.
45. Fazio N, Cinieri S, Lorizzo K, et al. Biological targeted therapies in patients with advanced enteropancreatic neuroendocrine carcinomas. Cancer Treat Rev. 2010;36 Suppl 3:S87-S94.
46. Fernando NH, Hurwitz HI. Inhibition of vascular endothelial growth factor in the treatment of colorectal cancer. Semin Oncol.

2003;30(3 Suppl 6):39-50.

47. Ferrara N. Role of vascular endothelial growth factor in physiologic and pathologic angiogenesis: Therapeutic implications. Semin Oncol. 2002;29(6 Suppl 16):10-14.
48. Figg WD, Kruger EA, Price DK, et al. Inhibition of angiogenesis: Treatment options for patients with metastatic prostate cancer. Invest New Drugs. 2002;20(2):183-194.
49. Franke AJ, Skelton Iv WP, Woody LE, et al. Role of bevacizumab for treatment-refractory meningiomas: A systematic analysis and literature review. Surg Neurol Int. 2018;9:133.
50. Fury MG, Lee NY, Sherman E, et al. A phase 2 study of bevacizumab with cisplatin plus intensity-modulated radiation therapy for stage III/IVB head and neck squamous cell cancer. Cancer. 2012;118(20):5008-5014.
51. Gaasch WH, Vander Salm TJ. Cardiac tumors. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed December 2019.
52. Gaffney DK, Erickson B, Jhingran A, et al; Expert Panel on Radiation Oncology-Gynecology. ACR Appropriateness Criteria® advanced cervical cancer. [online publication]. Reston, VA: American College of Radiology (ACR); 2012.
53. Garcia A, Oza A, Hirte H et al. Interim report of a phase II clinical trial of bevacizumab and low dose metronomic oral cyclophosphamide in recurrent ovarian and primary peritoneal carcinoma: A California Cancer Consortium Trial. J Clin Oncol 2005;23(16s): 455s.
54. Genentech Inc. Interim analysis of phase III trial shows Avastin plus chemotherapy extends survival of patients with first-line non-squamous, non-small cell lung cancer. First positive phase III results with an anti-angiogenesis therapy in lung cancer. Press Release. South San Francisco, CA: Genentech; March 14, 2005.
55. Genentech Inc. Interim analysis of phase III trial shows Avastin plus chemotherapy improved progression-free survival in patients with first-line metastatic breast cancer. Third solid tumor for Avastin shows improved clinical benefit in phase III trial; Avastin also being studied in phase III trials in pancreatic, renal, ovarian and prostate cancers. Press Release. South San Francisco, CA: Genentech; April 14, 2005.
56. Genentech, Inc. Avastin (bevacizumab) injection, for intravenous use. Prescribing Information. South San Francisco, CA:

Genentech; revised June 2019.

57. Genentech, Inc. Avastin (bevacizumab). Full Prescribing Information. South San Francisco, CA: Genentech; February 12, 2004.
58. Genentech, Inc. Genentech and OSI Pharmaceuticals announce topline results from phase III study evaluating the combination of Avastin and Tarceva as second-line treatment for advanced non-small cell lung cancer. Press Release. South San Francisco, CA: Genentech; October 5, 2008.
59. Giantonio BJ, Catalano PJ, Meropol NJ, et al; Eastern Cooperative Oncology Group Study E3200. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol. 2007;25(12):1539-1544.
60. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med. 2014;370(8):699-708.
61. Gill S, Thomas RR, Goldberg RM. Review article: Colorectal cancer chemotherapy. Aliment Pharmacol Ther. 2003;18(7):683-692.
62. Goey AK, Figg WD. Potential novel role of bevacizumab in glioblastoma and cervical cancer. Cancer Biol Ther. 2014;15(10):1296-1298.
63. Gonzalez J, Kumar AJ, Conrad CA, Levin VA. Effect of bevacizumab on radiation necrosis of the brain. Int J Radiat Oncol Biol Phys. 2007;67(2):323-326.
64. Gonzalez-Cao M, Viteri S, Díaz-Lagares A, et al. Preliminary results of the combination of bevacizumab and weekly Paclitaxel in advanced melanoma. Oncology. 2008;74(1-2):12-16.
65. Gonzalez-Cortijo L, Carballo N, González-Martín A, et al. Novel chemotherapy approaches in chemoradiation protocols. Gynecol Oncol. 2008;110(3 Suppl 2):S45-S48.
66. Gossage JR. The current role of bevacizumab in the treatment of hereditary hemorrhagic telangiectasia-related bleeding. Mayo Clin Proc. 2018 Feb;93(2):130-132.
67. Guenterberg KD, Grignol VP, Relekar KV, et al. A pilot study of bevacizumab and interferon-α2b in ocular melanoma. Am J Clin Oncol. 2011;34(1):87-91.

