RxAdvance

NEW DRUG APPROVAL

Brand Name	Vegzelma®
Generic Name	bevacizumab-adcd
Drug Manufacturer	Celltrion, Inc.

Indications for Use

Vegzelma® is a vascular endothelial growth factor inhibitor indicated for the treatment of:

Metastatic Colorectal Cancer:

- Combination with intravenous fluorouracil-based chemotherapy, is indicated for the first- or second-line treatment of patients with metastatic colorectal cancer (mCRC).
- Combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment of patients with mCRC who have progressed on a first-line bevacizumab product-containing regimen.

Limitations of Use: Not indicated for adjuvant treatment of colon cancer.

First-Line Non-Squamous Non–Small Cell Lung Cancer: Combination with carboplatin and paclitaxel, is indicated for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer (NSCLC).

Recurrent Glioblastoma: Indicated for the treatment of recurrent glioblastoma (GBM) in adults.

Metastatic Renal Cell Carcinoma: Combination with interferon alfa, is indicated for the treatment of metastatic renal cell carcinoma (mRCC).

Persistent, Recurrent, or Metastatic Cervical Cancer: Combination with paclitaxel and cisplatin or paclitaxel and topotecan, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.

Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer:

- Combination with carboplatin and paclitaxel, followed by Vegzelma® as a single agent, is indicated for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection.
- Combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan, is indicated for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than 2 prior chemotherapy regimens.
- Combination with carboplatin and paclitaxel, or with carboplatin and gemcitabine, followed by Vegzelma® as a single agent, is indicated for the treatment of patients with platinum sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

New Drug Approval

FDA approval date: September 27, 2022

Review designation: N/A

Type of review: Biologic License Application (BLA): 761268

Dispensing restriction: N/A

Therapeutic Class

Antineoplastic Agent; Monoclonal Antibody and Vascular Endothelial Growth Factor (VEGF) Inhibitor

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Metastatic Colorectal Cancer: Cancer is a disease characterized by the unchecked division of abnormal cells. When this type of growth occurs in the colon or rectum, it is called colorectal cancer (CRC). The colon and rectum (colorectum), along with the anus, make up the large intestine, the final segment of the gastrointestinal (GI) system. The large intestine is sometimes called the large bowel, which is why CRC is sometimes referred to as bowel cancer. The function of the large intestine is to absorb water and electrolytes from food matter and eliminate feces. Once a polyp progresses to cancer, it can grow into the wall of the colon or rectum where it may invade blood or lymph vessels that carry away cellular waste and fluid. Cancer cells typically spread first into nearby lymph nodes, which are bean-shaped structures that help fight infections. They can also be carried via blood vessels to other organs and tissues, such as the liver or lungs, or be shed directly into the peritoneum (membrane lining the abdomen). The spread of cancer cells to parts of the body distant from where the tumor started is called metastasis.

Epidemiology: In 2020, there will be an estimated 104,610 new cases of colon cancer and 43,340 cases of rectal cancer diagnosed in the US. Although the majority of CRCs are in adults ages 50 and older, 17,930 (12%) will be diagnosed in individuals younger than age 50, the equivalent of 49 new cases per day. An estimated 53,200 people will die from CRC in 2020, including 3,640 men and women younger than age 50. Unfortunately, reliable statistics on deaths from colon and rectal cancers separately are not available because almost 40% of deaths from rectal cancer are misclassified as colon cancer on death certificates.

Non-Squamous Non–Small Cell Lung Cancer: Non-small cell lung cancer (NSCLC) is a term that includes a variety of different lung cancers, most notably adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinoma is the most common type of lung cancer in this category and includes one-half of all lung cancer cases. Squamous cell carcinoma is another type of NSCLC that had been the most frequently diagnosed lung cancer before this time. Squamous cell carcinoma (SCC) usually originates at the origin of the tracheobronchial tree, but more cases are now diagnosed in the periphery of the lung. Large cell carcinoma is a subset of NSCLC that is a diagnosis of exclusion. It is poorly differentiated and cannot be further classified by immunohistochemistry (IHC) or electron microscopy. However, 90% of cases will show squamous, glandular, or neuroendocrine differentiation. NSCLC also includes other subsets of lung cancer, with both heterogeneous categories and broad terminology. These include adenosquamous carcinoma, sarcomatoid carcinoma, and non-small cell neuroendocrine tumors.

Epidemiology: Lung cancer is a diagnosis that approximately 230,000 United States citizens will receive annually. Deaths are estimated at 135,000 patients per year. Lung cancer deaths have become more numerous than the deaths from prostate, breast, brain, and colorectal cancer combined. It has now become the most common cause of cancer deaths in men and the second most common in women.

Recurrent Glioblastoma: Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults accounting for 45.2% of malignant primary brain and CNS tumors. GBM remains an incurable disease with a median survival of 15 months. Only 5.5 % of patients survived five years post-diagnosis. GBMs comprises primary and secondary subtypes that evolve through different genetic pathways affecting patients at different ages with differences in outcomes. Primary GBMs account for 80% of GBMs and occur in older patients with a mean age of 62 yrs while secondary GBMs occur from lower-grade astrocytoma or oligodendroglioma in younger patients with

a mean age of 45 years. Secondary GBMs are usually located in the frontal lobe, have a lesser degree of necrosis, and carry a better prognosis than primary GBMs.

Epidemiology: Based on the 2013 CBTRUS (Central Brain Tumour Registry of the United States) report, the average annual age-adjusted incidence rate (IR) of GBM is 3.19/100,000 population. This is the highest incidence rate among malignant brain and CNS tumors. GBM is primarily diagnosed in adults with a median age of 64 years. It is very rare in children. The incidence increases with age with a peak at 75-84 years of age and a drop after 85 years. The number of cases is expected to increase, given the increasing aging population in the United States. GBMs are reported more in men; the incidence rate in men is 1.57 % more than that of women. The frequency of primary GBMs is more in men, and secondary is more common in women. The incidence of GBM is more in whites, followed by blacks.

Metastatic Renal Cell Carcinoma: Renal cell cancer (RCC) develop metastatic spread in approximately 33% of cases. The clinical management of patients with metastatic RCC is complicated by the lack of significant efficacy from available therapies. Common sites of metastases include the lung, liver, bone, brain, and adrenal gland, with case reports detailing the capacity of RCC to appear almost anywhere in the body. More than one organ system is often involved in the metastatic process. Metastases may be found at diagnosis or at some interval after nephrectomy. Approximately 20% to 50% of patients will eventually develop metastatic disease after nephrectomy. A shorter interval between nephrectomy and the development of metastases is associated with a poorer prognosis. Patients with metastatic RCC face a dismal prognosis, with a median survival time of only 6 to 12 months and a 2-year survival rate of 10% to 20%.

Epidemiology: Though renal cell carcinoma (RCC) accounts for 2% of global cancer diagnoses and deaths, it has more than doubled in incidence in the developed world over the past half-century, and today is the ninth most common neoplasm in the United States (US). While North America and Western Europe have the highest disease burden (with the Belarus highest in incidence), Latin America, Asia and Africa are projected to see an increase in incidence as nation's transition to a Western lifestyle. Most cases of RCC are discovered incidentally on imaging, and survival is highly dependent on the stage at diagnosis, with the metastatic disease having only a 12% 5-year survival rate. Two-thirds of RCC diagnoses are made in men, and the average age of diagnosis in the US is 64.

Cervical Cancer: Cervical cancer continues to be listed among the top gynecologic cancers worldwide. According to current data, it is ranked fourteenth among all cancers and fourth-ranked cancer among women worldwide. HPV is the causative agent in cervical cancer. More than 75 percent of cases are due to high-risk HPV 16 and 18. Although there are more than a half-million cases of HPV identified annually, most are low-grade infections and will spontaneously resolve within two years. Progression of high-grade lesions and cancer are seen in the presence of other carcinogenic factors.

Epidemiology: Globally, there are more than 500,000 new cases of cervical cancer annually. Approximately 250,000 women die of cervical cancer annually. In the United States, about 4000 women die from cervical cancer annually with African Americans, Hispanics, and women in low-resource areas having higher disparities in evidenced-based care and a much higher mortality rate.

Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer: Ovarian epithelial tumors may arise within endometriosis or cortical inclusions of Müllerian epithelium, likely a form of endosalpingiosis. These include low-grade endometrioid carcinomas, clear cell carcinomas, borderline and low-grade serous carcinomas, and mucinous carcinomas. These tumors are thought to evolve slowly from lower-grade precursor conditions (endometriotic cysts, cystadenomas, etc) and are classified as type I tumors. Fallopian tube carcinomas arise in the distal fallopian tube and the majority of these are high-grade serous carcinomas. These are thought to evolve rapidly from more obscure precursors and are designated as type II tumors. This latter group encompasses high-grade endometrioid carcinomas and carcinosarcomas. All of these high-grade carcinomas are nearly always associated with mutations in the TP53 gene. The peritoneum, including the omentum and pelvic and abdominal

viscera, is the most common site for dissemination of ovarian and fallopian tube cancers. This includes the diaphragmatic and liver surfaces. Pleural involvement is also seen. Other extraperitoneal or extrapleural sites are relatively uncommon but can occur. After systematic pathologic analysis has excluded a tubal or ovarian site of origin, malignancies that appear to arise primarily on the peritoneum have an identical spread pattern, and frequently may involve the ovaries and fallopian tubes secondarily. These "peritoneal" tumors are thought to arise in endosalpingiosis.

Epidemiology: Malignant tumors of the ovaries occur at all ages with variation in histologic subtype by age. For example, in women younger than 20 years of age, germ cell tumors predominate, while borderline tumors typically occur in women in their 30s and 40s—10 or more years younger than in women with invasive epithelial ovarian cancers, which mostly occur after the age of 50 years. The lifetime risk of a woman in the USA developing ovarian cancer is approximately 1 in 70. Approximately 23% of gynecologic cancers are ovarian in origin, but 47% of all deaths from cancer of the female genital tract occur in women with ovarian cancer. Overall, epithelial ovarian cancer accounts for 4% of all new cancer diagnoses in women and 5% of all cancer-related deaths.

Efficacy

Metastatic Colorectal Cancer

Study AVF2107g: The safety and efficacy of bevacizumab was evaluated in a double-blind, active-controlled study [AVF2107g (NCT00109070)] in 923 patients with previously untreated mCRC who were randomized (1:1:1) to placebo with bolus-IFL (irinotecan 125 mg/m^2 , fluorouracil 500 mg/m^2 , and leucovorin 20 mg/m^2 given once weekly for 4 weeks every 6 weeks), bevacizumab (5 mg/kg every 2 weeks) with bolus-IFL, or bevacizumab (5 mg/kg every 2 weeks) with fluorouracil and leucovorin. Enrollment to the bevacizumab with fluorouracil and leucovorin arm was discontinued after enrollment of 110 patients in accordance with the protocol-specified adaptive design. Bevacizumab was continued until disease progression or unacceptable toxicity or for a maximum of 96 weeks. The main outcome measure was overall survival (OS).

The median age was 60 years; 60% were male, 79% were White, 57% had an ECOG performance status of 0, 21% had a rectal primary and 28% received prior adjuvant chemotherapy. The dominant site of disease was extra-abdominal in 56% of patients and was the liver in 38% of patients.

The addition of bevacizumab improved survival across subgroups defined by age (<65 years, ≥65 years) and sex. Results are presented in Table 1.

Table 1: Efficacy Results in Study AVF2107g

Efficacy Parameter	Bevacizumab with bolus-IFL (N=402)	Placebo with bolus-IFL (N=411)
Overall Survival		
Median, in months	20.3	15.6
Hazard ratio (95% CI)	0.66 (0.54, 0.81)	
p-value[a]	< 0.001	
Progression-Free Survival		
Median, in months	10.6	6.2
Hazard ratio (95% CI)	0.54 (0.45, 0.66)	
p-value[a]	< 0.001	
Overall Response Rate		
Rate (%)	45%	35%
p-value[b]	< 0.01	
Duration of Response		

Table 1: Efficacy Results in Study AVF2107g		
Efficacy Parameter	**Bevacizumab with bolus-IFL (N=402)**	**Placebo with bolus-IFL (N=411)**
Median, in months	10.4	7.1

[a] by stratified log-rank test.
[b] by χ^2 test.

Among the 110 patients randomized to bevacizumab with fluorouracil and leucovorin, median OS was 18.3 months, median progression-free survival (PFS) was 8.8 months, overall response rate (ORR) was 39%, and median duration of response was 8.5 months.

Study E3200: The safety and efficacy of bevacizumab were evaluated in a randomized, open-label, active-controlled study [E3200 (NCT00025337)] in 829 patients who were previously treated with irinotecan and fluorouracil for initial therapy for metastatic disease or as adjuvant therapy. Patients were randomized (1:1:1) to FOLFOX4 (Day 1: oxaliplatin 85 mg/m^2 and leucovorin 200 mg/m^2 concurrently, then fluorouracil 400 mg/m^2 bolus followed by 600 mg/m^2 continuously; Day 2: leucovorin 200 mg/m^2 , then fluorouracil 400 mg/m^2 bolus followed by 600 mg/m^2 continuously; every 2 weeks), bevacizumab (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1) with FOLFOX4, or bevacizumab alone (10 mg/kg every 2 weeks). Bevacizumab was continued until disease progression or unacceptable toxicity. The main outcome measure was OS.

The bevacizumab alone arm was closed to accrual after enrollment of 244 of the planned 290 patients following a planned interim analysis by the data monitoring committee based on evidence of decreased survival compared to FOLFOX4 alone.

The median age was 61 years; 60% were male, 87% were White, 49% had an ECOG performance status of 0, 26% received prior radiation therapy, and 80% received prior adjuvant chemotherapy, 99% received prior irinotecan with or without fluorouracil for metastatic disease, and 1% received prior irinotecan and fluorouracil as adjuvant therapy.

The addition of bevacizumab to FOLFOX4 resulted in significantly longer survival as compared to FOLFOX4 alone; median OS was 13.0 months vs. 10.8 months [hazard ratio (HR) 0.75 (95% CI: 0.63, 0.89), p-value of 0.001 stratified log-rank test] with clinical benefit seen in subgroups defined by age ($<$ 65 years, $\geq$ 65 years) and sex. PFS and ORR based on investigator assessment were higher in patients receiving bevacizumab with FOLFOX4.

Study TRC-0301: The activity of bevacizumab with fluorouracil (as bolus or infusion) and leucovorin was evaluated in a single arm study [TRC-0301 (NCT00066846)] enrolling 339 patients with mCRC with disease progression following both irinotecan- and oxaliplatin-based chemotherapy. Seventy-three percent of patients received concurrent bolus fluorouracil and leucovorin. One objective partial response was verified in the first 100 evaluable patients for an ORR of 1% (95% CI: 0%, 5.5%).

Study ML18147: The safety and efficacy of bevacizumab were evaluated in a prospective, randomized, open-label, multinational, controlled study [ML18147 (NCT00700102)] in 820 patients with histologically confirmed mCRC who had progressed on a first-line bevacizumab-containing regimen. Patients were excluded if they progressed within 3 months of initiating first-line chemotherapy and if they received bevacizumab for less than 3 consecutive months in the first-line setting. Patients were randomized (1:1) within 3 months after discontinuing bevacizumab as first-line treatment to receive fluoropyrimidine-irinotecan- or fluoropyrimidine oxaliplatin-based chemotherapy with or without bevacizumab (5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks). The choice of second-line treatment was contingent upon first-line chemotherapy. Second-line treatment was administered until progressive disease or unacceptable toxicity. The main outcome measure was OS. A secondary outcome measure was ORR.

The median age was 63 years (21 to 84 years); 64% were male, 52% had an ECOG performance status of 1, 44% had an ECOG performance status of 0, 58% received irinotecan-based therapy as first-line treatment, 55% progressed on first-line treatment within 9 months, and 77% received their last dose of bevacizumab as first line treatment

within 42 days of being randomized. Second-line chemotherapy regimens were generally balanced between each arm.

The addition of bevacizumab to fluoropyrimidine-based chemotherapy resulted in a statistically significant prolongation of OS and PFS. There was no significant difference in ORR. Results are presented in Table 2.

