HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MVASI safely and effectively. See full prescribing information for MVASI.

MVASI (bevacizumab-awwb) Solution for intravenous infusion
Initial U.S. Approval: 2017
MVASI (bevacizumab-awwb) is biosimilar* to AVASTIN® (bevacizumab)

WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND HEALING COMPLICATIONS, and HEMORRHAGE
See full prescribing information for complete boxed warning.

- **Gastrointestinal Perforation: Occurs in up to 3.2% of bevacizumab product-treated patients. Discontinue MVASI for gastrointestinal perforation. (5.1)**
- **Surgery and Wound Healing Complications: Discontinue in patients with wound dehiscence. Discontinue at least 28 days prior to elective surgery. Do not initiate MVASI for at least 28 days after surgery and until the surgical wound is fully healed. (5.3)**
- **Hemorrhage: Severe or fatal hemorrhage, hemoptysis, gastrointestinal bleeding, CNS hemorrhage, and vaginal bleeding are increased in bevacizumab product-treated patients. Do not administer MVASI to patients with serious hemorrhage or recent hemoptysis. (5.4)**

----------INDICATIONS AND USAGE----------

MVASI is a vascular endothelial growth factor-specific angiogenesis inhibitor indicated for the treatment of:

- Metastatic colorectal cancer, with intravenous 5-fluorouracil–based chemotherapy for first- or second-line treatment. (1.1)
- Metastatic colorectal cancer, with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab product-containing regimen. (1.1)
- Non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease. (1.2)
- Glioblastoma, as a single agent for adult patients with progressive disease following prior therapy. (1.3)
  -Effectiveness based on improvement in objective response rate. No data available demonstrating improvement in disease-related symptoms or survival with bevacizumab products.
- Metastatic renal cell carcinoma with interferon alfa. (1.4)
- Cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease. (1.5)

Limitation of Use: MVASI is not indicated for adjuvant treatment of colon cancer. (1.1)

----------DOSAGE AND ADMINISTRATION----------

- Administer only as an intravenous (IV) infusion. Do not administer as an IV push or bolus. (2.1)
- Do not initiate MVASI for 28 days following major surgery and until surgical wound is fully healed. (2.1)
- See Full Prescribing Information for preparation and administration instructions. (2.3)

Metastatic colorectal cancer (2.2)

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

Non-squamous non-small cell lung cancer (2.2)

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

Glioblastoma (2.2)

- 10 mg/kg IV every 2 weeks

Metastatic renal cell carcinoma (mRCC) (2.2)

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

Persistent, recurrent, or metastatic carcinoma of the cervix (2.2)

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

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 100 mg/4 mL (25 mg/ mL) in single dose vial (3)
- Injection: 400 mg/16 mL (25 mg/mL) in single dose vial (3)

----------CONTRAINDICATIONS----------

None (4)

----------WARNINGS AND PRECAUTIONS----------

- Perforation or Fistula: Discontinue MVASI if perforation or fistula occurs. (5.1, 5.2)
- Arterial Thromboembolic Events (e.g., myocardial infarction, cerebral infarction): Discontinue MVASI for severe ATE. (5.5)
- Venous Thromboembolic Events: Discontinue MVASI for life-threatening VTE (5.6)
- Hypertension: Monitor blood pressure and treat hypertension. Temporarily suspend MVASI if not medically controlled. Discontinue MVASI for hypertensive crisis or hypertensive encephalopathy. (5.7)
- Posterior Reversible Encephalopathy Syndrome (PRES): Discontinue MVASI. (5.8)
- Proteinuria: Monitor urine protein. Discontinue MVASI for nephrotic syndrome. Temporarily suspend MVASI for moderate proteinuria. (5.9)
- Infusion Reactions: Stop MVASI for severe infusion reactions. (5.10)
- Embryo-fetal Toxicity: Advise females of potential risk to a fetus and the need for use of effective contraception. (5.11, 8.1, 8.3)
- Ovarian Failure: Advise females of the potential risk. (5.12, 8.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions incidence (>10% and at least twice the control arm rate) are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of MVASI has been demonstrated for the condition(s) of use (e.g. indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

Revised: 09/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND HEALING COMPLICATIONS, and HEMORRHAGE

Gastrointestinal Perforations

The incidence of gastrointestinal perforation, some fatal, in bevacizumab product-treated patients ranges from 0.3 to 3.2%. Discontinue MVASI in patients with gastrointestinal perforation *[see Dosage and Administration (2.4), Warnings and Precautions (5.1)]*.

Surgery and Wound Healing Complications

The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in bevacizumab product-treated patients. Discontinue MVASI in patients with wound dehiscence. The appropriate interval between termination of bevacizumab products and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined. Discontinue at least 28 days prior to elective surgery. Do not initiate MVASI for at least 28 days after surgery and until the surgical wound is fully healed *[see Dosage and Administration (2.4), Warnings and Precautions (5.3), Adverse Reactions (6.1)]*.

Hemorrhage

Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, central nervous systems (CNS) hemorrhage, epistaxis, and vaginal bleeding occur up to five-fold more frequently in patients receiving bevacizumab products. Do not administer MVASI to patients with serious hemorrhage or recent hemoptysis *[see Dosage and Administration (2.4), Warnings and Precautions (5.4), Adverse Reactions (6.1)]*.

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer (mCRC)

MVASI is indicated for the first-or second-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with intravenous 5-fluorouracil–based chemotherapy.

MVASI, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy, is indicated for the second-line treatment of patients with metastatic colorectal cancer who have progressed on a first-line bevacizumab product-containing regimen.

Limitation of Use: MVASI is not indicated for adjuvant treatment of colon cancer *[see Clinical Studies (14.2)]*.

1.2 Non-Squamous Non–Small Cell Lung Cancer (NSCLC)

MVASI is indicated for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer in combination with carboplatin and paclitaxel.

1.3 Glioblastoma

MVASI is indicated for the treatment of glioblastoma with progressive disease in adult patients following prior therapy as a single agent.

The effectiveness of bevacizumab products in glioblastoma is based on an improvement in objective response rate. There are no data demonstrating an improvement in disease-related symptoms or increased survival with bevacizumab products *[see Clinical Studies (14.4)]*.

1.4 Metastatic Renal Cell Carcinoma (mRCC)

MVASI is indicated for the treatment of metastatic renal cell carcinoma in combination with interferon alfa.

1.5 Persistent, Recurrent, or Metastatic Carcinoma of the Cervix

MVASI in combination with paclitaxel and cisplatin or paclitaxel and topotecan is indicated for the treatment of persistent, recurrent, or metastatic carcinoma of the cervix *[see Clinical Studies (14.6)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Administration

Administer only as an intravenous (IV) infusion. Do not administer as an intravenous push or bolus.

- Do not initiate MVASI until at least 28 days following major surgery. Administer MVASI after the surgical incision has fully healed.
- First infusion: Administer infusion over 90 minutes.
- Subsequent infusions: Administer second infusion over 60 minutes if first infusion is tolerated; administer all subsequent infusions over 30 minutes if infusion over 60 minutes is tolerated.

2.2 Recommended Doses and Schedules

Patients should continue treatment until disease progression or unacceptable toxicity.

Metastatic Colorectal Cancer (mCRC)

The recommended doses are 5 mg/kg or 10 mg/kg every 2 weeks when used in combination with intravenous 5-FU-based chemotherapy.

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

Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

The recommended dose is 15 mg/kg every 3 weeks in combination with carboplatin and paclitaxel.

Glioblastoma

The recommended dose is 10 mg/kg every 2 weeks.

Metastatic Renal Cell Carcinoma (mRCC)

The recommended dose is 10 mg/kg every 2 weeks in combination with interferon alfa.

Cervical Cancer

The recommended dose of MVASI is 15 mg/kg every 3 weeks as an intravenous infusion administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin, or paclitaxel and topotecan.

2.3 Preparation for Administration

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. MVASI is a colorless to pale yellow solution. Do not use vial if solution is cloudy, discolored, or contains particulate matter.

Withdraw necessary amount of MVASI and dilute in a total volume of 100 mL of 0.9% Sodium

Chloride Injection, USP. Discard any unused portion left in a vial, as the product contains no preservatives.