68. Guilhem A, Fargeton AE, Simon AC, et al. Intra-venous bevacizumab in hereditary hemorrhagic telangiectasia (HHT): A retrospective study of 46 patients. PLoS One. 2017;12(11):e0188943.
69. Gupta B, Elagouz M, Sivaprasad S. Intravitreal bevacizumab for choroidal neovascularization secondary to causes other than age-related macular degeneration. Eye.2010;24:203-213.
70. Guzman J M, Villegas R. Bevacizumab in the treatment of advanced colon cancer- review. Report 1/2005. Sevilla, Spain: Agencia e Evaluacion de Tecnologias Sanitarias de Andalucia (AETSA); 2005.
71. Hahn NM, Stadler WM, Zon RT, et al; Hoosier Oncology Group. Phase II trial of cisplatin, gemcitabine, and bevacizumab as first-line therapy for metastatic urothelial carcinoma: Hoosier Oncology Group GU 04-75. J Clin Oncol. 2011;29(12):1525-1530.
72. Hainsworth JD, Spigel DR, Thompson DS, et al. Paclitaxel/carboplatin plus bevacizumab/erlotinib in the first-line treatment of patients with carcinoma of unknown primary site. Oncologist. 2009;14(12):1189-1197.
73. Halderman AA, Ryan MW, Marple BF, et al. Bevacizumab for epistaxis in hereditary hemorrhagic telangiectasia: An evidence-based review. Am J Rhinol Allergy. 2018;32(4):258-268.
74. Hensley ML, Miller A, O'Malley DM, et al. Randomized phase III trial of gemcitabine plus docetaxel plus bevacizumab or placebo as first-line treatment for metastatic uterine leiomyosarcoma: An NRG Oncology/Gynecologic Oncology Group study. J Clin Oncol. 2015;33(10):1180-1185.
75. Hobday TJ, Qin R, Reidy-Lagunes D, et al. Multicenter phase II trial of temsirolimus and bevacizumab in pancreatic neuroendocrine tumors. J Clin Oncol. 2015;33(14):1551-1556.
76. Hu Q, Li H, Du Y, He J. Comparison of intravitreal bevacizumab and ranibizumab used for myopic choroidal neovascularization: A PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2019;98(12):e14905.
77. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350(23):2335-2342.

78. Iyer VN, Apala DR, Pannu BS, et al. Intravenous bevacizumab for refractory hereditary hemorrhagic telangiectasia-related epistaxis and gastrointestinal bleeding. Mayo Clin Proc. 2018;93(2):155-166.
79. Jackman DM, Kindler HL, Yeap BY, et al. Erlotinib plus bevacizumab in previously treated patients with malignant pleural mesothelioma. Cancer. 2008;113(4):808-814.
80. Jain RK. Tumor angiogenesis and accessibility: Role of vascular endothelial growth factor. Semin Oncol. 2002;29(6 Suppl 16):3-9.
81. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol. 2004;22(11):2184-2191.
82. Jordan K, Wolf HH, Voigt W, et al. Bevacizumab in combination with sequential high-dose chemotherapy in solid cancer, a feasibility study. Bone Marrow Transplant. 2010;45(12):1704-1709.
83. Kabbinavar F, Hurwitz HI, Fehrenbacher L, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol. 2003;21(1):60-65.
84. Kaklamani V, O'Regan RM. New targeted therapies in breast cancer. Semin Oncol. 2004;31(2 Suppl 4):20-25.
85. Kamat AA, Merritt WM, Coffey D, et al. Clinical and biological significance of vascular endothelial growth factor in endometrial cancer. Clin Cancer Res. 2007;13(24):7487-7495.
86. Kerbel RS. Antiangiogenic drugs and current strategies for the treatment of lung cancer. Semin Oncol. 2004;31(1 Suppl 1):54-60.
87. Kim JH, Kim JW, Lee TG, Lew YJ. Treatment outcomes in eyes with polypoidal choroidal vasculopathy with poor baseline visual acuity. J Ocul Pharmacol Ther. 2015;31(4):241-247.
88. Kim KB, Sosman JA, Fruehauf JP, et al. BEAM: A randomized phase II study evaluating the activity of bevacizumab in combination with carboplatin plus paclitaxel in patients with previously untreated advanced melanoma. J Clin Oncol. 2012;30(1):34-41.
89. Kindler HL, Karrison TG, Gandara DR, et al. Multicenter, double-blind, placebo-controlled, randomized phase II trial of

