NEW DRUG APPROVAL

Brand Name	Alymsys®
Generic Name	bevacizumab-maly
Drug Manufacturer	Amneal Pharmaceuticals LLC

New Drug Approval

FDA approval date: April 13, 2022

Review designation: N/A

Type of review: Biologic License Application (BLA): 761231

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Metastatic colorectal cancer: Cancer cells may break away from a tumor in the colon or rectum and spread to other parts of the body through the bloodstream or lymphatic system. These cells may settle and form new tumors on a different organ. Even though the cancer has spread to a new organ, it is still named after the part of the body where it originally started. So colorectal cancer that spreads, or metastasizes, to the lungs, liver or any other organ is called metastatic colorectal cancer.

Epidemiology: The most common site of metastases for colorectal cancer, which includes colon cancer or rectal cancer is the liver. Colorectal cancer cells may also spread to the lungs, bones, brain or spinal cord. If you have been treated for colorectal cancer and cancer cells have been found in these areas, it may be a sign that the original colorectal cancer has spread. Metastatic colorectal cancer is different from recurrent colorectal cancer. Recurrent colorectal cancer is cancer that returns to the same part of the colon or rectum after treatment, rather than spreading to other parts of the body.

In the United States, both the incidence and mortality have been slowly but steadily decreasing. Annually, approximately 151,030 new cases of large bowel cancer are diagnosed, 106,180 of which are colon cancer, and the remainder are rectal cancer. Annually, approximately 52,580 Americans die of CRC, accounting for approximately 8 percent of all cancer deaths.

In the United States, the lifetime incidence of CRC in patients at average risk is approximately 4 percent. CRC incidence is approximately 25 percent higher in males than in females and is approximately 20 percent higher in African Americans than in White Americans. The incidence is higher in patients with specific inherited conditions that predispose them to the development of CRC.

In the United States, CRC incidence rates had been declining by approximately 2 percent per year, but this rate of decline has slowed to approximately 1 percent per year in the period 2013 to 2017. Incidence rates in most other western countries have been stable or increased slightly during this period. By contrast, CRC incidence rates have rapidly increased in several areas historically at low risk, including Spain, and a number of countries within Eastern Asia and Eastern Europe.

Death rates from CRC have declined progressively since the mid-1980s in the United States and in many other western countries. However, at least in the United States, the decline in CRC mortality started well before the widespread implementation of CRC screening and before effective adjuvant therapy became widely used.

However, notably, in the United States the declining mortality overall is masking trends in younger adults.

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Non-Squamous Non-Small Cell Lung Cancer: NSCLC is any type of epithelial lung cancer other than small cell lung cancer (SCLC). The most common types of NSCLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma, but there are several other types that occur less frequently, and all types can occur in unusual histologic variants. Although NSCLCs are associated with cigarette smoke, adenocarcinomas may be found in patients who have never smoked.

As a class, NSCLC is usually less sensitive to chemotherapy and radiation therapy compared with SCLC. Patients with resectable disease may be cured by surgery or surgery followed by chemotherapy. Local control can be achieved with radiation therapy in a large number of patients with unresectable disease, but cure is seen only in a small number of patients. Patients with locally advanced unresectable disease may achieve long-term survival with radiation therapy combined with chemotherapy. Patients with advanced metastatic disease may achieve improved survival and palliation of symptoms with chemotherapy, targeted agents, and other supportive measures.

Epidemiology: Non-Small Cell Lung Cancer in the United States

- U.S. data shows that 80-85% of lung cancers are NSCLC.
- In 2015 there were 221,200 new diagnosis of NSCLC and 158,040 deaths in the United States.
- In disease thought to be amenable to cure (stage I, II and III), surgery and or radiotherapy is warranted with additional chemotherapy.

Lung cancer is the number one cause of cancer death in the United States, expected to cause 158,000 deaths in 2016, and accounting for 26.5% of all cancer deaths. It is the second most common cancer in both men (after prostate cancer) and women (after breast cancer), with 118,000 and 106,000 new cases expected in 2016, respectively. Lung cancer includes different pathological types, broadly divided into small-cell lung cancer and non-small-cell lung cancer (NSCLC). NSCLC makes up about 85% of lung cancers and comprises mainly squamous cell carcinoma, adenocarcinoma, and large-cell lung cancer.