Diluted MVASI solutions may be stored at 2-8°C (36-46°F) for up to 8 hours.

DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.

2.4 Dose Modifications

There are no recommended dose reductions.

Discontinue MVASI for:

- Gastrointestinal perforations (gastrointestinal perforations, fistula formation in the gastrointestinal tract, intra-abdominal abscess), fistula formation involving an internal organ *[see Boxed Warning, Warnings and Precautions (5.1, 5.2)]*.
- Wound dehiscence and wound healing complications requiring medical intervention *[see Warnings and Precautions (5.3)]*.
- Serious hemorrhage (i.e., requiring medical intervention) *[see Boxed Warning, Warnings and Precautions (5.4)]*.
- Severe arterial thromboembolic events *[see Warnings and Precautions (5.5)]*.
- Life-threatening (Grade 4) venous thromboembolic events, including pulmonary embolism *[see Warnings and Precautions (5.6)]*.
- Hypertensive crisis or hypertensive encephalopathy *[see Warnings and Precautions (5.7)]*.
- Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (5.8)]*.
- Nephrotic syndrome *[see Warnings and Precautions (5.9)]*.

Temporarily suspend MVASI for:

- At least 4 weeks prior to elective surgery *[see Warnings and Precautions (5.3)]*.
- Severe hypertension not controlled with medical management *[see Warnings and Precautions (5.7)]*.
- Moderate to severe proteinuria *[see Warnings and Precautions (5.9)]*.
- Severe infusion reactions *[see Warnings and Precautions (5.10)]*.

3 DOSAGE FORMS AND STRENGTHS

- Injection: 100 mg/4 mL (25 mg/mL) colorless to pale yellow, preservative-free, single-dose vial.
- Injection: 400 mg/16 mL (25 mg/mL colorless to pale yellow, preservative-free, single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Perforations and Fistulae

Serious and sometimes fatal gastrointestinal perforation occurs at a higher incidence in bevacizumab-treated patients compared to controls. The incidence of gastrointestinal perforation ranged from 0.3 to 3.2% across clinical studies *[see Adverse Reactions (6.1)]*. From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (Study 9), gastrointestinal perforations were reported in 3.2% of bevacizumab treated patients, all of whom had a history of prior pelvic radiation. Fatal outcome was reported in <1% of bevacizumab-treated patients.

The typical presentation may include abdominal pain, nausea, emesis, constipation, and fever. Perforation can be complicated by intra-abdominal abscess, fistula formation, and the need for diverting ostomies. The majority of cases occurred within the first 50 days of initiation of

bevacizumab. Permanently discontinue MVASI in patients with gastrointestinal perforation.

In bevacizumab clinical trials, gastrointestinal fistulae have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer. In a cervical cancer trial (Study 9), the incidence of gastrointestinal-vaginal fistulae was 8.3% in bevacizumab-treated patients and 0.9% in control patients, all of whom had a history of prior pelvic radiation. Patients who develop GI vaginal fistulas may also have bowel obstructions and require surgical intervention as well as diverting ostomies *[see Boxed Warning, Dosage and Administration (2.4)]*.

5.2 Non-Gastrointestinal Fistulae

Serious and sometimes fatal fistula formation involving tracheo-esophageal, bronchopleural, biliary, vaginal, and renal and bladder sites occurs at a higher incidence in bevacizumab-treated patients compared to controls. Uncommon (<1%) reports of fistulae that involve areas of the body other than the gastrointestinal tract were observed in clinical trials across various indications and have also been reported in post-marketing experience. Most events occurred within the first 6 months of bevacizumab therapy.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (Study 9), 1.8% of bevacizumab-treated patients and 1.4% of control patients were reported to have had non-gastrointestinal vaginal, vesical, or female genital tract fistulae.

Permanently discontinue MVASI in patients with tracheo-esophageal (TE) fistula or any Grade 4 fistula. Discontinue MVASI in patients with fistula formation involving an internal organ *[see Dosage and Administration (2.4)]*.

5.3 Surgery and Wound Healing Complications

Bevacizumab products impair wound healing in animal models *[see Nonclinical Toxicology (13.2)]*. In clinical trials, administration of bevacizumab was not allowed until at least 28 days after surgery. In a controlled clinical trial, the incidence of wound healing complications, including serious and fatal complications, in patients with mCRC who underwent surgery during the course of bevacizumab treatment was 15% and in patients who did not receive bevacizumab, was 4% *[see Adverse Reactions (6.1)]*.

MVASI should not be initiated for at least 28 days following surgery and until the surgical wound is fully healed. Discontinue MVASI in patients with wound healing complications requiring medical intervention.

The appropriate interval between the last dose of a bevacizumab product and elective surgery is unknown; however, the half-life of bevacizumab products is approximately 20 days. Suspend MVASI for at least 28 days prior to elective surgery. Do not administer MVASI until the wound is fully healed *[see Boxed Warning, Dosage and Administration (2.4)]*.

Necrotizing fasciitis including fatal cases, has been reported in patients treated with bevacizumab products; usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Discontinue MVASI therapy in patients who develop necrotizing fasciitis *[see Adverse Reactions (6.3)]*.

5.4 Hemorrhage

Bevacizumab products can result in two distinct patterns of bleeding: minor hemorrhage, most commonly Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in

patients receiving bevacizumab compared to patients receiving only chemotherapy. Across indications, the incidence of Grade ≥ 3 hemorrhagic events among patients receiving bevacizumab ranged from 0.4 to 6.9 % *[see Adverse Reactions (6.1)]*.

Serious or fatal pulmonary hemorrhage occurred in four of 13 (31%) patients with squamous cell histology and two of 53 (4%) patients with non-squamous non-small cell lung cancer receiving bevacizumab and chemotherapy compared to none of the 32 (0%) patients receiving chemotherapy alone.

In clinical studies in non-small cell lung cancer where patients with CNS metastases who completed radiation and surgery more than 4 weeks prior to the start of bevacizumab were evaluated with serial CNS imaging, symptomatic Grade 2 CNS hemorrhage was documented in one of 83 bevacizumab-treated patients (rate 1.2%, 95% CI: 0.06%-5.93%).

Intracranial hemorrhage occurred in 8 of 163 patients with previously treated glioblastoma; two patients had Grade 3-4 hemorrhage.

Do not administer MVASI to patients with recent history of hemoptysis of ≥1/2 teaspoon of red blood. Discontinue MVASI in patients with hemorrhage *[see Boxed Warning, Dosage and Administration (2.4)]*.

5.5 Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a higher incidence in patients receiving bevacizumab compared to those in the control arm. Across indications, the incidence of Grade ≥3 ATE in the bevacizumab-containing arms was 2.6% compared to 0.8% in the control arms. Among patients receiving bevacizumab in combination with chemotherapy, the risk of developing ATE during therapy was increased in patients with a history of arterial thromboembolism, diabetes, or age greater than 65 years *[see Use in Specific Populations (8.5)]*.

The safety of resumption of bevacizumab products therapy after resolution of an ATE has not been studied. Discontinue MVASI in patients who experience a severe ATE *[see Dosage and Administration (2.4)]*.

5.6 Venous Thromboembolic Events

Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab products may be at increased risk of venous thromboembolic events (VTE).

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (Study 9), Grade ≥3 VTE were reported in 10.6% of patients treated with chemotherapy and bevacizumab compared with 5.4% in patients receiving chemotherapy alone. Permanently discontinue MVASI in patients with life-threatening (Grade 4) VTE, including pulmonary embolism *[see Dosage and Administration (2.4), Adverse Reactions (6.1)]*.

5.7 Hypertension

The incidence of severe hypertension is increased in patients receiving bevacizumab products as compared to controls. Across clinical studies the incidence of Grade 3 or 4 hypertension ranged from 5-18%.

Monitor blood pressure every two to three weeks during treatment with MVASI. Treat with appropriate anti-hypertensive therapy and monitor blood pressure regularly. Continue to monitor

blood pressure at regular intervals in patients with MVASI-induced or-exacerbated hypertension after discontinuation of MVASI.