gemcitabine/cisplatin plus bevacizumab or placebo in patients with malignant mesothelioma. J Clin Oncol. 2012;30(20):2509-2515.

90. Kindler HL, Niedzwiecki D, Hollis D, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: Phase III trial of the Cancer and Leukemia Group B (CALGB 80303). J Clin Oncol. 2010;28(22):3617-3622.
91. Kindler HL. Moving beyond chemotherapy: Novel cytostatic agents for malignant mesothelioma. Lung Cancer. 2004;45 Suppl 1:S125-S127.
92. Kini SD, Yiu DW, Weisberg RA, et al. Bevacizumab as treatment for epistaxis in hereditary hemorrhagic telangiectasia: A literature review. Ann Otol Rhinol Laryngol. 2019;128(5):467-471.
93. Kulke MH, Siu LL, Tepper JE, et al. Future directions in the treatment of neuroendocrine tumors: Consensus report of the National Cancer Institute Neuroendocrine Tumor clinical trials planning meeting. J Clin Oncol. 2011;29(7):934-943.
94. Kurtoglu M, Davarpanah NN, Qin R, et al. Elevating the horizon: Emerging molecular and genomic targets in the treatment of advanced urothelial carcinoma. Clin Genitourin Cancer. 2015;13(5):410-420.
95. Lin X, DeAngelis LM. Treatment of brain metastases. J Clin Oncol. 2015;33(30):3475-3484.
96. Liu AK, Macy ME, Foreman NK. Bevacizumab as therapy for radiation necrosis in four children with pontine gliomas. Int J Radiat Oncol Biol Phys. 2009;75(4):1148-1154.
97. Lordick F, Ridwelski K, Al-Batran SE, et al. Treatment of gastric cancer. Onkologie. 2008;31 Suppl 5:32-39.
98. Lu VM, Ravindran K, Graffeo CS, et al. Efficacy and safety of bevacizumab for vestibular schwannoma in neurofibromatosis type 2: A systematic review and meta-analysis of treatment outcomes. J Neurooncol. 2019;144(2):239-248.
99. Mansour J, Fields B, Macomson S, Rixe O. Significant anti-tumor effect of bevacizumab in treatment of pineal gland glioblastoma multiforme. Target Oncol. 2014;9(4):395-398.
100. Martín M, Loibl S, von Minckwitz G, et al. Phase III trial evaluating the addition of bevacizumab to endocrine therapy as first-line

treatment for advanced breast cancer: The letrozole/fulvestrant and avastin (LEA) study. J Clin Oncol. 2015;33(9):1045-1052.