Table 2: Efficacy Results in Study ML18147

Efficacy Parameter	Bevacizumab with Chemotherapy (N=409)	Chemotherapy (N=411)
Overall Survival[a]		
Median, in months	11.2	9.8
Hazard ratio (95% CI)	0.81 (0.69, 0.94)	
Progression-Free Survival[b]		
Median, in months	5.7	4.0
Hazard ratio (95% CI)	0.68 (0.59, 0.78)	

[a] p=0.0057 by unstratified log-rank test.
[b] p-value < 0.0001 by unstratified log-rank test.

Lack of Efficacy in Adjuvant Treatment of Colon Cancer

Lack of efficacy of bevacizumab as an adjunct to standard chemotherapy for the adjuvant treatment of colon cancer was determined in two randomized, open-label, multicenter clinical studies. The first study [BO17920 (NCT00112918)] was conducted in 3451 patients with high-risk stage II and III colon cancer, who had undergone surgery for colon cancer with curative intent. Patients were randomized to receive bevacizumab at a dose equivalent to 2.5 mg/kg/week on either a 2-weekly schedule with FOLFOX4 (N=1155) or on a 3-weekly schedule with XELOX (N=1145) or FOLFOX4 alone (N=1151). The main outcome measure was disease free survival (DFS) in patients with stage III colon cancer.

The median age was 58 years; 54% were male, 84% were White and 29% were ≥ 65 years. Eighty-three percent had stage III disease.

The addition of bevacizumab to chemotherapy did not improve DFS. As compared to FOLFOX4 alone, the proportion of stage III patients with disease recurrence or with death due to disease progression were numerically higher for patients receiving bevacizumab with FOLFOX4 or with XELOX. The hazard ratios for DFS were 1.17 (95% CI: 0.98,1.39) for bevacizumab with FOLFOX4 versus FOLFOX4 alone and 1.07 (95% CI: 0.90, 1.28) for bevacizumab with XELOX versus FOLFOX4 alone. The hazard ratios for OS were 1.31 (95% CI: 1.03, 1.67) and 1.27 (95% CI: 1, 1.62) for the comparison of bevacizumab with FOLFOX4 versus FOLFOX4 alone and bevacizumab with XELOX versus FOLFOX4 alone, respectively. Similar lack of efficacy for DFS was observed in the bevacizumab-containing arms compared to FOLFOX4 alone in the high-risk stage II cohort.

In a second study [NSABP-C-08 (NCT00096278)], patients with stage II and III colon cancer who had undergone surgery with curative intent, were randomized to receive either bevacizumab administered at a dose equivalent to 2.5 mg/kg/week with mFOLFOX6 (N=1354) or mFOLFOX6 alone (N=1356). The median age was 57 years, 50% were male and 87% White. Seventy-five percent had stage III disease. The main outcome was DFS among stage III patients. The HR for DFS was 0.92 (95% CI: 0.77, 1.10). OS was not significantly improved with the addition of bevacizumab to mFOLFOX6 [HR 0.96 (95% CI: 0.75,1.22)].

First-Line Non–Squamous Non–Small Cell Lung Cancer

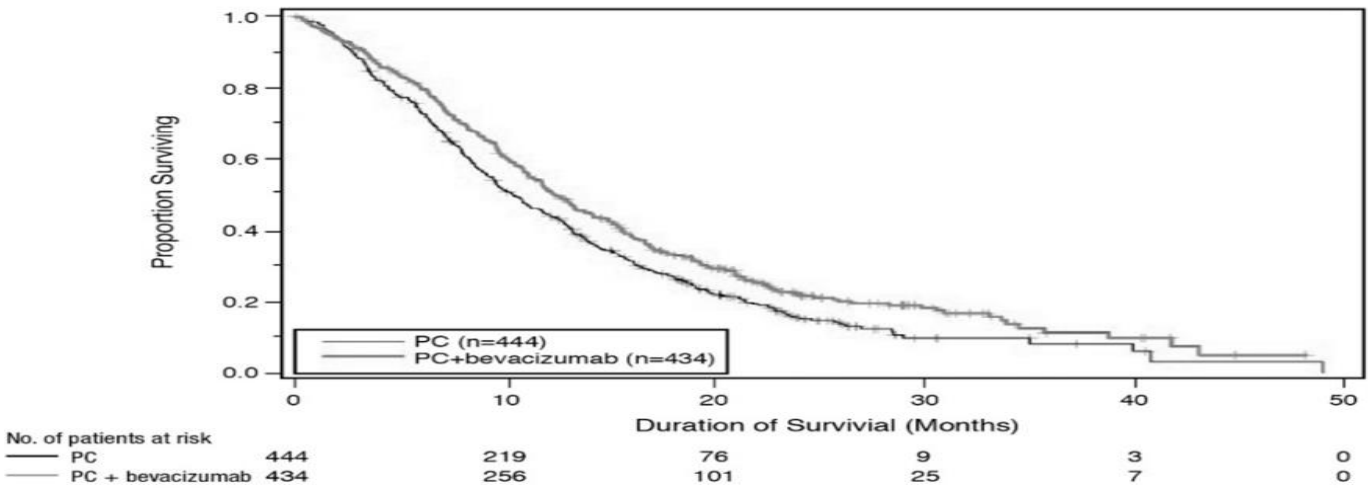
Study E4599: The safety and efficacy of bevacizumab as first-line treatment of patients with locally advanced, metastatic, or recurrent non–squamous NSCLC was studied in a single, large, randomized, active-controlled, open-

label, multicenter study [E4599 (NCT00021060)]. A total of 878 chemotherapy-naïve patients with locally advanced, metastatic or recurrent non–squamous NSCLC were randomized (1:1) to receive six 21-day cycles of paclitaxel (200 mg/m^2) and carboplatin (AUC 6) with or without bevacizumab 15 mg/kg. After completing or discontinuing chemotherapy, patients randomized to receive bevacizumab continued to receive bevacizumab alone until disease progression or until unacceptable toxicity. The trial excluded patients with predominant squamous histology (mixed cell type tumors only), CNS metastasis, gross hemoptysis (1/2 teaspoon or more of red blood), unstable angina, or receiving therapeutic anticoagulation. The main outcome measure was duration of survival.

The median age was 63 years; 54% were male, 43% were ≥ 65 years, and 28% had ≥ 5% weight loss at study entry. Eleven percent had recurrent disease. Of the 89% with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had Stage IV disease.

OS was statistically significantly longer for patients receiving bevacizumab with paclitaxel and carboplatin compared with those receiving chemotherapy alone. Median OS was 12.3 months vs. 10.3 months [HR 0.80 (95% CI: 0.68, 0.94), final p-value of 0.013, stratified log-rank test]. Based on investigator assessment, which was not independently verified, patients were reported to have longer PFS with bevacizumab with paclitaxel and carboplatin compared to chemotherapy alone. Results are presented in Figure 1.

Figure 1: Kaplan-Meier Curves for Duration of Survival in First-Line Non-Squamous Non-Small Cell Lung Cancer in Study E4599



In an exploratory analysis across patient subgroups, the impact of bevacizumab on OS was less robust in the following subgroups: women [HR 0.99 (95% CI: 0.79, 1.25)], patients ≥ 65 years [HR 0.91 (95% CI: 0.72, 1.14)] and patients with ≥ 5% weight loss at study entry [HR 0.96 (95% CI: 0.73, 1.26)].

Study BO17704: The safety and efficacy of bevacizumab in patients with locally advanced, metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy was studied in another randomized, double blind, placebo-controlled study [BO17704 (NCT00806923)]. A total of 1043 patients were randomized (1:1:1) to receive cisplatin and gemcitabine with placebo, bevacizumab 7.5 mg/kg or bevacizumab 15 mg/kg. The main outcome measure was PFS. Secondary outcome measure was OS.

The median age was 58 years; 36% were female and 29% were ≥ 65 years. Eight percent had recurrent disease and 77% had Stage IV disease.