Temporarily suspend MVASI in patients with severe hypertension that is not controlled with medical management. Discontinue MVASI in patients with hypertensive crisis or hypertensive encephalopathy *[see Dosage and Administration (2.4)]*.

5.8 Posterior Reversible Encephalopathy Syndrome (PRES)

PRES has been reported with an incidence of <0.5% in clinical studies. The onset of symptoms occurred from 16 hours to 1 year after initiation of bevacizumab. 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 (MRI) is necessary to confirm the diagnosis of PRES.

Discontinue MVASI in patients developing PRES. Symptoms usually resolve or improve within days, although some patients have experienced ongoing neurologic sequelae. The safety of reinitiating bevacizumab product therapy in patients previously experiencing PRES is not known *[see Dosage and Administration (2.4)]*.

5.9 Proteinuria

The incidence and severity of proteinuria is increased in patients receiving bevacizumab products as compared to controls. Nephrotic syndrome occurred in <1% of patients receiving bevacizumab in clinical trials, in some instances with fatal outcome *[see Adverse Reactions (6.1)]*. In a published case series, kidney biopsy of six patients with proteinuria showed findings consistent with thrombotic microangiopathy.

Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria with serial urinalyses during MVASI therapy. Patients with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection.

Suspend MVASI administration for ≥2 grams of proteinuria/24 hours and resume when proteinuria is <2 gm/24 hours. Discontinue MVASI in patients with nephrotic syndrome *[see Dosage and Administration (2.4)]*. Data from a post-marketing safety study showed poor correlation between UPCR (Urine Protein/Creatinine Ratio) and 24 hour urine protein (Pearson Correlation 0.39 (95% CI 0.17, 0.57) *[see Use in Specific Populations (8.5)]*.

5.10 Infusion Reactions

Infusion reactions reported in the clinical trials and post-marketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. In clinical studies, infusion reactions with the first dose of bevacizumab were uncommon (<3%) and severe reactions occurred in 0.2% of patients.

Stop infusion if a severe infusion reaction occurs and administer appropriate medical therapy *[see Dosage and Administration (2.4)]*.

5.11 Embryo-fetal Toxicity

Bevacizumab products may cause fetal harm based on the drug's mechanism of action and findings from animal studies. 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. Furthermore, animal models link angiogenesis and VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryo-fetal development, and postnatal

development.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with and for 6 months after the last dose of MVASI *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)]*.

5.12 Ovarian Failure

The incidence of ovarian failure was higher (34% vs. 2%) in premenopausal women receiving bevacizumab in combination with mFOLFOX chemotherapy as compared to those receiving mFOLFOX chemotherapy alone for adjuvant treatment for colorectal cancer, a use for which bevacizumab products are not approved. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with MVASI *[see Adverse Reactions (6.1), Use in Specific Populations (8.3)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Gastrointestinal Perforations and Fistulae *[see Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.1)]*.
- Non-Gastrointestinal Fistulae *[see Dosage and Administration (2.4), Warnings and Precautions (5.2)]*.
- Surgery and Wound Healing Complications *[see Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.3)]*.
- Hemorrhage *[see Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.4)]*.
- Arterial Thromboembolic Events *[see Dosage and Administration (2.4), Warnings and Precautions (5.5)]*.
- Venous Thromboembolic Events *[see Dosage and Administration (2.4), Warnings and Precautions (5.6)]*.
- Hypertensive Crisis *[see Dosage and Administration (2.4), Warnings and Precautions (5.7)]*.
- Posterior Reversible Encephalopathy Syndrome *[see Dosage and Administration (2.4), Warnings and Precautions (5.8)]*.
- Proteinuria *[see Dosage and Administration (2.4), Warnings and Precautions (5.9)]*.
- Infusion Reactions *[see Dosage and Administration (2.4), Warnings and Precautions (5.10)]*.
- Ovarian Failure *[see Warnings and Precautions (5.12), Use in Specific Populations (8.3)]*.

The most common adverse reactions observed in bevacizumab patients at a rate >10% and at least twice the control arm rate, are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis. Some of the adverse reactions are commonly seen with chemotherapy; however, bevacizumab products may exacerbate these reactions when combined with chemotherapeutic agents. Examples include palmar-plantar erythrodysesthesia syndrome with capecitabine, peripheral sensory neuropathy with paclitaxel or oxaliplatin, and nail disorders or alopecia with paclitaxel.

Across all studies, bevacizumab was discontinued in 8.4 to 21% of patients because of adverse reactions.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data below reflect exposure to bevacizumab in more than 5500 patients with CRC, non-squamous NSCLC, glioblastoma, mRCC, or cervical cancer, including controlled (Studies 1, 2, 4, 5, 8 and 9), or uncontrolled, single arm trials (Study 6), or other cancers treated at the recommended dose and schedule for a median of 6 to 23 doses of bevacizumab *[see Clinical Studies (14)]*. The population was aged 18-89 years (median 60 years), 42% male and 86% White. The population included 2184 first-and second-line mCRC patients who received a median of 10 doses of bevacizumab, 480 first-line metastatic NSCLC patients who received a median of 8 doses of bevacizumab, 163 glioblastoma patients who received a median of 9 doses of bevacizumab, 337 mRCC patients who received a median of 16 doses of bevacizumab, 218 cervical cancer patients who received a median of 6 doses of bevacizumab. These data also reflect exposure to bevacizumab in 363 patients with metastatic breast cancer (MBC) who received a median of 9.5 doses of bevacizumab, 1338 adjuvant CRC patients, including 669 female patients, who received a median of 23 doses of bevacizumab, 403 previously untreated patients with diffuse large B-cell lymphoma (DLBCL) who received a median of 8 doses of bevacizumab and 572 patients with other cancers. Bevacizumab products are not approved for use in MBC, adjuvant CRC, or DLBCL.

Surgery and Wound Healing Complications
The incidence of post-operative wound healing and/or bleeding complications was increased in patients with mCRC receiving bevacizumab as compared to patients receiving only chemotherapy.

Among patients requiring surgery on or within 60 days of receiving study treatment, wound healing and/or bleeding complications occurred in 15% (6/39) of patients receiving bolus-IFL plus bevacizumab as compared to 4% (1/25) of patients who received bolus-IFL alone.

In Study 6, events of post-operative wound healing complications (craniotomy site wound dehiscence and cerebrospinal fluid leak) occurred in patients with previously treated glioblastoma: 3/84 patients in the bevacizumab alone arm and 1/79 patients in the bevacizumab plus irinotecan arm *[see Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.3)]*.

Hemorrhage
The incidence of epistaxis was higher (35% vs. 10%) in patients with mCRC receiving bolus-IFL plus bevacizumab compared with patients receiving bolus-IFL plus placebo. All but one of these events were Grade 1 in severity and resolved without medical intervention. Grade 1 or 2 hemorrhagic events were more frequent in patients receiving bolus-IFL plus bevacizumab when compared to those receiving bolus-IFL plus placebo and included gastrointestinal hemorrhage (24% vs. 6%), minor gum bleeding (2% vs. 0), and vaginal hemorrhage (4% vs. 2%) *[see Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.4)]*.

Venous Thromboembolic Events
The overall incidence of Grade 3-4 venous thromboembolic events in Study 1 was 15.1% in patients receiving bolus-IFL plus bevacizumab and 13.6% in patients receiving bolus-IFL plus placebo. In Study 1, more patients in the bevacizumab containing arm experienced deep venous thrombosis (34 vs. 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

The risk of developing a second thromboembolic event while on bevacizumab and oral anticoagulants was evaluated in two randomized studies. In Study 1, 53 patients (14%) on the bolus-IFL plus bevacizumab arm and 30 patients (8%) on the bolus-IFL plus placebo arm received full dose warfarin following a venous thromboembolic event (VTE). Among these patients, an additional thromboembolic event occurred in 21% (11/53) of patients receiving bolus-IFL plus bevacizumab and 3% (1/30) of patients receiving bolus-IFL alone.