101. Matsuda M, Ishikawa E, Yamamoto T, et al. Efficacy of bevacizumab therapy in recurrent malignant gliomas in relation to the prior recurrence pattern or tumor location. J Clin Neurosci. 2017;40:115-119.
102. Maturo S, Hartnick CJ. Use of 532-nm pulsed potassium titanyl phosphate laser and adjuvant intralesional bevacizumab for aggressive respiratory papillomatosis in children: Initial experience. Arch Otolaryngol Head Neck Surg. 2010;136(6):561-565.
103. Mayer RJ. Targeted therapy for advanced colorectal cancer -- more is not always better. N Engl J Med. 2009;360(6):623-625.
104. Michaelides M, Kaines A, Hamilton RD, et al. A prospective randomized trial of intravitreal bevacizumab or laser therapy in the management of diabetic macular edema (BOLT Study) 12-month data: Report 2. Ophthalmology. 2010;117:1078-1086.
105. Micromedex Solutions [database online]. Truven Health Analytics, Greenwood Village, CO; updated periodically.. Available at: http://www.micromedexsolutions.com/. Accessed February 13, 2019.
106. Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol. 2005;23(4):792-799.
107. Miller KD. E2100: A phase III trial of paclitaxel versus paclitaxel/bevacizumab for metastatic breast cancer. Clin Breast Cancer. 2003;3(6):421-422.
108. Mintz-Hittner HA, Kennedy KA, Chuang AZ, et al. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. 2011;364(7):603-615.
109. Mirshahi A, Roohipoor R, Lashay A, et al. Bevacizumab-augmented retinal laser photocoagulation in proliferative diabetic retinopathy: A randomized double-masked clinical trial. Eur J Ophthalmol. 2008;18(2):263-269.
110. Monk BJ, Choi DC, Pugmire G, et al. Activity of bevacizumab (rhuMAB VEGF) in advanced refractory epithelial ovarian cancer. Gynecol Oncol, 2005;96:902-905.

111. Monk BJ, Sill MW, Burger RA, et al. Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: A gynecologic oncology group study. J Clin Oncol. 2009;27(7):1069-1074.
112. Moore DH. Chemotherapy for advanced, recurrent, and metastatic cervical cancer. J Natl Compr Canc Netw. 2008;6(1):53-57.
113. Moschovi M, Chrousos GP. Pineal gland masses. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed June 2015.
114. Narayana A, Kelly P, Golfinos J, et al. Antiangiogenic therapy using bevacizumab in recurrent high-grade glioma: Impact on local control and patient survival. J Neurosurg. 2009;110(1):173-180.
115. National Cancer Institute (NCI), PDQ Adult Treatment Editorial Board. Vaginal cancer treatment (PDQ). Health Professional Version. In: PDQ Cancer Information Summaries [Internet]. Bethesda, MD: NCI; February 27, 2019.
116. National Cancer Institute (NCI). Bevacizumab combined with chemotherapy prolongs survival for some patients with advanced lung cancer. News. Bethesda, MD: NCI: March 14, 2005.
117. National Cancer Institute (NCI). Bevacizumab combined with chemotherapy improves progression-free survival for patients with advanced breast cancer. News. Bethesda, MD: NCI; April 14, 2005.
118. National Cancer Institute (NCI). Bladder cancer treatment -- for health professionals (PDQ). Bethesda, MD: NCI; updated July 1, 2015.
119. National Cancer Institute (NCI). Vaginal Cancer Treatment–for health professionals (PDQ). Bethesda, MD: NCI; updated July 1, 2015.
120. National Comprehensive Cancer Network (NCCN). Anal carcinoma. NCCN Clinical Practice Guidelines in Oncology, Version 1.2019. Fort Washington, PA: NCCN; 2019
121. National Comprehensive Cancer Network (NCCN). Bevacizumab. NCCN Drugs & Biologics Compendium. Fort Washington, PA: NCCN; 2015.
122. National Comprehensive Cancer Network (NCCN). Bevacizumab. NCCN Drugs & Biologics Compendium. Fort Washington, PA: NCCN; 2017.