PFS was significantly higher in both bevacizumab-containing arms compared to the placebo arm [HR 0.75 (95% CI: 0.62, 0.91), p-value of 0.0026 for bevacizumab 7.5 mg/kg and HR 0.82 (95% CI: 0.68; 0.98), p-value of 0.0301 for

bevacizumab 15 mg/kg]. The addition of bevacizumab to cisplatin and gemcitabine failed to demonstrate an improvement in the duration of OS [HR 0.93 (95% CI: 0.78; 1.11), p-value of 0.420 for bevacizumab 7.5 mg/kg and HR 1.03 (95% CI: 0.86, 1.23), p-value of 0.761 for bevacizumab 15 mg/kg].

Recurrent Glioblastoma

Study EORTC 26101: The safety and efficacy of bevacizumab were evaluated in a multicenter, randomized (2:1), open-label study in patients with recurrent GBM (EORTC 26101, NCT01290939). Patients with first progression following radiotherapy and temozolomide were randomized (2:1) to receive bevacizumab (10 mg/kg every 2 weeks) with lomustine (90 mg/m^2 every 6 weeks) or lomustine (110 mg/m^2 every 6 weeks) alone until disease progression or unacceptable toxicity. Randomization was stratified by World Health Organization performance status (0 vs. >0), steroid use (yes vs. no), largest tumor diameter (≤ 40 vs. > 40 mm), and institution. The main outcome measure was OS. Secondary outcome measures were investigator-assessed PFS and ORR per the modified Response Assessment in Neuro-oncology (RANO) criteria, health related quality of life (HRQoL), cognitive function, and corticosteroid use.

A total of 432 patients were randomized to receive lomustine alone (N=149) or bevacizumab with lomustine (N=283). The median age was 57 years; 24.8% of patients were ≥ 65 years. The majority of patients with were male (61%); 66% had a WHO performance status score > 0; and in 56% the largest tumor diameter was ≤ 40 mm. Approximately 33% of patients randomized to receive lomustine received bevacizumab following documented progression.

No difference in OS (HR 0.91, p-value of 0.4578) was observed between arms; therefore, all secondary outcome measures are descriptive only. PFS was longer in the bevacizumab with lomustine arm [HR 0.52 (95% CI: 0.41, 0.64)] with a median PFS of 4.2 months in the bevacizumab with lomustine arm and 1.5 months in the lomustine arm. Among the 50% of patients receiving corticosteroids at the time of randomization, a higher percentage of patients in the bevacizumab with lomustine arm discontinued corticosteroids (23% vs. 12%).

Study AVF3708g and Study NCI 06-C-0064E: The efficacy and safety of bevacizumab 10 mg/kg every 2 weeks in patients with previously treated GBM were evaluated in one single arm single center study (NCI 06-C-0064E) and a randomized noncomparative multicenter study [AVF3708g (NCT00345163)]. Response rates in both studies were evaluated based on modified WHO criteria that considered corticosteroid use. In AVF3708g, the response rate was 25.9% (95% CI: 17%, 36.1%) with a median duration of response of 4.2 months (95% CI: 3, 5.7). In Study NCI 06-C-0064E, the response rate was 19.6% (95% CI: 10.9%, 31.3%) with a median duration of response of 3.9 months (95% CI: 2.4, 17.4).

Metastatic Renal Cell Carcinoma

Study BO17705: The safety and efficacy of bevacizumab were evaluated in patients with treatment-naïve mRCC in a multicenter, randomized, double-blind, international study [BO17705 (NCT00738530)] comparing interferon alfa and bevacizumab versus interferon alfa and placebo. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to receive either bevacizumab (10 mg/kg every 2 weeks; N = 327) or placebo (every 2 weeks;

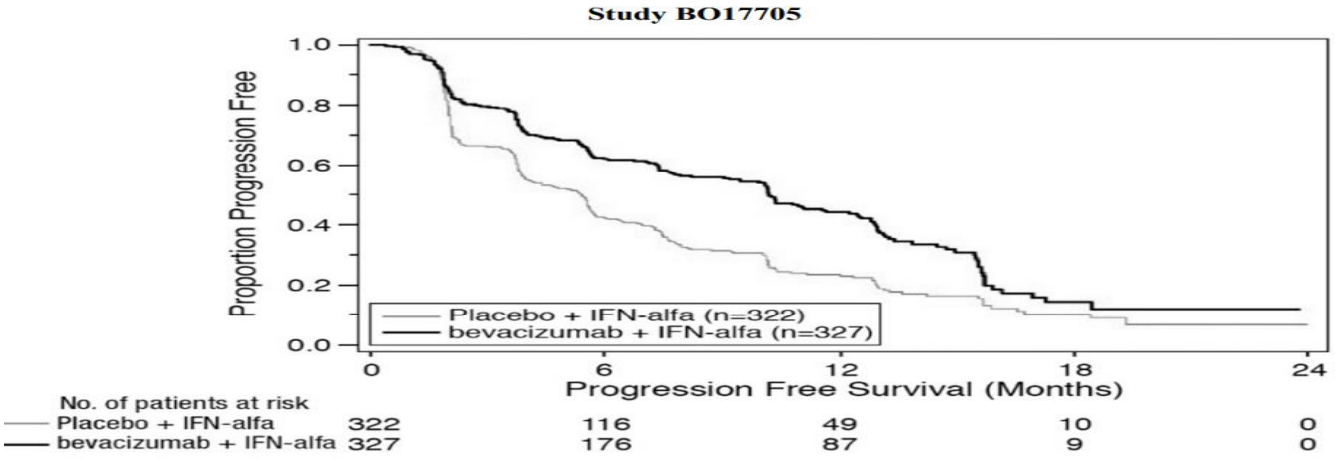
N = 322) with interferon alfa (9 MIU subcutaneously three times weekly for a maximum of 52 weeks). Patients were treated until disease progression or unacceptable toxicity. The main outcome measure was investigator assessed PFS. Secondary outcome measures were ORR and OS.

The median age was 60 years (18 to 82 years); 70% were male and 96% were White. The study population was characterized by Motzer scores as follows: 28% favorable (0), 56% intermediate (1-2), 8% poor (3–5), and 7% missing.

PFS was statistically significantly prolonged among patients receiving bevacizumab compared to placebo; median PFS was 10.2 months vs. 5.4 months [HR 0.60 (95% CI: 0.49, 0.72), p-value < 0.0001, stratified log-rank test]. Among the 595 patients with measurable disease, ORR was also significantly higher (30% vs. 12%, p-value < 0.0001,

stratified CMH test). There was no improvement in OS based on the final analysis conducted after 444 deaths, with a median OS of 23 months in the patient's receiving bevacizumab with interferon alfa and 21 months in patients receiving interferon alone [HR 0.86, (95% CI: 0.72, 1.04)]. Results are presented in Figure 2.

Figure 2: Kaplan-Meier Curves for Progression-Free Survival in Metastatic Renal Cell Carcinoma in Study BO17705



Persistent, Recurrent, or Metastatic Cervical Cancer

Study GOG-0240: The safety and efficacy of bevacizumab were evaluated in patients with persistent, recurrent, or metastatic cervical cancer in a randomized, four-arm, multicenter study comparing bevacizumab with chemotherapy versus chemotherapy alone [GOG-0240 (NCT00803062)]. A total of 452 patients were randomized (1:1:1:1) to receive paclitaxel and cisplatin with or without bevacizumab, or paclitaxel and topotecan with or without bevacizumab.

The dosing regimens for bevacizumab, paclitaxel, cisplatin and topotecan were as follows:

- Day 1: Paclitaxel 135 mg/m^2 over 24 hours, Day 2: cisplatin 50 mg/m^2 with bevacizumab;
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours, Day 2: cisplatin 50 mg/m^2 with bevacizumab;
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours with cisplatin 50 mg/m^2 with bevacizumab;
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours with bevacizumab, Days 1-3: topotecan IV 0.75 mg/m^2 over 30 minutes.

Patients were treated until disease progression or unacceptable adverse reactions. The main outcome measure was OS. Secondary outcome measures included ORR.

The median age was 48 years (20 to 85 years). Of the 452 patients randomized at baseline, 78% of patients were White, 80% had received prior radiation, 74% had received prior chemotherapy concurrent with radiation, and 32% had a platinum-free interval (PFI) of less than 6 months. Patients had a GOG performance status of 0 (58%) or 1 (42%). Demographic and disease characteristics were balanced across arms. Results are presented in Table 3.