In a second, randomized, 4-arm study in 1401 patients with mCRC, prospectively evaluating the incidence of VTE (all grades), the overall incidence of first VTE was higher in the bevacizumab containing arms (13.5%) than the chemotherapy alone arms (9.6%). Among the 116 patients treated with anticoagulants following an initial VTE event (73 in the bevacizumab plus chemotherapy arms and 43 in the chemotherapy alone arms), the overall incidence of subsequent VTEs was also higher among the bevacizumab treated patients (31.5% vs. 25.6%). In this subgroup of patients treated with anticoagulants, the overall incidence of bleeding, the majority of which were Grade 1, was higher in the bevacizumab treated arms than the chemotherapy arms (27.4% vs. 20.9%).

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (Study 9), Grade 3 or 4 VTE have been reported in 10.6% of patients treated with chemotherapy and bevacizumab compared with 5.4% in patients receiving chemotherapy alone. There were no patients with Grade 5 VTE. *[see Dosage and Administration (2.4), Warnings and Precautions (5.6)]*.

Neutropenia and Infection
The incidences of neutropenia and febrile neutropenia are increased in patients receiving bevacizumab products plus chemotherapy compared to chemotherapy alone. In Study 1, the incidence of Grade 3 or 4 neutropenia was increased in mCRC patients receiving IFL plus bevacizumab (21%) compared to patients receiving IFL alone (14%). In Study 5, the incidence of Grade 4 neutropenia was increased in NSCLC patients receiving paclitaxel/carboplatin (PC) plus bevacizumab (26.2%) compared with patients receiving PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC plus bevacizumab vs. 1.8% for PC alone). There were 19 (4.5%) infections with Grade 3 or 4 neutropenia in the PC plus bevacizumab arm of which 3 were fatal compared to 9 (2%) neutropenic infections in patients receiving PC alone, of which none were fatal. During the first 6 cycles of treatment, the incidence of serious infections including pneumonia, febrile neutropenia, catheter infections and wound infections was increased in the PC plus bevacizumab arm [58 patients (13.6%)] compared to the PC alone arm [29 patients (6.6%)].

In Study 6, one fatal event of neutropenic infection occurred in a patient with previously treated glioblastoma receiving bevacizumab alone. The incidence of any grade of infection in patients receiving bevacizumab alone was 55% and the incidence of Grade 3-5 infection was 10%.

Proteinuria
Grade 3-4 proteinuria ranged from 0.7 to 7.4% in Studies 1, 2, 4, 5 and 8. The overall incidence of proteinuria (all grades) was only adequately assessed in Study 8, in which the incidence was 20%. Median onset of proteinuria was 5.6 months (range 15 days to 37 months) after initiation of bevacizumab. Median time to resolution was 6.1 months (95% CI 2.8 months, 11.3 months). Proteinuria did not resolve in 40% of patients after median follow up of 11.2 months and required permanent discontinuation of bevacizumab in 30% of the patients who developed proteinuria (Study 8).

In an exploratory, pooled analysis of 8273 patients treated in 7 randomized clinical trials, 5.4% (271 of 5037) of patients receiving bevacizumab in combination with chemotherapy experienced Grade ≥2 proteinuria. The Grade ≥2 proteinuria resolved in 74.2% (201 of 271) of patients. Bevacizumab was re-initiated in 41.7% (113 of 271) of patients. Of the 113 patients who re-initiated bevacizumab, 47.8% (54 of 113) experienced a second episode of Grade ≥2 proteinuria *[see Warnings and Precautions (5.9)]*.

Renal Injury
A retrospective analysis across clinical trials where 5805 patients had received bevacizumab and chemotherapy and 3713 had received chemotherapy alone has shown higher rates of elevated serum creatinine levels (ranging between 1.5 – 1.9 times baseline levels) in patients who had received

bevacizumab. Creatinine levels did not return to baseline in approximately one-third of patients who received bevacizumab.

Congestive Heart Failure (CHF)
The incidence of Grade ≥3 left ventricular dysfunction was 1.0% in patients receiving bevacizumab compared to 0.6% in the control arm across indications. In patients with metastatic breast cancer (MBC), an indication for which bevacizumab products are not approved, the incidence of Grade 3-4 CHF was increased in patients in the bevacizumab plus paclitaxel arm (2.2%) as compared to the control arm (0.3%). Among patients receiving prior anthracyclines for MBC, the rate of CHF was 3.8% for patients receiving bevacizumab as compared to 0.6% for patients receiving paclitaxel alone. The safety of continuation or resumption of bevacizumab products in patients with cardiac dysfunction has not been studied.

In previously untreated patients with diffuse large B-cell lymphoma (DLBCL), an indication for which bevacizumab products are not approved, the incidence of CHF and decline in left-ventricular ejection fraction (LVEF) were significantly increased in the bevacizumab plus R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) arm (n = 403) compared to the placebo plus R-CHOP arm (n = 379); both regimens were given for 6 to 8 cycles. At the completion of R-CHOP therapy, the incidence of CHF was 10.9% in the bevacizumab plus R-CHOP arm compared to 5.0% in the R-CHOP alone arm [relative risk (95% CI) of 2.2 (1.3, 3.7)]. The incidence of a LVEF event, defined as a decline from baseline of 20% or more in LVEF or a decline from baseline of 10% or more to a LVEF value of less than 50%, was also increased in the bevacizumab plus R-CHOP arm (10.4%) compared to the R-CHOP alone arm (5.0%). Time to onset of left-ventricular dysfunction or CHF was 1-6 months after initiation of therapy in at least 85% of the patients and was resolved in 62% of the patients experiencing CHF in the bevacizumab arm compared to 82% in the control arm.

Ovarian Failure
The incidence of new cases of ovarian failure (defined as amenorrhea lasting 3 or more months, FSH level ≥30 mIU/mL and a negative serum β-HCG pregnancy test) was prospectively evaluated in a subset of 179 women receiving mFOLFOX chemotherapy alone (n = 84) or with bevacizumab (n = 95). New cases of ovarian failure were identified in 34% (32/95) of women receiving bevacizumab in combination with chemotherapy compared with 2% (2/84) of women receiving chemotherapy alone [relative risk of 14 (95% CI 4, 53)]. After discontinuation of bevacizumab treatment, recovery of ovarian function at all time points during the post-treatment period was demonstrated in 22% (7/32) of the bevacizumab-treated women. Recovery of ovarian function is defined as resumption of menses, a positive serum β-HCG pregnancy test, or a FSH level <30 mIU/mL during the post-treatment period. Long term effects of bevacizumab product exposure on fertility are unknown *[see Warnings and Precautions (5.12), Use in Specific Populations (8.3)]*.

Post-Treatment Vascular Events
In an open-label, randomized, controlled trial of bevacizumab in adjuvant colorectal cancer, an indication for which bevacizumab products are not approved, the overall incidence rate of post-treatment Grade ≥3 vascular events was 3.1% (41 of 1338) among patients receiving mFOLFOX6 plus bevacizumab, compared to 1.6% (21 of 1349) among patients receiving mFOLFOX6 alone. Post-treatment vascular events included arterial and venous thromboembolic events, ischemic events, and vascular aneurysms.

Metastatic Colorectal Cancer (mCRC)
The data in Table 1 and Table 2 were obtained in Study 1, a randomized, double-blind, controlled trial comparing chemotherapy plus bevacizumab with chemotherapy plus placebo. Bevacizumab was administered at 5 mg/kg every 2 weeks.

All Grade 3-4 adverse events and selected Grade 1-2 adverse events (hypertension, proteinuria, thromboembolic events) were collected in the entire study population. Severe and life-threatening (Grade 3-4) adverse events, which occurred at a higher incidence (≥2%) in patients receiving bolus-IFL plus bevacizumab as compared to bolus-IFL plus placebo, are presented in Table 1.

Table 1: NCI-CTC Grade 3-4 Adverse Events in Study 1 (Occurring at Higher Incidence [≥2%] Bevacizumab vs. Control)

	Arm 1 IFL + Placebo (n = 396)	Arm 2 IFL + Bevacizumab (n = 392)
NCI-CTC Grade 3-4 Events	74%	87%
Body as a Whole		
Asthenia	7%	10%
Abdominal Pain	5%	8%
Pain	5%	8%
Cardiovascular		
Hypertension	2%	12%
Deep Vein Thrombosis	5%	9%
Intra-Abdominal Thrombosis	1%	3%
Syncope	1%	3%
Digestive		
Diarrhea	25%	34%
Constipation	2%	4%
Hemic/Lymphatic		
Leukopenia	31%	37%
Neutropenia[a]	14%	21%

[a] Central laboratories were collected on Days 1 and 21 of each cycle.
Neutrophil counts are available in 303 patients in Arm 1 and 276 in Arm 2.