123. National Comprehensive Cancer Network (NCCN). Bevacizumab. NCCN Drugs & Biologics Compendium. Fort Washington, PA: NCCN; 2018.
124. National Comprehensive Cancer Network (NCCN). Bevacizumab. NCCN Drugs & Biologics Compendium. Fort Washington, PA: NCCN; 2019.
125. National Comprehensive Cancer Network (NCCN). Bevacizumab. NCCN Drugs & Biologics Compendium. Fort Washington, PA: NCCN; 2020.
126. National Comprehensive Cancer Network (NCCN). Bladder cancer. NCCN Clinical Practice Guidelines in Oncology, Version 2.2015. Fort Washington, PA: NCCN; 2015.
127. National Comprehensive Cancer Network (NCCN). Cervical cancer. NCCN Clinical Practice Guidelines in Oncology, Version 1.2015. Fort Washington, PA: NCCN; 2015.
128. National Comprehensive Cancer Network (NCCN). Colon cancer. NCCN Clinical Practice Guidelines in Oncology, Version 2.2019. Fort Washington, PA: NCCN; 2019
129. National Comprehensive Cancer Network (NCCN). Ovarian cancer including fallopian tube cancer and primary peritoneal cancer. NCCN Clinical Practice Guidelines in Oncology v.1.2009. Fort Washington, PA: NCCN; 2009.
130. National Comprehensive Cancer Network (NCCN). Ovarian cancer. Clinical Practice Guidelines in Oncology - v.1.2006. Jenkinstown, PA: NCCN; 2006.
131. National Comprehensive Cancer Network (NCCN). Paclitaxel, albumin-bound. NCCN Drugs & Biologics Compendium. Fort Washington, PA: NCCN; 2019.
132. National Comprehensive Cancer Network (NCCN). Rectal cancer. NCCN Clinical Practice Guidelines in Oncology, Version 2.2019. Fort Washington, PA: NCCN; 2019
133. National Comprehensive Cancer Network (NCCN). Hepatobiliary cancer. NCCN Clinical Practice Guidelines in Oncology, Version 1.2020. Fort Washington, PA: NCCN; 2020.
134. National Horizon Scanning Centre (NHSC). Bevacizumab (Avastin) for first-line treatment of metastatic colorectal cancer. Birmingham, UK: NHSC; 2004.
135. National Horizon Scanning Centre. Bevacizumab (Avastin) for advanced and metastatic breast cancer (stages III and IV):

Horizon scanning review. New and Emerging Technology Briefing. Birmingham, UK: National Horizon Scanning Centre (NHSC); 2006:1-6.

136. National Horizon Scanning Centre. Bevacizumab (Avastin) for advanced renal cell carcinoma: Horizon scanning review. New and Emerging Technology Briefing. Birmingham, UK: National Horizon Scanning Centre (NHSC); 2006:1-5.
137. National Horizon Scanning Centre. Bevacizumab (Avastin) for non-small cell lung cancer (NSCLC) - horizon scanning review. Birmingham, UK: National Horizon Scanning Centre (NHSC); 2005:1-5.
138. National Institute for Health and Clinical Excellence (NICE). Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. Technology Appraisal Guidance 118. London, UK: NICE; January 2007.
139. No authors listed. FDA Drug Approvals. Avastin (bevacizumab). Formulary. 2004;39(3):138, 140.
140. Norden AD, Young GS, Setayesh K, et al. Bevacizumab for recurrent malignant gliomas: Efficacy, toxicity, and patterns of recurrence. Neurology. 2008;70(10):779-787.
141. Ohtsu A. Chemotherapy for metastatic gastric cancer: Past, present, and future. J Gastroenterol. 2008;43(4):256-264.
142. Oishi A. The evidence for the treatment of polypoidal choroidal vasculopathy. Nippon Ganka Gakkai. Zasshi. 2015;119(11):781-786.
143. O'Neil BH, Goldberg RM. Novel chemotherapeutic and targeted agents in metastatic colorectal cancer: The time has arrived. Expert Opin Investig Drugs. 2003;12(12):1939-1949.
144. Packer RJ, Jakacki R, Horn M, et al. Objective response of multiply recurrent low-grade gliomas to bevacizumab and irinotecan. Pediatr Blood Cancer. 2009;52(7):791-795.
145. Parravano M, Menchini F, Virgili G. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for diabetic macular oedema. Cochrane Database Syst Rev. 2009
146. Pellegrini I, Sibille A, Paulus A, et al. How I manage... Malignant pleural mesothelioma in 2019. Rev Med Liege. 2019;74(12):627-632.
147. Philip PA, Mahoney MR, Holen KD, et al. Phase 2 study of bevacizumab plus erlotinib in patients with advanced

hepatocellular cancer. Cancer. 2012;118(9):2424-2430.