Table 3: Efficacy Results in Study GOG-0240

Efficacy Parameter	Bevacizumab with Chemotherapy (N=227)	Chemotherapy (N=225)
Overall Survival		
Median, in months[a]	16.8	12.9
Hazard ratio (95% CI)	0.74 (0.58, 0.94)	
p-value[b]	0.0132	

[a] Kaplan-Meier estimates.
[b] log-rank test (stratified).

The ORR was higher in patients who received bevacizumab with chemotherapy [45% (95% CI: 39, 52)] compared to patients who received chemotherapy alone [34% (95% CI: 28,40)].

Table 4: Efficacy Results in Study GOG-0240

Efficacy Parameter	Topotecan and Paclitaxel with or without Bevacizumab (N=223)	Cisplatin and Paclitaxel with or without Bevacizumab (N=229)
Overall Survival		
Median, in months[a]	13.3	15.5
Hazard ratio (95% CI)	1.15 (0.91, 1.46)	
p-value	0.23	

[a] Kaplan-Meier estimates

The HR for OS with bevacizumab with cisplatin and paclitaxel as compared to cisplatin and paclitaxel alone was 0.72 (95% CI: 0.51,1.02). The HR for OS with bevacizumab with topotecan and paclitaxel as compared to topotecan and paclitaxel alone was 0.76 (95% CI: 0.55, 1.06).

Stage III or IV Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Following Initial Surgical Resection

Study GOG-0218: The safety and efficacy of bevacizumab were evaluated in a multicenter, randomized, double-blind, placebo controlled, three arm study [Study GOG-0218 (NCT00262847)] evaluating the effect of adding bevacizumab to carboplatin and paclitaxel for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer (N=1873) following initial surgical resection. Patients were randomized (1:1:1) to one of the following arms:

- CPP: carboplatin (AUC 6) and paclitaxel (175 mg/m$^{2)}$ for six cycles, with concurrent placebo started at cycle 2, followed by placebo alone every three weeks for a total of up to 22 cycles of therapy (n=625) or
- CPB15: carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for six cycles, with concurrent bevacizumab started at cycle 2, followed by placebo alone every three weeks for a total of up to 22 cycles of therapy (n=625) or
- CPB15+: carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for six cycles, with concurrent bevacizumab started at cycle 2, followed by bevacizumab as a single agent every three weeks for a total of up to 22 cycles of therapy (n=623)

The main outcome measure was investigator-assessed PFS. OS was a secondary outcome measure.

The median age was 60 years (range 22-89 years) and 28% of patients were >65 years of age. Overall, approximately 50% of patients had a GOG PS of 0 at baseline, and 43% a GOG PS score of 1. Patients had either epithelial ovarian cancer (83%), primary peritoneal cancer (15%), or fallopian tube cancer (2%). Serous adenocarcinoma was the most common histologic type (85% in CPP and CPB15 arms, 86% in CPB15+ arm). Overall, approximately 34% of patients had resected FIGO Stage III with residual disease < 1 cm, 40% had resected Stage III with residual disease >1 cm, and 26% had resected Stage IV disease.

The majority of patients in all three treatment arms received subsequent antineoplastic treatment, 78.1% in the CPP arm, 78.6% in the CPB15 arm, and 73.2% in the CPB15+ arm. A higher proportion of patients in the CPP arm (25.3%) and CPB15 arm (26.6%) received at least one anti-angiogenic (including bevacizumab) treatment after discontinuing from study compared with the CPB15+ arm (15.6%). Study results are presented in Table 5.

Table 5: Efficacy Results in Study GOG-0218			
Efficacy Parameter	**Bevacizumab with carboplatin and paclitaxel followed by Bevacizumab alone (N=623)**	**Bevacizumab with carboplatin and paclitaxel (N=625)**	**Carboplatin and paclitaxel (N= 625)**
Progression-Free Survival per Investigator			
Median, in months	18.2	12.8	12.0
Hazard ratio (95% CI) [a]	0.62 (0.52, 0.75)	0.83 (0.70, 0.98)	
p –value[b]	< 0.0001	NS	
Overall Survival[c]			
Median, in months	43.8	38.8	40.6
Hazard ratio (95% CI) [a]	0.89 (0.76, 1.05)	1.06 (0.90, 1.24)	

NS=not significant
[a] Relative to the control arm; stratified hazard ratio.
[b] Two-sided p-value based on re-randomization test.
[c] Final overall survival analysis.

Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study MO22224: The safety and efficacy of bevacizumab were evaluated in a multicenter, open-label, randomized study [MO22224 (NCT00976911)] comparing bevacizumab with chemotherapy versus chemotherapy alone in patients with platinum-resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that recurred within < 6months from the most recent platinum-based therapy (N=361). Patients had received no more than 2 prior chemotherapy regimens. Patients received one of the following chemotherapy regimens at the discretion of the investigator: paclitaxel (80 mg/m^2 on days 1, 8, 15 and 22 every 4 weeks; pegylated liposomal doxorubicin 40 mg/m^2 on day 1 every 4 weeks; or topotecan 4 mg/m^2 on days 1, 8 and 15 every 4 weeks or 1.25 mg/m2 on days 1-5 every 3 weeks). Patients were treated until disease progression, unacceptable toxicity, or withdrawal. Forty percent of patients on the chemotherapy alone arm received bevacizumab alone upon progression. The main outcome measure was investigator-assessed PFS. Secondary outcome measures were ORR and OS.

The median age was 61 years (25 to 84 years) and 37% of patients were ≥65 years. Seventy-nine percent had measurable disease at baseline, 87% had baseline CA-125 levels ≥2 times ULN and 31% had ascites at baseline. Seventy-three percent had a PFI of 3 months to 6 months and 27% had PFI of < 3 months. ECOG performance status was 0 for 59%, 1 for 34% and 2 for 7% of the patients.

The addition of bevacizumab to chemotherapy demonstrated a statistically significant improvement in investigator assessed PFS, which was supported by a retrospective independent review analysis. Results for the ITT population are presented in Table 6. Results for the separate chemotherapy cohorts are presented in Table 7.

Table 6: Efficacy Results in Study MO22224		
Efficacy Parameter	**Bevacizumab with Chemotherapy (N=179)**	**Chemotherapy (N=182)**
Progression-Free Survival per Investigator		
Median (95% CI), in months	6.8 (5.6, 7.8)	3.4 (2.1, 3.8)
HR (95% CI) [a]	0.38 (0.30, 0.49)	
p-value [b]	<0.0001	
Overall Survival		
Median (95% CI), in months	16.6 (13.7, 19.0)	13.3 (11.9, 16.4)
HR (95% CI) [a]	0.89 (0.69, 1.14)	
Overall Response Rate		
Number of Patients with Measurable Disease at Baseline	142	144
Rate, % (95% CI)	28% (21%, 36%)	13% (7%, 18%)
Duration of Response		
Median, in months	9.4	5.4

[a] per stratified Cox proportional hazards model.
[b] per stratified log-rank test.

Table 7: Efficacy Results in Study MO22224 by Chemotherapy						
Efficacy Parameter	**Paclitaxel**		**Topotecan**		**Pegylated Liposomal Doxorubicin**	
	Bevacizumab with Chemotherapy (N=60)	**Chemotherapy (N=55)**	**Bevacizumab with Chemotherapy (N=57)**	**Chemotherapy (N=63)**	**Bevacizumab with Chemotherapy (N=62)**	**Chemotherapy (N=64)**
Progression-Free Survival per Investigator						
Median, in months (95% CI)	9.6 (7.8, 11.5)	3.9 (3.5, 5.5)	6.2 (5.3, 7.6)	2.1 (1.9, 2.3)	5.1 (3.9, 6.3)	3.5 (1.9, 3.9)
Hazard ratio[a] (95% CI)	0.47 (0.31, 0.72)		0.24 (0.15, 0.38)		0.47 (0.32, 0.71)	
Overall Survival						
Median, in Months (95% CI)	22.4 (16.7, 26.7)	13.2 (8.2, 19.7)	13.8 (11.0, 18.3)	13.3 (10.4, 18.3)	13.7 (11.0, 18.3)	14.1 (9.9, 17.8)

Table 7: Efficacy Results in Study MO22224 by Chemotherapy						
Efficacy Parameter	**Paclitaxel**		**Topotecan**		**Pegylated Liposomal Doxorubicin**	
	Bevacizumab with Chemotherapy (N=60)	**Chemotherapy (N=55)**	**Bevacizumab with Chemotherapy (N=57)**	**Chemotherapy (N=63)**	**Bevacizumab with Chemotherapy (N=62)**	**Chemotherapy (N=64)**
Hazard ratio [a] (95% CI)	0.64 (0.41, 1.01)		1.12 (0.73, 1.73)		0.94 (0.63, 1.42)	
Overall Response Rate						
Number of patients with measurable disease at baseline	45	43	46	50	51	51
Rate, % (95% CI)	53 (39, 68)	30 (17, 44)	17 (6, 28)	2 (0, 6)	16 (6, 26)	8 (0,15)
Duration of Response						
Median, in months	11.6	6.8	5.2	NE	8.0	4.6

[a] per stratified Cox proportional hazards model.
NE=Not Estimable.

Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study AVF4095g: The safety and efficacy of bevacizumab were evaluated in a randomized, double-blind, placebo-controlled study [AVF4095g (NCT00434642)] studying bevacizumab with chemotherapy versus chemotherapy alone in the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior chemotherapy in the recurrent setting or prior bevacizumab treatment (N=484). Patients were randomized (1:1) to receive bevacizumab (15 mg/kg day 1) or placebo every 3 weeks with carboplatin (AUC 4, day 1) and gemcitabine (1000 mg/m^2 on days 1 and 8) for 6 to 10 cycles followed by bevacizumab or placebo alone until disease progression or unacceptable toxicity. The main outcome measures were investigator-assessed PFS. Secondary outcome measures were ORR and OS.

The median age was 61 years (28 to 87 years) and 37% of patients were ≥65 years. All patients had measurable disease at baseline, 74% had baseline CA-125 levels >ULN (35 U/mL). The platinum-free interval (PFI) was 6 months to 12 months in 42 % of patients and >12 months in 58% of patients. The ECOG performance status was 0 or 1 for 99.8% of patients.

A statistically significant prolongation in PFS was demonstrated among patients receiving bevacizumab with chemotherapy compared to those receiving placebo with chemotherapy (Table 8). Independent radiology review of PFS was consistent with investigator assessment [HR 0.45 (95% CI: 0.35, 0.58)]. OS was not significantly improved with the addition of bevacizumab to chemotherapy [HR 0.95 (95% CI: 0.77, 1.17)].

Table 8: Efficacy Results in Study AVF4095g		
Efficacy Parameter	**Bevacizumab with Gemcitabine and Carboplatin (N=242)**	**Placebo with Gemcitabine and Carboplatin (N=242)**
Progression-Free Survival		
Median, in months	12.4	8.4
Hazard ratio (95% CI)	0.46 (0.37, 0.58)	
p-value	< 0.0001	
Overall Response Rate		
% patients with overall response	78%	57%
p-value	< 0.0001	

Study GOG-0213: The safety and efficacy of bevacizumab were evaluated in a randomized, controlled, open-label study [Study GOG-0213 (NCT00565851)] of bevacizumab with chemotherapy versus chemotherapy alone in the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have not received more than one previous regimen of chemotherapy (N=673). Patients were randomized (1:1) to receive carboplatin (AUC 5) and paclitaxel (175 mg/m^2 IV over 3 hours) every 3 weeks for 6 to 8 cycles (N=336) or bevacizumab (15 mg/kg) every 3 weeks with carboplatin (AUC 5) and paclitaxel (175 mg/m^2 IV over 3 hours) for 6 to 8 cycles followed by bevacizumab (15 mg/kg every 3 weeks) as a single agent until disease progression or unacceptable toxicity. The main outcome measure was OS. Other outcome measures were investigator-assessed PFS, and ORR.

The median age was 60 years (23 to 85 years) and 33% of patients were ≥65 years. Eighty-three percent had measurable disease at baseline and 74% had abnormal CA-125 levels at baseline. Ten percent of patients had received prior bevacizumab. Twenty-six percent had a PFI of 6 months to 12 months and 74% had a PFI of >12 months. GOG performance status was 0 or 1 for 99% of patients. Results are presented in Table 9.

Table 9: Efficacy Results in Study GOG-0213		
Efficacy Parameter	**Bevacizumab with Carboplatin and Paclitaxel (N=337)**	**Carboplatin and Paclitaxel (N=336)**
Overall Survival		
Median, in months	42.6	37.3
Hazard ratio (95% CI) (IVRS)[a]	0.84 (0.69, 1.01)	
Hazard ratio (95% CI) (eCRF)[b]	0.82 (0.68, 0.996)	
Progression-Free Survival		
Median, in months	13.8	10.4
Hazard ratio (95% CI) (IVRS)[a]	0.61 (0.51, 0.72)	
Overall Response Rate		
Number of patients with measurable disease at baseline	274	286

Table 9: Efficacy Results in Study GOG-0213		
Efficacy Parameter	**Bevacizumab with Carboplatin and Paclitaxel (N=337)**	**Carboplatin and Paclitaxel (N=336)**
Rate, %	213 (78%)	159 (56%)

[a] HR was estimated from Cox proportional hazards models stratified by the duration of treatment free interval prior to enrolling onto this study per IVRS (interactive voice response system) and secondary surgical debulking status.
[b] HR was estimated from Cox proportional hazards models stratified by the duration of platinum free interval prior to enrolling onto this study per eCRF (electronic case report form) and secondary surgical debulking status.

Most common adverse reactions incidence (incidence > 10%) are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, hemorrhage, lacrimation disorder, back pain, and exfoliative dermatitis.

Safety

ADVERSE EVENTS

Metastatic Colorectal Cancer

In Combination with bolus-IFL: All Grades 3–4 adverse reactions and selected Grades 1–2 adverse reactions (i.e., hypertension, proteinuria, thromboembolic events) were collected in the entire study population. Adverse reactions are presented in Table 10.

Table 10: Grades 3-4 Adverse Reactions Occurring at Higher Incidence (≥2%) in Patients Receiving Bevacizumab vs. Placebo in Study AVF2107g		
Adverse Reaction[a]	**Bevacizumab with IFL (N=392)**	**Placebo with IFL (N=396)**
Hematology		
Leukopenia	37%	31%
Neutropenia	21%	14%
Gastrointestinal		
Diarrhea	34%	25%
Abdominal pain	8%	5%
Constipation	4%	2%
Vascular		
Hypertension	12%	2%
Deep vein thrombosis	9%	5%
Intra-abdominal thrombosis	3%	1%
Syncope	3%	1%
General		
Asthenia	10%	7%
Pain	8%	5%

[a] NCI-CTC version 3.

In Combination with FOLFOX4: Selected Grades 3–5 non-hematologic and Grades 4–5 hematologic occurring at a higher incidence (≥ 2%) in patients receiving bevacizumab with FOLFOX4 compared to FOLFOX4 alone were fatigue (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%), vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8% vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache (3% vs. 0%). These data are likely to underestimate the true adverse reaction rates due to the reporting mechanisms.

First-Line Non-Squamous Non-Small Cell Lung Cancer

Only Grades 3-5 non-hematologic and Grades 4-5 hematologic adverse reactions were collected. Grades 3-5 non-hematologic and Grades 4-5 hematologic adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving bevacizumab with paclitaxel and carboplatin compared with patients receiving chemotherapy alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs. 0.7%), infection without neutropenia (7% vs. 3%), venous thromboembolism (5% vs. 3%), febrile neutropenia (5% vs. 2%), pneumonitis/pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3% vs. 0%).

Recurrent Glioblastoma

In the bevacizumab with lomustine arm, 22% of patients discontinued treatment due to adverse reactions compared with 10% of patients in the lomustine arm. In patients receiving bevacizumab with lomustine, the adverse reaction profile was similar to that observed in other approved indications.