Grade 1-4 adverse events which occurred at a higher incidence (≥5%) in patients receiving bolus-IFL plus bevacizumab as compared to the bolus-IFL plus placebo arm are presented in Table 2.

Grade 1-4 adverse events were collected for the first approximately 100 patients in each of the three treatment arms who were enrolled until enrollment in Arm 3 (5-FU/LV + bevacizumab) was discontinued.

Table 2: NCI-CTC Grade 1-4 Adverse Events in Study 1
(Occurring at Higher Incidence [≥5%] in IFL + Bevacizumab vs. IFL)

	Arm 1 IFL+ Placebo (n = 98)	Arm 2 IFL+ Bevacizumab (n = 102)	Arm 3 5-FU/LV + Bevacizumab (n = 109)
Body as a Whole			
Pain	55%	61%	62%
Abdominal Pain	55%	61%	50%
Headache	19%	26%	26%
Cardiovascular			
Hypertension	14%	23%	34%
Hypotension	7%	15%	7%
Deep Vein Thrombosis	3%	9%	6%
Digestive			
Vomiting	47%	52%	47%
Anorexia	30%	43%	35%
Constipation	29%	40%	29%
Stomatitis	18%	32%	30%
Dyspepsia	15%	24%	17%
GI Hemorrhage	6%	24%	19%
Weight Loss	10%	15%	16%
Dry Mouth	2%	7%	4%
Colitis	1%	6%	1%
Hemic/Lymphatic			
Thrombocytopenia	0%	5%	5%
Nervous			
Dizziness	20%	26%	19%
Respiratory			
Upper Respiratory Infection	39%	47%	40%
Epistaxis	10%	35%	32%
Dyspnea	15%	26%	25%
Voice Alteration	2%	9%	6%
Skin/Appendages			
Alopecia	26%	32%	6%
Skin Ulcer	1%	6%	6%
Special Senses			
Taste Disorder	9%	14%	21%
Urogenital			
Proteinuria	24%	36%	36%

Bevacizumab in Combination with FOLFOX4 in Second-line mCRC
Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events related to treatment were collected in Study 2. The most frequent adverse events (selected Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events) occurring at a higher incidence (≥2%) in 287 patients receiving FOLFOX4 plus bevacizumab compared to 285 patients receiving 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 under-estimate the true adverse event rates due to the reporting mechanisms used in Study 2.

Bevacizumab in Combination with Fluoropyrimidine-Irinotecan or Fluoropyrimidine-Oxaliplatin Based Chemotherapy in Second-line mCRC Patients who have Progressed on a Bevacizumab Containing Regimen in First-line mCRC:
No new safety signals were observed in Study 4 when bevacizumab was administered in second line mCRC patients who progressed on a bevacizumab containing regimen in first line mCRC. The safety data was consistent with the known safety profile established in first and second line mCRC.

Unresectable Non-Squamous Non-Small Cell Lung Cancer (NSCLC)
Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected in Study 5. Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events (occurring at a higher incidence (≥2%) in 427 patients receiving PC plus bevacizumab compared with 441 patients receiving PC alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs.0.7%), infection without neutropenia (7% vs. 3%), venous thrombus/embolism (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%).

Glioblastoma
All adverse events were collected in 163 patients enrolled in Study 6 who either received bevacizumab alone or bevacizumab plus irinotecan. All patients received prior radiotherapy and temozolomide.

Bevacizumab was administered at 10 mg/kg every 2 weeks alone or in combination with irinotecan. Bevacizumab was discontinued due to adverse events in 4.8% of patients treated with bevacizumab alone.

In patients receiving bevacizumab alone (N = 84), the most frequently reported adverse events of any grade were infection (55%), fatigue (45%), headache (37%), hypertension (30%), epistaxis (19%) and diarrhea (21%). Of these, the incidence of Grade ≥3 adverse events was infection (10%), fatigue (4%), headache (4%), hypertension (8%) and diarrhea (1%). Two deaths on study were possibly related to bevacizumab: one retroperitoneal hemorrhage and one neutropenic infection.

In patients receiving bevacizumab alone or bevacizumab plus irinotecan (N =163), the incidence of bevacizumab-related adverse events (Grade 1-4) were bleeding/hemorrhage (40%), epistaxis (26%), CNS hemorrhage (5%), hypertension (32%), venous thromboembolic event (8%), arterial thromboembolic event (6%), wound-healing complications (6%), proteinuria (4%), gastrointestinal perforation (2%), and PRES (1%). The incidence of Grade 3-5 events in these 163 patients were bleeding/hemorrhage (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic event (7%), arterial thromboembolic event (3%), wound-healing complications (3%), proteinuria

(1%), and gastrointestinal perforation (2%).

Metastatic Renal Cell Carcinoma (mRCC)
All grade adverse events were collected in Study 8. Grade 3-5 adverse events occurring at a higher incidence (≥2%) in 337 patients receiving interferon alfa (IFN-α) plus bevacizumab compared to 304 patients receiving IFN-α plus placebo arm 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, haemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma).

Grade 1-5 adverse events occurring at a higher incidence (≥5%) in patients receiving IFN-α plus bevacizumab compared to the IFN-α plus placebo arm are presented in Table 3.

Table 3: NCI-CTC Grades 1-5 Adverse Events in Study 8 (Occurring at Higher Incidence [≥5%] in IFN-α + Bevacizumab vs. IFN-α + Placebo)

System Organ Class/Preferred term[a]	IFN-α + Placebo (n = 304)	IFN-α + Bevacizumab (n = 337)
Gastrointestinal disorders		
Diarrhea	16%	21%
General disorders and administration site conditions		
Fatigue	27%	33%
Investigations		
Weight decreased	15%	20%
Metabolism and nutrition disorders		
Anorexia	31%	36%
Musculoskeletal and connective tissue disorders		
Myalgia	14%	19%
Back pain	6%	12%
Nervous system disorders		
Headache	16%	24%
Renal and urinary disorders		
Proteinuria	3%	20%
Respiratory, thoracic and mediastinal disorders		
Epistaxis	4%	27%
Dysphonia	0%	5%
Vascular disorders		
Hypertension	9%	28%

[a] Adverse events were encoded using MedDRA, Version 10.1.

The following adverse events were reported at a 5-fold greater incidence in the IFN-α plus bevacizumab arm compared to IFN-α alone 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 Carcinoma of the Cervix
All grade adverse reactions were collected in Study 9.

Grade 1-4 adverse reactions occurring where the incidence difference is ≥5% in patients receiving bevacizumab plus chemotherapy compared to chemotherapy alone are presented in Table 4.

Table 4: NCI-CTC Grades 1-4 and 3-4 Adverse Reactions in Study 9 (Incidence Difference of ≥5% Between Treatment Arms in Chemo + bevacizumab vs. Chemo Alone)

	Grade 1-4 reactions		Grade 3-4 reactions	
	Chemo Alone (n = 222)	Chemo +bevacizumab (n = 218)	Chemo Alone (n = 222)	Chemo +bevacizumab (n = 218)
Metabolism and Nutrition Disorders				
Decreased Appetite	26%	34%		
Hyperglycemia	19%	26%		
Hypomagnesemia	15%	24%		
Hyponatremia	10%	19%		
Hypoalbuminemia	11%	16%		
General Disorders and Administration Site Conditions				
Fatigue	75%	80%		
Edema Peripheral	22%	15%		
Investigations				
Weight Decreased	7%	21%		
Blood Creatinine Increased	10%	16%		
Infections and Infestations				
Urinary Tract Infection	14%	22%		
Infection	5%	10%		
Vascular Disorders				
Hypertension	6%	29%	0.5%	11.5%
Thrombosis	3%	10%	2.7%	8.3%
Nervous System Disorders				
Headache	13%	22%		
Dysarthria	1%	8%		
Gastrointestinal Disorders				
Stomatitis	10%	15%		
Proctalgia	1%	6%		
Anal Fistula	—	6%		
Blood and Lymphatic System Disorders				
Neutropenia	6%	12%		
Lymphopenia	5%	12%		
Psychiatric Disorders				
Anxiety	10%	17%		
Reproductive System and Breast Disorders				
Pelvic Pain	8%	14%		
Respiratory, Thoracic and				