148. Pichon Riviere A, Augustovski F, Ferrante D, et al. Usefulness of bevacizumab in colon cancer patients. Buenos Aires, Argentina: Institute for Clinical Effectiveness and Health Policy (IECS); 2004.
149. Pichon-Riviere A, Augustovski F, Garcia Marti S, et al. Bevacizumab for the treatment of patients with advanced colorectal cancer [summary]. IRR No. 147. Buenos Aires, Argentina: Institute for Clinical Effectiveness and Health Policy (IECS); July 2008.
150. Picus J, Halabi S, Kelly WK, et al. A phase 2 study of estramustine, docetaxel, and bevacizumab in men with castrate-resistant prostate cancer: Results from Cancer and Leukemia Group B Study 90006. Cancer. 2011;117(3):526-533.
151. Plotkin SR, Stemmer-Rachamimov AO, Barker FG 2nd, et al. Hearing improvement after bevacizumab in patients with neurofibromatosis type 2. N Engl J Med. 2009;361(4):358-367.
152. Plotkin SR, Duda DG, Muzikansky A, et al. Multicenter, prospective, phase II and biomarker study of high-dose bevacizumab as induction therapy in patients with neurofibromatosis type 2 and progressive vestibular schwannoma. J Clin Oncol. 2019;37(35):3446-3454.
153. Porret E, Madelaine J, Galateau-Sallé F, et al. Epidemiology, molecular biology, diagnostic and therapeutic strategy of malignant pleural mesothelioma in 2007 - an update. Rev Mal Respir. 2007;24(8 Pt 2):6S157-6S164.
154. Psimaras D, Tafani C, Ducray F, et al. Bevacizumab in late-onset radiation-induced myelopathy. Neurology. 2016;86(5):454-457.
155. Quan K, Tang X, Song J, et al. Salvage therapy for brain arteriovenous malformations after failure of gamma knife stereotactic radiosurgery. World Neurosurg. 2018;110:e942-e951.
156. Ramaswamy B, Shapiro CL. Phase II trial of bevacizumab in combination with docetaxel in women with advanced breast cancer. Clin Breast Cancer. 2003;4(4):292-294.
157. Raymond E, Hobday T, Castellano D, et al. Therapy innovations: Tyrosine kinase inhibitors for the treatment of pancreatic neuroendocrine tumors. Cancer Metastasis Rev. 2011;30 Suppl 1:19-26.

158. Reid KM, Ramos-De la Medina A, Donohue JH. Diagnosis and surgical management of gallbladder cancer: A review. J Gastrointest Surg. 2007;11(5):671-681.
159. Riklin C, Seystahl K, Hofer S, et al. Antiangiogenic treatment for multiple CNS hemangioblastomas. Onkologie.2012;35(7-8):443-445.
160. Ross RW, Galsky MD, Febbo P, et al. Phase 2 study of neoadjuvant docetaxel plus bevacizumab in patients with high-risk localized prostate cancer: A Prostate Cancer Clinical Trials Consortium trial. Cancer. 2012;118(19):4777-4784.
161. Russo V, Barone A, Conte E, et al. Bevacizumab compared with macular laser grid photocoagulation for cystoid macular edema in branch retinal vein occlusion. Retina. 2009;29:511-5.
162. Sakata Y, Kawamura K, Shingu N, Ichikado K. Erlotinib plus bevacizumab as an effective treatment for leptomeningeal metastases from EGFR mutation-positive non-small cell lung cancer. Lung Cancer. 2016;99:120-122.
163. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006;355(24):2542-2550.
164. Shah MA, Ramanathan RK, Ilson DH, et al. Multicenter phase II study of irinotecan, cisplatin, and bevacizumab in patients with metastatic gastric or gastroesophageal junction adenocarcinoma. J Clin Oncol. 2006;24(33):5201-5206.
165. Shan F, Zhang B, Sun L, et al. The role of combination maintenance with pemetrexed and bevacizumab for advanced stage nonsquamous non-small cell lung cancer: A systematic review and meta-analysis. Biomed Res Int. 2018;2018:5839081.
166. Shih KC, Chowdhary S, Rosenblatt P, et al. A phase II trial of bevacizumab and everolimus as treatment for patients with refractory, progressive intracranial meningioma. J Neurooncol. 2016;129(2):281-288.
167. Shovlin C. Management of hereditary hemorrhagic telangiectasia. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed May 2019.
168. Siegel AB, Cohen EI, Ocean A, et al. Phase II trial evaluating the clinical and biologic effects of bevacizumab in unresectable hepatocellular carcinoma. J Clin Oncol. 2008;26(18):2992-2998.