Recurrent Glioblastoma: Glioblastoma is the most common and aggressive malignant primary brain cancer in adults. The prognosis remains poor following standard-of-care treatment with surgery, radiotherapy and chemotherapy, with a median overall survival of about 15 months. Theoretically, all glioblastoma patients relapse. Once tumors progress after first-line therapy, treatment options are limited and management of recurrent glioblastoma remains challenging. In recent years, new treatments have been tested on recurrent glioblastoma patients. These include immunotherapy, antiangiogenic treatment, targeted therapy and combination regimens.

Epidemiology: With an incidence rate of 3.19 per 100,000 persons in the United States and a median age of 64 years, it is uncommon in children. The incidence is 1.6 times higher in males compared to females and 2.0 times higher in Caucasians compared to Africans and Afro-Americans, with lower incidence in Asians and American Indians. Survival from Glioblastoma is poor only few patients survive 2.5 years and less than 5% of patients survive 5 years following diagnosis. Survival rates for patients with GBM have shown no notable improvement in population statistics in the last three decades. Molecular epidemiology integrates molecular technology into epidemiological studies and outcomes. The future of the epidemiology of GBM will depend on multicenter studies generating large clinical data sets of genomic data potentially leading to further understanding of the roles of genes and environment in the development of this devastating disease.

Metastatic Renal Cell Carcinoma: Renal cell cancer (also called kidney cancer or renal cell adenocarcinoma) is a disease in which malignant (cancer) cells are found in the lining of tubules (very small tubes) in the kidney. There are 2 kidneys, one on each side of the backbone, above the waist. Tiny tubules in the kidneys filter and clean the blood. They take out waste products and make urine. The urine passes from each kidney through a long tube called a ureter into the bladder. The bladder holds the urine until it passes through the urethra and leaves the body.

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Epidemiology**:** Kidney Cancer includes cancer of the kidney and renal pelvis. Median age at diagnosis of 64 years of age. The American Cancer Society's most recent estimates for kidney cancer in the United States for 2022 are:

- About 79,000 new cases of kidney cancer (50,290 in men and 28,710 in women) will be diagnosed.
- About 13,920 people (8,960 men and 4,960 women) will die from this disease.

Persistent, Recurrent, or Metastatic Cervical Cancer: Cervical cancer is the third most common gynecological cancer diagnosed in the United States. Human papillomavirus is central to the development of cervical neoplasia and can be detected in 99.75 of cervical cancers.

Epidemiology**:** The most common histologic types of cervical cancer are squamous cell (70 percent of cervical cancers) and adenocarcinoma (25 percent). Metastatic disease is thought to develop in 15%-61% of women with cervical cancer.

Ovarian Cancer: Ovarian cancer is the leading cause of death in women diagnosed with gynecological cancers. It is also the fifth most frequent cause of death in women, in general. Most of the cases are diagnosed at an advanced stage, which leads to poor outcomes of this disease. The existing screening tests have a low predictive value contributing further to this misery. Detailed gynecological evaluation along with transvaginal ultrasound and laboratory marker like cancer antigen-125 (CA-125) assay are the key early detection strategies which have shown no significant beneficial effect in the morbidity or mortality of this cancer. The standard line of care treatment includes surgery and platinum-based chemotherapy; however, anti-angiogenic bevacizumab and Poly(ADP-ribose) polymerase (PARP) inhibitors have gained momentum in the management of this gynecological malignancy in the past decade.

Epidemiology: There are an estimated 195,770 women in the United States living with ovarian cancer. Survival rate at 5 years is less than 50%.

Table 1: Overall PD-1 Tumor Prevalence

Tumor Type	Estimated PD-1 prevalence (%)
Non-Squamous Non-Small Cell Lung Cancer (NSCLC) (Squamous)	50
NSCLC (adenocarcinoma)	45
Colon cancer	45
Melanoma	40
Renal cell carcinoma	20

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/m2, fluorouracil 500 mg/m2, and leucovorin 20 mg/m2 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).

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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.

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.

Table 2: The addition of bevacizumab improved survival across subgroups defined by age (< 65 years, ⩾ 65 years) and sex.