Mediastinal Disorders		
Epistaxis	1%	17%
Renal and Urinary Disorders		
Proteinuria	3%	10%

Grade 3 or 4 adverse reactions occurring at a higher incidence (≥2%) in 218 patients receiving chemotherapy plus bevacizumab compared to 222 patients receiving chemotherapy alone were abdominal pain (11.9% vs. 9.9%), diarrhea (5.5% vs. 2.7%), anal fistula (3.7% vs. 0%), proctalgia (2.8% vs.0%), urinary tract infection (8.3% vs. 6.3%), cellulitis (3.2% vs. 0.5%), fatigue (14.2% vs. 9.9%), hypokalemia (7.3% vs. 4.5%), hyponatremia (3.7% vs. 1.4%), dehydration (4.1% vs. 0.5%), neutropenia (7.8% vs. 4.1%), lymphopenia (6.0% vs. 3.2%), back pain (5.5% vs. 3.2%), and pelvic pain (5.5% vs. 1.4%).

There were no Grade 5 adverse reactions occurring at a higher incidence (≥2%) in patients receiving chemotherapy plus bevacizumab compared to patients receiving chemotherapy alone.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and the specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other bevacizumab products may be misleading.

In clinical trials of adjuvant colon carcinoma, 14 of 2233 evaluable patients (0.63%) tested positive for treatment-emergent anti-bevacizumab antibodies detected by an electrochemiluminescent (ECL) based assay. Among these 14 patients, three tested positive for neutralizing antibodies against bevacizumab using an enzyme-linked immunosorbent assay (ELISA). The clinical significance of these anti-product antibody responses to bevacizumab products is unknown.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of bevacizumab products. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: Polyserositis
Cardiovascular: Pulmonary hypertension, PRES, Mesenteric venous occlusion
Eye disorders (from unapproved intravitreal use for treatment of various ocular disorders): Permanent loss of vision; Endophthalmitis (infectious and sterile); Intraocular inflammation; Retinal detachment; Increased intraocular pressure; Hemorrhage including conjunctival, vitreous hemorrhage or retinal hemorrhage; Vitreous floaters; Ocular hyperemia; Ocular pain or discomfort
Gastrointestinal: Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration
Hemic and lymphatic: Pancytopenia
Hepatobiliary disorders: Gallbladder perforation
Infections and infestations: Necrotizing fasciitis, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation
Musculoskeletal and Connective Tissue Disorders: Osteonecrosis of the jaw; Non-mandibular osteonecrosis (cases have been observed in pediatric patients who have received bevacizumab products)
Neurological: Posterior Reversible Encephalopathy Syndrome (PRES)

Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)
Respiratory: Nasal septum perforation, dysphonia
Systemic Events (from unapproved intravitreal use for treatment of various ocular disorders):
Arterial thromboembolic events, Hypertension, Gastrointestinal perforation, Hemorrhage

7 DRUG INTERACTIONS

A drug interaction study was performed in which irinotecan was administered as part of the FOLFIRI regimen with or without bevacizumab. The results demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan or its active metabolite SN38.

In a randomized study in 99 patients with NSCLC, based on limited data, there did not appear to be a difference in the mean exposure of either carboplatin or paclitaxel when each was administered alone or in combination with bevacizumab. However, 3 of the 8 patients receiving bevacizumab plus paclitaxel/carboplatin had substantially lower paclitaxel exposure after four cycles of treatment (at Day 63) than those at Day 0, while patients receiving paclitaxel/carboplatin without bevacizumab had a greater paclitaxel exposure at Day 63 than at Day 0.

In Study 8, there was no difference in the mean exposure of interferon alfa administered in combination with bevacizumab when compared to interferon alfa alone.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Bevacizumab products may cause fetal harm based on findings from animal studies and the drug's mechanism of action *[see Clinical Pharmacology (12.1)]*. Limited postmarketing reports describe cases of fetal malformations with use of bevacizumab products in pregnancy; however, these reports are insufficient to determine drug associated risks. In animal reproduction studies, intravenous administration of bevacizumab to pregnant rabbits every 3 days during organogenesis at doses approximately 1 to 10 times the clinical dose of 10 mg/kg produced fetal resorptions, decreased maternal and fetal weight gain and multiple congenital malformations including corneal opacities and abnormal ossification of the skull and skeleton including limb and phalangeal defects *[see Data]*. Furthermore, animal models link angiogenesis and VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Pregnant rabbits dosed with 10 to 100 mg/kg bevacizumab (approximately 1 to 10 times the clinical dose of 10 mg/kg) every three days during the period of organogenesis (gestation day 6-18) exhibited decreases in maternal and fetal body weights and increased number of fetal resorptions.
There were dose-related increases in the number of litters containing fetuses with any type of malformation (42.1% for the 0 mg/kg dose, 76.5% for the 30 mg/kg dose, and 95% for the 100 mg/kg dose) or fetal alterations (9.1% for the 0 mg/kg dose, 14.8% for the 30 mg/kg dose, and 61.2% for the 100 mg/kg dose). Skeletal deformities were observed at all dose levels, with some abnormalities including meningocele observed only at the 100 mg/kg dose level. Teratogenic effects included: reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws; fontanel, rib and hindlimb deformities; corneal opacity; and absent hindlimb phalanges.

8.2 Lactation

No data are available regarding the presence of bevacizumab products in human milk, the effects on the breast fed infant, or the effects on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential for serious adverse reactions in breastfed infants from bevacizumab products, advise a nursing woman that breastfeeding is not recommended during treatment with MVASI.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Bevacizumab products may cause fetal harm when administered to a pregnant woman. Advise female patients of reproductive potential to use effective contraception during treatment with MVASI and for 6 months following the last dose of MVASI *[see Use in Specific Populations (8.1)]*.

Infertility

Females

Bevacizumab products increase the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with MVASI. Long term effects of bevacizumab products exposure on fertility are unknown.

In a prospectively designed substudy of 179 premenopausal women randomized to receive chemotherapy with or without bevacizumab, the incidence of ovarian failure was higher in the bevacizumab arm (34%) compared to the control arm (2%). After discontinuation of bevacizumab and chemotherapy, recovery of ovarian function occurred in 22% (7/32) of these bevacizumab-treated patients *[see Warnings and Precautions (5.12), Adverse Reactions (6.1)]*.

8.4 Pediatric Use

The safety, effectiveness and pharmacokinetic profile of bevacizumab products in pediatric patients have not been established. In published literature reports, cases of non-mandibular osteonecrosis have been observed in patients under the age of 18 years who have received bevacizumab. Bevacizumab products are not approved for use in patients under the age of 18 years.

Antitumor activity was not observed among eight children with relapsed glioblastoma treated with bevacizumab and irinotecan. There is insufficient information to determine the safety and efficacy of bevacizumab products in children with glioblastoma.

Animal Data

Juvenile cynomolgus monkeys with open growth plates exhibited physeal dysplasia following 4 to 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure). The incidence and severity of physeal dysplasia were dose-related and were partially reversible upon cessation of treatment.

8.5 Geriatric Use

In Study 1, severe adverse events that occurred at a higher incidence (≥2%) in patients aged ≥65 years as compared to younger patients were asthenia, sepsis, deep thrombophlebitis, hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhea, constipation, anorexia, leukopenia, anemia, dehydration, hypokalemia, and hyponatremia. The effect of bevacizumab products on overall survival was similar in elderly patients as compared to younger patients.

In Study 2, patients aged ≥65 years receiving bevacizumab plus FOLFOX4 had a greater relative risk

as compared to younger patients for the following adverse events: nausea, emesis, ileus, and fatigue.

In Study 5, patients aged ≥65 years receiving carboplatin, paclitaxel, and bevacizumab had a greater relative risk for proteinuria as compared to younger patients *[see Warnings and Precautions (5.9)]*.