169. Simonsen TG, Gaustad JV, Rofstad EK, et al. Bevacizumab treatment of meningeal melanoma metastases. J Transl Med. 2020;18(1):13.
170. Singer RJ, Ogilvy CS, Rordorf G. Brain arteriovenous malformations. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed June 2019.
171. Stokes P, Rimmer J. Intranasal bevacizumab in the treatment of HHT-related epistaxis: A systematic review. Rhinology. 2018;56(1):3-10.
172. Sun WL, Hutarew G, Gradl J, et al. Successful antiangiogenic combination therapy for pseudomyxoma peritonei with bevacizumab and capecitabine. Cancer Biol Ther. 2009;8(15):1459-1462.
173. Synderman C, Lin D, Brockstein BE, Foote R. Olfactory neuroblastoma (esthesioneuroblastoma). UpToDate [online serial]. Waltham, MA: UpToDate; reviewed May 2017.
174. Tewari KS, Sill MW, Long HJ 3rd, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med. 2014;370(8):734-743.
175. Thomas MB, Morris JS, Chadha R, et al. Phase II trial of the combination of bevacizumab and erlotinib in patients who have advanced hepatocellular carcinoma. J Clin Oncol. 2009;27(6):843-850.
176. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med. 2009;360(6):563-572.
177. Tsang H, Yau T, Khong PL, Epstein RJ. Bevacizumab-based therapy for advanced small bowel adenocarcinoma. Gut. 2008;57(11):1631-1632.
178. U.S. Food and Drug Administration (FDA). Bevacizumab (Avastin) in combination with interferon alfa. FDA News. Rockville, MD: FDA; July 31, 2009.
179. U.S. Food and Drug Administration (FDA). FDA approves Avastin to treat patients with aggressive and late-stage cervical cancer. Press Announcements. Silver Spring, MD: FDA; August 14, 2014.
180. U.S. Food and Drug Administration (FDA). FDA approves drug for treatment of aggressive brain cancer. FDA News. Rockville, MD: FDA; May 8, 2009.

181. U.S. Food and Drug Administration (FDA). FDA approves first angiogenesis inhibitor to treat colorectal cancer. FDA News. Rockville, MD: FDA; February 26, 2004.
182. U.S. Food and Drug Administration (FDA). FDA approves new combination therapy for lung cancer. FDA News. P06-166. Rockville, MD: FDA; October 12, 2006.
183. Uldrick TS, Wyvill KM, Kumar P, et al. Phase II study of bevacizumab in patients with HIV-associated Kaposi's sarcoma receiving antiretroviral therapy. J Clin Oncol. 2012;30(13):1476-1483.
184. Van Cutsem E, Vervenne WL, Bennouna J, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. J Clin Oncol. 2009;27(13):2231-2237.
185. VanderVeen DK, Melia M, Yang MB, et al. Anti-vascular endothelial growth factor therapy in primary treatment of type 1 retinopathy of prematurity: A report by the American Academy of Ophthalmology. Ophthalmology. 2017;124(5):619-633.
186. Varghese AM, Cardin DB, Hersch J, et al. Phase I study of trifluridine/tipiracil plus irinotecan and bevacizumab in advanced gastrointestinal tumors. Clin Cancer Res. 2020 Jan 10 [Epub ahead of print].
187. Vici P, Mariani L, Pizzuti L, et al. Emerging biological treatments for uterine cervical carcinoma. J Cancer. 2014;5(2):86-97.
188. Vredenburgh JJ, Desjardins A, Herndon JE, et al. Phase II trial of bevacizumab and irenotecan in recurrent malignant glioma. Clin Cancer Res. 2007;13(4):1253-1259.
189. Wagner ADADW, Arnold D, Grothey AAG, et al. Anti-angiogenic therapies for metastatic colorectal cancer. Cochrane Database Syst Rev. 2009;(3):CD005392.
190. Walker EP. FDA panel nixes bevacizumab for breast cancer. Medpage Today, July 20, 2010. .
191. Walter T, Brixi-Benmansour H, Lombard-Bohas C, Cadiot G. New treatment strategies in advanced neuroendocrine tumours. Dig Liver Dis. 2012;44(2):95-105.
192. White D, Kassim A, Bhaskar B, et al. Results from AMBER, a randomized phase 2 study of bevacizumab and bortezomib versus bortezomib in relapsed or refractory multiple myeloma. Cancer. 2013;119(2):339-347.