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		
Median, in months	10.4	7.1

[a]by stratified log-rank test.
[b]by $\chi 2$ test

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/m2 and leucovorin 200 mg/m2 concurrently, then fluorouracil 400 mg/m2 bolus followed by 600 mg/m2 continuously; Day 2: leucovorin 200 mg/m2, then fluorouracil 400 mg/m2 bolus followed by 600 mg/m2 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.

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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, ≥ 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-oxaliplatinbased 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 3.

Table 3: 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: 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

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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/m2) 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.

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, placebocontrolled study [BO17704 (NCT00806923)]. A total of 1,043 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].

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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/m2 every 6 weeks) or lomustine (110 mg/m2 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 to 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 logrank 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 below screenshot.

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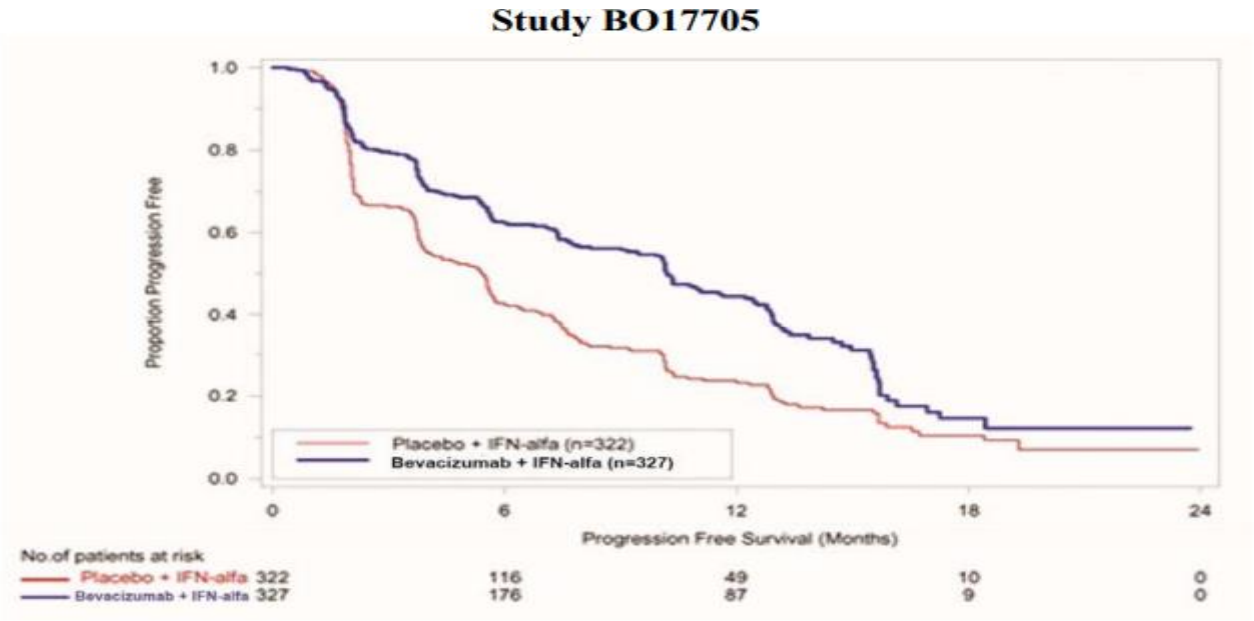
Figure 1: Kaplan-Meier Curves for Progression-Free Survival in Metastatic Renal Cell Carcinoma in Study BO17705



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/m2 over 24 hours, Day 2: cisplatin 50 mg/m2 with bevacizumab;
- Day 1: Paclitaxel 175 mg/m2 over 3 hours, Day 2: cisplatin 50 mg/m2 with bevacizumab;
- Day 1: Paclitaxel 175 mg/m2 over 3 hours with cisplatin 50 mg/m2 with bevacizumab;
- Day 1: Paclitaxel 175 mg/m2 over 3 hours with bevacizumab, Days 1 to 3: topotecan intravenously 0.75 mg/m2 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 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 below screenshot.