Of the 742 patients enrolled in clinical studies in which all adverse events were captured, 212 (29%) were age 65 or older and 43 (6%) were age 75 or older. Adverse events of any severity that occurred at a higher incidence in the elderly as compared to younger patients, in addition to those described above, were dyspepsia, gastrointestinal hemorrhage, edema, epistaxis, increased cough, and voice alteration.

In an exploratory, pooled analysis of 1745 patients treated in five randomized, controlled studies, there were 618 (35%) patients aged ≥ 65 years and 1127 patients <65 years of age. The overall incidence of arterial thromboembolic events was increased in all patients receiving bevacizumab with chemotherapy as compared to those receiving chemotherapy alone, regardless of age. However, the increase in arterial thromboembolic events incidence was greater in patients aged ≥65 years (8.5% vs. 2.9%) as compared to those <65 years (2.1% vs. 1.4%) *[see Warnings and Precautions (5.5)]*.

10 OVERDOSAGE

The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of 16 patients and with severe headache in three of 16 patients.

11 DESCRIPTION

MVASI (bevacizumab-awwb) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay systems. Bevacizumab products contain human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. MVASI has an approximate molecular weight of 149 kD. MVASI is produced in a mammalian cell (Chinese Hamster Ovary) expression system.

MVASI is a colorless to pale yellow, sterile, pH 6.2 solution for intravenous infusion. MVASI is supplied in 100 mg and 400 mg preservative-free, single-use vials to deliver 4 mL or 16 mL of bevacizumab-awwb (25 mg/mL). The 100 mg product is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The 400 mg product is formulated in 960 mg α,α-trehalose dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism 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 products to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

12.3 Pharmacokinetics

The pharmacokinetic profile of bevacizumab was assessed using an assay that measures total serum bevacizumab concentrations (i.e., the assay did not distinguish between free bevacizumab and bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of 491 patients who received 1 to 20 mg/kg of bevacizumab weekly, every 2 weeks, or every 3 weeks, the estimated

half-life of bevacizumab was approximately 20 days (range 11-50 days). The predicted time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg of bevacizumab every 2 weeks was 2.8.

The clearance of bevacizumab varied by body weight, gender, and tumor burden. After correcting for body weight, males had a higher bevacizumab clearance (0.262 L/day vs. 0.207 L/day) and a larger Vc (3.25 L vs. 2.66 L) than females. Patients with higher tumor burden (at or above median value of tumor surface area) had a higher bevacizumab clearance (0.249 L/day vs. 0.199 L/day) than patients with tumor burdens below the median. In Study 1, there was no evidence of lesser efficacy (hazard ratio for overall survival) in males or patients with higher tumor burden treated with bevacizumab as compared to females and patients with low tumor burden. The relationship between bevacizumab products exposure and clinical outcomes has not been explored.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity studies of bevacizumab products have been conducted.

Bevacizumab products may impair fertility. Female cynomolgus monkeys treated with 0.4 to 20 times the recommended human dose of bevacizumab exhibited arrested follicular development or absent corpora lutea as well as dose-related decreases in ovarian and uterine weights, endometrial proliferation, and the number of menstrual cycles. Following a 4- or 12-week recovery period, there was a trend suggestive of reversibility. After the 12-week recovery period, follicular maturation arrest was no longer observed, but ovarian weights were still moderately decreased. Reduced endometrial proliferation was no longer observed at the 12-week recovery time point; however, decreased uterine weight, absent corpora lutea, and reduced number of menstrual cycles remained evident.

13.2 Animal Toxicology and/or Pharmacology

Rabbits dosed with bevacizumab exhibited reduced wound healing capacity. Using full-thickness skin incision and partial thickness circular dermal wound models, bevacizumab dosing resulted in reductions in wound tensile strength, decreased granulation and re-epithelialization, and delayed time to wound closure.

14 CLINICAL STUDIES

14.1 Metastatic Colorectal Cancer (mCRC)

Study 1

In this double-blind, active-controlled study, patients were randomized (1:1:1) to IV bolus-IFL (irinotecan 125 mg/m^2, 5-FU 500 mg/m^2, and leucovorin (LV) 20 mg/m^2 given once weekly for 4 weeks every 6 weeks) plus placebo (Arm 1), bolus-IFL plus bevacizumab (5 mg/kg every 2 weeks) (Arm 2), or 5-FU/LV plus bevacizumab (5 mg/kg every 2 weeks) (Arm 3). Enrollment in Arm 3 was discontinued, as pre-specified, when the toxicity of bevacizumab in combination with the bolus-IFL regimen was deemed acceptable. The main outcome measure was overall survival (OS).

Of the 813 patients randomized to Arms 1 and 2, the median age was 60, 40% were female, 79% were Caucasian, 57% had an ECOG performance status of 0, 21% had a rectal primary and 28% received prior adjuvant chemotherapy. In 56% of the patients, the dominant site of disease was extra-abdominal, while the liver was the dominant site in 38% of patients.

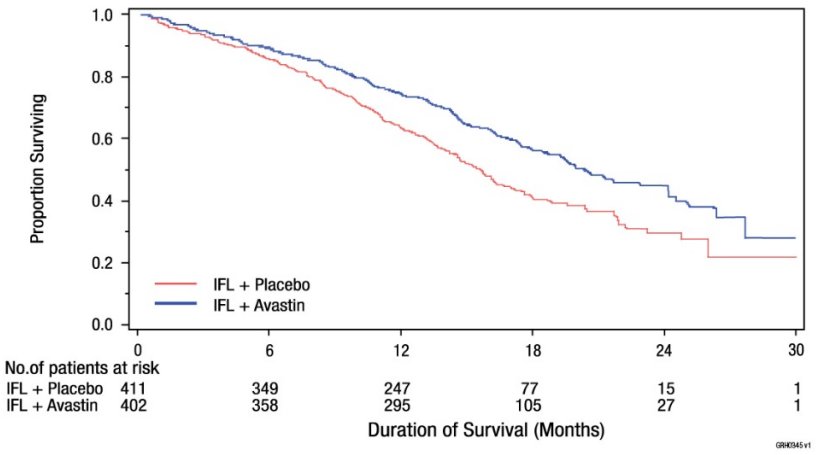
The addition of bevacizumab resulted in an improvement in survival across subgroups defined by age (<65 yrs, ≥65 yrs) and gender. Results are presented in Table 5 and Figure 1.

Table 5: Study 1 Efficacy Results

	IFL+ Placebo	IFL+ bevacizumab 5 mg/kg q 2 wks
Number of Patients	411	402
Overall Survival[a]		
Median (months)	15.6	20.3
Hazard ratio		0.66
Progression-free Survival[a]		
Median (months)	6.2	10.6
Hazard ratio		0.54
Overall Response Rate[b]		
Rate (percent)	35%	45%
Duration of Response		
Median (months)	7.1	10.4

[a] $p < 0.001$ by stratified log rank test.
[b] $p < 0.01$ by χ^2 test.

Figure 1: Duration of Survival in Study 1



Among the 110 patients enrolled in Arm 3, median OS was 18.3 months, median progression-free survival (PFS) was 8.8 months, objective response rate (ORR) was 39%, and median duration of response was 8.5 months.

Study 2
Study 2 was a randomized, open-label, active-controlled trial in patients who were previously treated with irinotecan ± 5-FU for initial therapy for metastatic disease or as adjuvant therapy. Patients were randomized (1:1:1) to IV FOLFOX4 (Day 1: oxaliplatin 85 mg/m^2 and LV 200 mg/m^2 concurrently, then 5-FU 400 mg/m^2 bolus followed by 600 mg/m^2 continuously; Day 2: LV 200 mg/m^2, then 5-FU 400 mg/m^2 bolus followed by 600 mg/m^2 continuously; repeated every 2 weeks), FOLFOX4 plus bevacizumab (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1), or bevacizumab monotherapy

(10 mg/kg every 2 weeks). The main outcome measure was OS.

The bevacizumab monotherapy 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.

Of the 829 patients randomized to the three arms, the median age was 61 years, 40% were female, 87% were Caucasian, 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 5-FU as therapy for metastatic disease, and 1% received prior irinotecan and 5-FU as adjuvant therapy.