193. Whitehead KJ, Sautter NB, McWilliams JP, et al. Effect of topical intranasal therapy on epistaxis frequency in patients with hereditary hemorrhagic telangiectasia: A randomized clinical trial. JAMA. 2016;316(9):943-951.
194. Williams BJ, Park DM, Sheehan JP. Bevacizumab used for the treatment of severe, refractory perilesional edema due to an arteriovenous malformation treated with stereotactic radiosurgery. J Neurosurg. 2012;116(5):972-977.
195. Winer I, Buckanovich RJ. Bevacizumab for the treatment of non-resectable pseudomyxoma peritonei associated with mucinous ovarian tumor of low malignant potential - A comparison of two cases. Case Rep Oncol. 2009;3(1):1-8.
196. Wong ET, Joseph J, Wu JK. Hemangioblastoma. UpToDate [online serial]. Waltham, MA: UpToDate; reviewed May 2018.
197. Worley MJ Jr, Elias KM, Horowitz NS, et al. Durable remission for a woman with refractory choriocarcinoma treated with anti-endoglin monoclonal antibody and bevacizumab: A case from the New England Trophoblastic Disease Center, Brigham and Women's Hospital and Dana-Farber Cancer Institute. Gynecol Oncol. 2018;148(1):5-11.
198. Yang H, Jager MJ, Grossniklaus HE. Bevacizumab suppression of establishment of micrometastases in experimental ocular melanoma. Invest Ophthalmol Vis Sci. 2010;51(6):2835-2842.
199. Yang J, Zong L, Wang J, et al. Epithelioid trophoblastic tumors: Treatments, outcomes, and potential therapeutic targets. J Cancer. 2019;10(1):11-19.
200. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med. 2003;349(5):427-434.
201. Yazdani S, Hendi K, Pakravan M, et al. Intravitreal bevacizumab for neovascular glaucoma: A randomized controlled trial. J Glaucoma.2009;18(8):632-637.
202. Yong M, Zhou M, Deng G. Photodynamic therapy versus anti-vascular endothelial growth factor agents for polypoidal choroidal vasculopathy: A meta-analysis. BMC Ophthalmol. 2015;15:82.
203. Zalcman G, Mazières J, Margery J, et al. Bevacizumab 15mg/kg plus cisplatin-pemetrexed (CP) triplet versus CP doublet in

Malignant Pleural Mesothelioma (MPM): Results of the IFCT-GFPC-0701 MAPS randomized phase 3 trial [abstract]. J Clin Oncol. 2015;33:Abstract 7500.

204. Zalcman G, Mazieres J, Margery J, et al; French Cooperative Thoracic Intergroup (IFCT). Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet. 2016;387(10026):1405-1414.
205. Zhan Q, Miao F, Huang R, et al. Efficacy and safety of bevacizumab combined with chemotherapy in symptomatic brain metastases from lung adenocarcinoma: A retrospective analysis. J Thorac Dis. 2019;11(11):4725-4734.
206. Zhang S, Mao XD, Wang HT, et al. Efficacy and safety of bevacizumab plus erlotinib versus bevacizumab or erlotinib alone in the treatment of non-small-cell lung cancer: A systematic review and meta-analysis. BMJ Open. 2016;6(6):e011714.
207. Zhao B, Zhang W, Yu D, et al. Erlotinib in combination with bevacizumab has potential benefit in non-small cell lung cancer: A systematic review and meta-analysis of randomized clinical trials. Lung Cancer. 2018;122:10-21.
208. Zuniga RM, Torcuator R, Jain R, et al. Efficacy, safety and patterns of response and recurrence in patients with recurrent high-grade gliomas treated with bevacizumab plus irinotecan. J Neurooncol. 2009;91(3):329-336.