Metastatic Renal Cell Carcinoma

Grades 3-5 adverse reactions occurring at a higher incidence (>2%) were fatigue (13% vs. 8%), asthenia (10% vs. 7%), proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis), and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, hemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma). The following adverse reactions were reported at a 5-fold greater incidence in patients receiving bevacizumab with interferon-alfa compared to patients receiving placebo with interferon-alfa and not represented in Table 3: gingival bleeding (13 patients vs. 1 patient); rhinitis (9 vs. 0); blurred vision (8 vs. 0); gingivitis (8 vs. 1); gastroesophageal reflux disease (8 vs. 1); tinnitus (7 vs. 1); tooth abscess (7 vs. 0); mouth ulceration (6 vs. 0); acne (5 vs. 0); deafness (5 vs. 0); gastritis (5 vs. 0); gingival pain (5 vs. 0) and pulmonary embolism (5 vs. 1).

Persistent, Recurrent, or Metastatic Cervical Cancer

Grades 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in 218 patients receiving bevacizumab with chemotherapy compared to 222 patients receiving chemotherapy alone were abdominal pain (12% vs. 10%), hypertension (11% vs. 0.5%), thrombosis (8% vs. 3%), diarrhea (6% vs. 3%), anal fistula (4% vs. 0%), proctalgia (3% vs. 0%), urinary tract infection (8% vs. 6%), cellulitis (3% vs. 0.5%), fatigue (14% vs. 10%), hypokalemia (7% vs. 4%), hyponatremia (4% vs. 1%), dehydration (4% vs. 0.5%), neutropenia (8% vs. 4%), lymphopenia (6% vs. 3%), back pain (6% vs. 3%), and pelvic pain (6% vs. 1%).

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

Stage III or IV Following Initial Surgical Resection: Grades 3-4 adverse reactions occurring at a higher incidence (≥2%) in either of the bevacizumab arms versus the control arm were fatigue (CPB15+ - 9%, CPB15 - 6%, CPP - 6%), hypertension (CPB15+ - 10%, CPB15 - 6%, CPP - 2%), thrombocytopenia (CPB15+ - 21%, CPB15 - 20%, CPP - 15%) and leukopenia (CPB15+ - 51%, CPB15 - 53%, CPP - 50%). Adverse reactions are presented in Table 11.

Table 11: Grades 1-5 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Bevacizumab with Chemotherapy vs. Chemotherapy Alone in GOG-0218

Adverse Reaction[a]	Bevacizumab with carboplatin and paclitaxel followed by bevacizumab alone[*]	Bevacizumab with carboplatin and paclitaxel[**] (N= 607)	Carboplatin and paclitaxel[***] (N= 602)

Table 11: Grades 1-5 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Bevacizumab with Chemotherapy vs. Chemotherapy Alone in GOG-0218			
	(N=608)		
General			
Fatigue	80%	72%	73%
Gastrointestinal			
Nausea	58%	53%	51%
Diarrhea	38%	40%	34%
Stomatitis	25%	19%	14%
Musculoskeletal and connective tissue			
Arthralgia	41%	33%	35%
Pain in extremity	25%	19%	17%
Muscular weakness	15%	13%	9%
Nervous system			
Headache	34%	26%	21%
Dysarthria	12%	10%	2%
Vascular			
Hypertension	32%	24%	14%
Respiratory, thoracic and mediastinal			
Epistaxis	31%	30%	9%
Dyspnea	26%	28%	20%
Nasal mucosal disorder	10%	7%	4%

[a] NCI-CTC version 3, * CPB15+, ** CPB15, ***CPP

Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer: Grades 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in 179 patients receiving bevacizumab with chemotherapy compared to 181 patients receiving chemotherapy alone were hypertension (6.7% vs. 1.1%) and palmar-plantar erythrodysaesthesia syndrome (4.5% vs. 1.7%). Adverse reactions are presented in Table 12.

Table 12: Grades 2–4 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Bevacizumab with Chemotherapy vs. Chemotherapy Alone in Study MO22224		
Adverse Reaction[a]	**Bevacizumab with Chemotherapy (N=179)**	**Chemotherapy (N=181)**
Hematology		
Neutropenia	31%	25%
Vascular		
Hypertension	19%	6%
Nervous system		
Peripheral sensory neuropathy	18%	7%
General		
Mucosal inflammation	13%	6%
Renal and urinary		
Proteinuria	12%	0.6%
Skin and subcutaneous tissue		
Palmar-plantar erythrodysaesthesia	11%	5%

Infections		
Infection	11%	4%
Respiratory, thoracic and mediastinal		
Epistaxis	5%	0%

[a] NCI-CTC version 3.

Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study AVF4095g: Grades 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving bevacizumab with chemotherapy compared to placebo with chemotherapy were: thrombocytopenia (40% vs. 34%), nausea (4% vs. 1.3%), fatigue (6% vs. 4%), headache (4% vs. 0.9%), proteinuria (10% vs. 0.4%), dyspnea (4% vs. 1.7%), epistaxis (5% vs. 0.4%), and hypertension (17% vs. 0.9%). Adverse reactions are presented in Table 13.

Table 13: Grades 1–5 Adverse Reactions Occurring at a Higher Incidence (≥ 5%) in Patients Receiving Bevacizumab with Chemotherapy vs. Placebo with Chemotherapy in Study AVF4095g

Adverse Reaction[a]	Bevacizumab with Carboplatin and Gemcitabine (N=247)	Placebo with Carboplatin and Gemcitabine (N=233)
General		
Fatigue	82%	75%
Mucosal inflammation	15%	10%
Gastrointestinal		
Nausea	72%	66%
Diarrhea	38%	29%
Stomatitis	15%	7%
Hemorrhoids	8%	3%
Gingival bleeding	7%	0%
Hematology		
Thrombocytopenia	58%	51%
Respiratory, thoracic and mediastinal		
Epistaxis	55%	14%
Dyspnea	30%	24%
Cough	26%	18%
Oropharyngeal pain	16%	10%
Dysphonia	13%	3%
Rhinorrhea	10%	4%
Sinus congestion	8%	2%
Nervous system		
Headache	49%	30%
Dizziness	23%	17%
Vascular		
Hypertension	42%	9%
Musculoskeletal and connective tissue		
Arthralgia	28%	19%
Back pain	21%	13%
Psychiatric		
Insomnia	21%	15%
Renal and urinary		
Proteinuria	20%	3%
Injury and procedural		
Contusion	17%	9%

Table 13: Grades 1–5 Adverse Reactions Occurring at a Higher Incidence (≥ 5%) in Patients Receiving Bevacizumab with Chemotherapy vs. Placebo with Chemotherapy in Study AVF4095g		
Infections		
Sinusitis	15%	9%

[a] NCI-CTC version 3.

Study GOG-0213: Grades 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving bevacizumab with chemotherapy compared to chemotherapy alone were: hypertension (11% vs. 0.6%), fatigue (8% vs. 3%), febrile neutropenia (6% vs. 3%), proteinuria (8% vs. 0%), abdominal pain (6% vs. 0.9%), hyponatremia (4% vs. 0.9%), headache (3% vs. 0.9%), and pain in extremity (3% vs. 0%). Adverse reactions are presented in Table 14.

Table 14: Grades 1–5 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Bevacizumab with Chemotherapy vs. Chemotherapy Alone in Study GOG-0213		
Adverse Reaction[a]	**Bevacizumab with Carboplatin and Paclitaxel (N=325)**	**Carboplatin and Paclitaxel (N=332)**
Musculoskeletal and connective tissue		
Arthralgia	45%	30%
Myalgia	29%	18%
Pain in extremity	25%	14%
Back pain	17%	10%
Muscular weakness	13%	8%
Neck pain	9%	0%
Vascular		
Hypertension	42%	3%
Gastrointestinal		
Diarrhea	39%	32%
Abdominal pain	33%	28%
Vomiting	33%	25%
Stomatitis	33%	16%
Nervous system		
Headache	38%	20%
Dysarthria	14%	2%
Dizziness	13%	8%
Metabolism and nutrition		
Decreased appetite	35%	25%
Hyperglycemia	31%	24%
Hypomagnesemia	27%	17%
Hyponatremia	17%	6%
Weight loss	15%	4%
Hypocalcemia	12%	5%
Hypoalbuminemia	11%	6%
Hyperkalemia	9%	3%
Respiratory, thoracic and mediastinal		
Epistaxis	33%	2%
Dyspnea	30%	25%
Cough	30%	17%
Rhinitis allergic	17%	4%
Nasal mucosal disorder	14%	3%
Skin and subcutaneous tissue		

Table 14: Grades 1–5 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Bevacizumab with Chemotherapy vs. Chemotherapy Alone in Study GOG-0213		
Exfoliative rash	23%	16%
Nail disorder	10%	2%
Dry skin	7%	2%
Renal and urinary		
Proteinuria	17%	1%
Increased blood creatinine	13%	5%
Hepatic		
Increased aspartate aminotransferase	15%	9%
General		
Chest pain	8%	2%
Infections		
Sinusitis	7%	2%

[a] NCI-CTC version 3

WARNINGS & PRECAUTIONS

Gastrointestinal Perforations and Fistulae: Serious, and sometimes fatal, gastrointestinal perforation occurred at a higher incidence in patients receiving bevacizumab products 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 products 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 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.