Figure 2: Kaplan-Meier Curves for Overall Survival in Persistent, Recurrent, or Metastatic Cervical Cancer in Study GOG-0240

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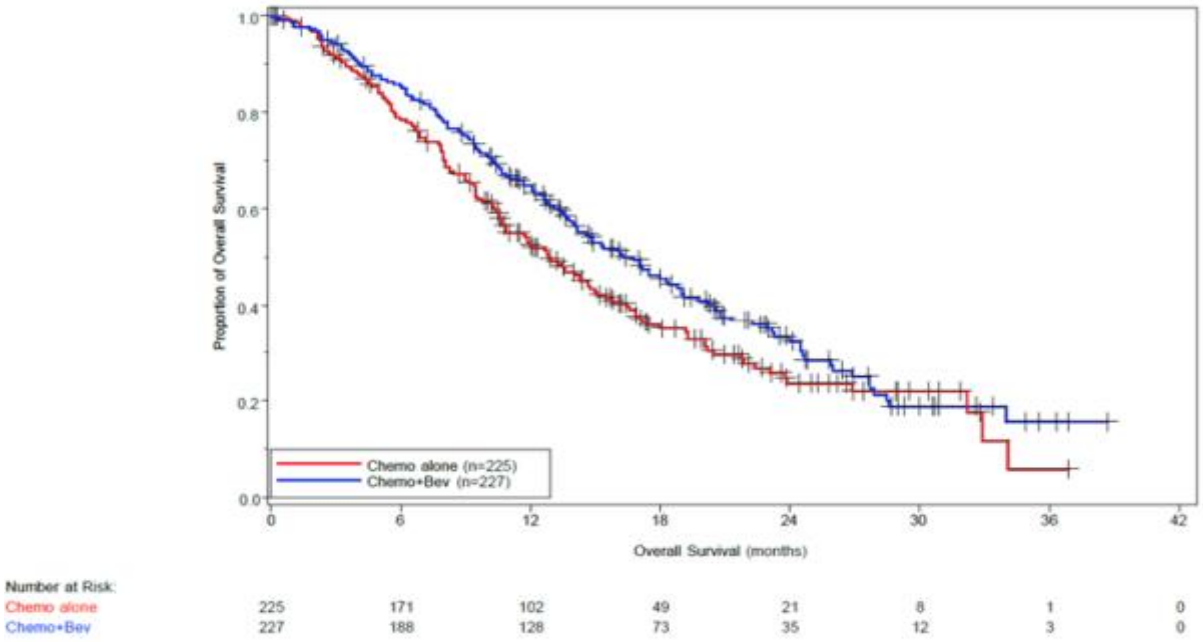

Table 4: Efficacy Results in Study GOG-0240		
Efficacy Parameter	**bevacizumab with Chemotherapy (N=227)**	**Chemotherapy (N=225)**
Overall Survival		
Median, in months[a]	16.8	12.9
Hazard ratio (95% CI)	0.74 (0.58, 0.94)	
p-value[b]	0.0132	

[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 5: 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).

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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 <6 months 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/m2 on days 1, 8, 15 and 22 every 4 weeks; pegylated liposomal doxorubicin 40 mg/m2 on day 1 every 4 weeks; or topotecan 4 mg/m2 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 platinum-free interval (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

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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)
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

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Safety

ADVERSE EVENTS

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.

WARNINGS & PRECAUTIONS

- Gastrointestinal Perforations and Fistula: Discontinue for gastrointestinal perforations, tracheoesophageal fistula, grade 4 fistula, or fistula formation involving any organ.
- Surgery and Wound Healing Complications: In patients who experience wound healing complications during Alymsys® treatment, withhold Alymsys® until adequate wound healing. Withhold for at least 28 days prior to elective surgery. Do not administer Alymsys® for at least 28 days following a major surgery, and until adequate wound healing. The safety of resumption of bevacizumab products after resolution of wound healing complication has not been established. Discontinue for wound healing complication of necrotizing fasciitis.
- Hemorrhage: Severe or fatal hemorrhages have occurred. Do not administer for recent hemoptysis. Discontinue for Grade 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 infusionrelated 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 Alymsys® 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: In combination with intravenous fluorouracil-based chemotherapy:

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- 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: Recurrent Disease

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

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) clear to slightly opalescent, colourless to pale brown solution in a single-dose vial.

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