Surgery and Wound Healing Complications: In a controlled clinical study in which bevacizumab was not administered within 28 days of major surgical procedures, the incidence of wound healing complications, including serious and fatal complications, was 15% in patients with mCRC who underwent surgery while receiving bevacizumab and 4% in patients who did not receive bevacizumab. In a controlled clinical study in patients with relapsed or recurrent GBM, the incidence of wound healing events was 5% in patients who received bevacizumab and 0.7% in patients who did not receive bevacizumab. Necrotizing fasciitis including fatal cases, has been reported in patients receiving bevacizumab, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Discontinue in patients who develop necrotizing fasciitis.

Hemorrhage: Bevacizumab products can result in two distinct patterns of bleeding: minor hemorrhage, which is most commonly Grade 1 epistaxis, and serious hemorrhage, which in some cases has been fatal. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving bevacizumab compared to patients receiving chemotherapy alone. Across clinical studies, the incidence of Grades 3-5 hemorrhagic events ranged from 0.4% to 7% in patients receiving bevacizumab. Serious or fatal pulmonary hemorrhage occurred in 31% of patients with squamous NSCLC and 4% of patients with non-squamous NSCLC receiving bevacizumab with chemotherapy

compared to none of the patients receiving chemotherapy alone. Do not administer to patients with recent history of hemoptysis of 1/2 teaspoon or more of red blood. Discontinue in patients who develop a Grades 3-4 hemorrhage.

Arterial Thromboembolic Events: Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, and angina, occurred at a higher incidence in patients receiving bevacizumab compared to patients receiving chemotherapy. Across clinical studies, the incidence of Grades 3-5 ATE was 5% in patients receiving bevacizumab with chemotherapy compared to ≤2% in patients receiving chemotherapy alone; the highest incidence occurred in patients with GBM. The risk of developing ATE was increased in patients with a history of arterial thromboembolism, diabetes, or >65 years. Discontinue in patients who develop a severe ATE. The safety of reinitiating bevacizumab products after an ATE is resolved is not known.

Venous Thromboembolic Events: An increased risk of venous thromboembolic events (VTE) was observed across clinical studies. Discontinue in patients with a Grade 4 VTE, including pulmonary embolism.

Hypertension: Severe hypertension occurred at a higher incidence in patients receiving bevacizumab products as compared to patients receiving chemotherapy alone. Across clinical studies, the incidence of Grades 3-4 hypertension ranged from 5% to 18%. Discontinue in patients who develop hypertensive crisis or hypertensive encephalopathy.

Posterior Reversible Encephalopathy Syndrome: Posterior reversible encephalopathy syndrome (PRES) was reported in <0.5% of patients across clinical studies. The onset of symptoms occurred from 16 hours to 1 year after the first dose. PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES. Discontinue in patients who develop PRES is not known.

Renal Injury and Proteinuria: The incidence and severity of proteinuria was higher in patients receiving bevacizumab products compared to patients receiving chemotherapy. In an exploratory, pooled analysis of patients from seven randomized clinical studies, 5% of patients receiving bevacizumab with chemotherapy experienced Grades 2-4 (defined as urine dipstick 2+ or greater or > 1 gram of protein per 24 hours or nephrotic syndrome) proteinuria. Grades 2-4 proteinuria resolved in 74% of patients. Bevacizumab was reinitiated in 42% of patients. Of the 113 patients who reinitiated bevacizumab, 48% experienced a second episode of Grades 2-4 proteinuria. Discontinue in patients who develop nephrotic syndrome.

Infusion-Related Reactions: Infusion-related reactions reported across clinical studies and postmarketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, anaphylactoid/anaphylactic reactions, chest pain, headaches, rigors, and diaphoresis. In clinical studies, infusion-related reactions with the first dose occurred in < 3% of patients and severe reactions occurred in 0.4% of patients. Discontinue in patients who develop a severe infusion-related reaction and administer appropriate medical therapy (e.g., epinephrine, corticosteroids, intravenous antihistamines, bronchodilators and/or oxygen).

Embryo-Fetal Toxicity: Based on its mechanism of action and findings from animal studies, bevacizumab products may cause fetal harm when administered to pregnant women. Congenital malformations were observed with the administration of bevacizumab to pregnant rabbits during organogenesis every 3 days at a dose as low as a clinical dose of 10 mg/kg. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after the last dose.

Ovarian Failure: The incidence of ovarian failure was 34% vs. 2% in premenopausal women receiving bevacizumab with chemotherapy as compared to those receiving chemotherapy alone for adjuvant treatment of a solid tumor. After discontinuing bevacizumab, recovery of ovarian function at all time points during the post-treatment period

was demonstrated in 22% of women receiving bevacizumab. Inform females of reproductive potential of the risk of ovarian failure prior to initiating Vegelma®.

Congestive Heart Failure (CHF): Not indicated for use with anthracycline-based chemotherapy. The incidence of Grade > 3 left ventricular dysfunction was 1% in patients receiving bevacizumab compared to 0.6% of patients receiving chemotherapy alone. Among patients who received prior anthracycline treatment, the rate of CHF was 4% for patients receiving bevacizumab with chemotherapy as compared to 0.6% for patients receiving chemotherapy alone. Discontinue in patients who develop CHF.

CONTRAINDICATIONS

None reported.

Clinical Pharmacology

MECHANISMS OF ACTION

Bevacizumab products bind VEGF and prevent 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.

Dose & Administration

ADULTS

Metastatic Colorectal Cancer: Administered in combination with intravenous fluorouracil-based chemotherapy is:

- 5 mg/kg intravenously every 2 weeks in combination with bolus-IFL.
- 10 mg/kg intravenously every 2 weeks in combination with FOLFOX4.
- 5 mg/kg intravenously every 2 weeks or 7.5 mg/kg intravenously every 3 weeks in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy in patients who have progressed on a first-line bevacizumab product-containing regimen.

First-Line Non-Squamous Non-Small Cell Lung Cancer: 15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel.

Recurrent Glioblastoma: 10 mg/kg intravenously every 2 weeks.

Metastatic Renal Cell Carcinoma: 10 mg/kg intravenously every 2 weeks in combination with interferon alfa.

Persistent, Recurrent, or Metastatic Cervical Cancer: 15 mg/kg intravenously every 3 weeks in combination with paclitaxel and cisplatin or in combination with paclitaxel and topotecan.

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer:

Stage III or IV Disease Following Initial Surgical Resection: 15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel for up to 6 cycles, followed by Vegzelma® 15 mg/kg every 3 weeks as a single agent for a total of up to 22 cycles or until disease progression, whichever occurs earlier.

Recurrent Disease

Platinum Resistant: 10 mg/kg intravenously every 2 weeks in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan (every week). 15 mg/kg intravenously every 3 weeks in combination with topotecan (every 3 weeks).

Platinum Sensitive: 15 mg/kg intravenously every 3 weeks, in combination with carboplatin and paclitaxel for 6 to 8 cycles, followed by Vegzelma® 15 mg/kg every 3 weeks as a single agent until disease progression. 15 mg/kg intravenously every 3 weeks, in combination with carboplatin and gemcitabine for 6 to 10 cycles, followed by Vegzelma® 15 mg/kg every 3 weeks as a single agent until disease progression.

PEDIATRICS

None.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None.

HEPATIC IMPAIRMENT

None.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Injection: 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL) in a single-dose vial.