The addition of bevacizumab to FOLFOX4 resulted in significantly longer survival as compared to FOLFOX4 alone (median OS 13.0 months vs. 10.8 months; hazard ratio 0.75 [95% CI 0.63, 0.89], $p = 0.001$ stratified log rank test) with clinical benefit seen in subgroups defined by age (<65 yrs, ≥65 yrs) and gender. PFS and ORR based on investigator assessment were higher in the bevacizumab plus FOLFOX4 arm.

Study 3
The activity of bevacizumab in combination with bolus or infusional 5-FU/LV was evaluated in a single arm study enrolling 339 patients with mCRC with disease progression following both irinotecan-and oxaliplatin-containing chemotherapy regimens. Seventy-three percent of patients received concurrent bolus 5-FU/LV. One objective partial response was verified in the first 100 evaluable patients for an overall response rate of 1% (95% CI 0-5.5%).

Study 4
Study 4 was a prospective, randomized, open-label, multinational, controlled trial in patients with histologically confirmed metastatic colorectal cancer 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 discontinuation of bevacizumab as first-line therapy to receive fluoropyrimidine/oxaliplatin- or fluoropyrimidine/irinotecan-based chemotherapy with or without bevacizumab administered at 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks. The choice of second line therapy was contingent upon first-line chemotherapy treatment. Second-line treatment was administered until progressive disease or unacceptable toxicity. The main outcome measure was OS defined as the time from randomization until death from any cause.

Of the 820 patients randomized, the majority of patients were male (64%) and the median age was 63.0 years (range 21 to 84 years). At baseline, 52% of patients were ECOG performance status (PS) 1, 44% were ECOG PS 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 treatment arm.

The addition of bevacizumab to fluoropyrimidine-based chemotherapy resulted in a statistically significant prolongation of survival and PFS; there was no significant difference in overall response rate, a key secondary outcome measure. Results are presented in Table 6 and Figure 2.

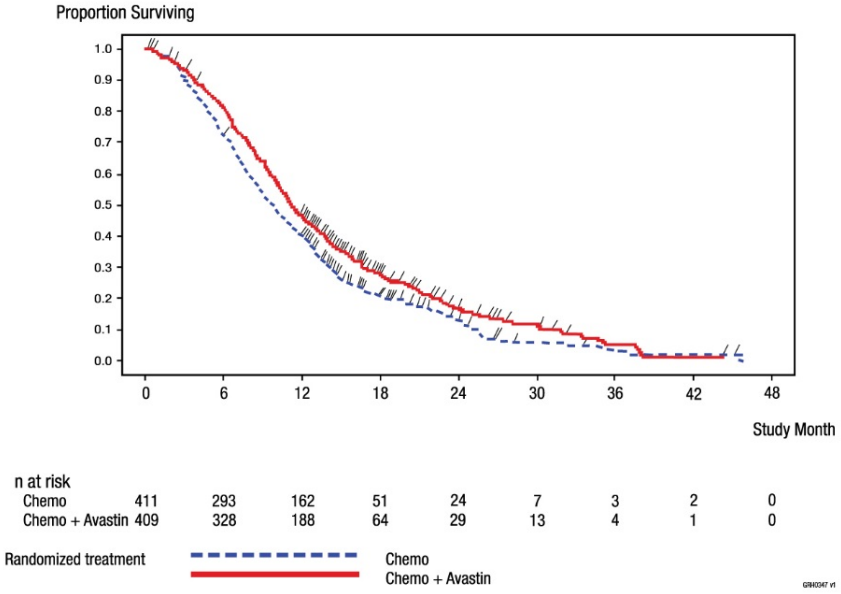
Table 6: Study 4 Efficacy Results

	Chemotherapy	Bevacizumab + Chemotherapy
Number of Patients	411	409
Overall Survival[a]		
Median (months)	9.8	11.2
Hazard ratio (95% CI)	0.81 (0.69, 0.94)	
Progression-Free Survival[b]		
Median (months)	4.0	5.7
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.

Figure 2: Duration of Survival in Study 4



14.2 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 trials.

The first study conducted in 3451 patients with high risk stage II and III colon cancer, who had undergone surgery for colon cancer with curative intent, was a 3-arm study of bevacizumab administered at a dose equivalent to 2.5 mg/kg/week on either a 2-weekly schedule in combination with FOLFOX4, or on a 3-weekly schedule in combination with XELOX and FOLFOX4 alone. Patients were randomized as follows: 1151 patients to FOLFOX4 arm, 1155 to FOLFOX4 plus bevacizumab arm, and 1145 to XELOX plus bevacizumab arm. The median age was 58 years, 54% were male, 84% were Caucasian and 29% were ≥ age 65. Eighty-three percent had stage III disease.

The main efficacy outcome of the study was disease free survival (DFS) in patients with stage III colon cancer. Addition of bevacizumab to chemotherapy did not improve DFS. As compared to the control arm, the proportion of stage III patients with disease recurrence or with death due to disease

progression were numerically higher in the FOLFOX4 plus bevacizumab and in the XELOX plus bevacizumab arms. The hazard ratios for DFS were 1.17 (95% CI: 0.98-1.39) for the FOLFOX4 plus bevacizumab versus FOLFOX4 and 1.07 (95% CI: 0.90-1.28) for the XELOX plus bevacizumab versus FOLFOX4.

The hazard ratios for overall survival were 1.31 (95% CI = 1.03, 1.67) and 1.27 (95% CI = 1.00, 1.62) for the comparison of bevacizumab plus FOLFOX4 versus FOLFOX4 and bevacizumab plus XELOX versus FOLFOX4, respectively. Similar lack of efficacy for DFS was observed in the bevacizumab-containing arms compared to control in the high-risk stage II cohort.

In a second study, 2710 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 in combination with mFOLFOX6 (N = 1354) or mFOLFOX6 alone (N = 1356). The median age was 57 years, 50% were male and 87% Caucasian. Seventy-five percent had stage III disease. The main efficacy outcome was DFS among stage III patients. The hazard ratio for DFS was 0.92 (95% CI: 0.77, 1.10). Overall survival, an additional efficacy outcome, was not significantly improved with the addition of bevacizumab to mFOLFOX6 (HR = 0.96, 95% CI = [0.75, 1.22].

14.3 Unresectable Non–Squamous Non–Small Cell Lung Cancer (NSCLC)

Study 5

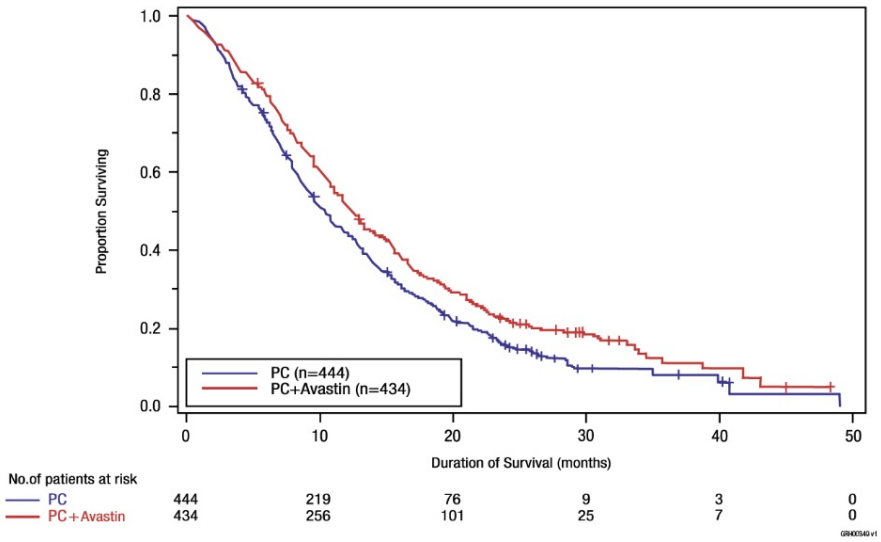
The safety and efficacy of bevacizumab as first-line treatment of patients with locally advanced, metastatic, or recurrent non–squamous NSCLC was studied in a single, large, randomized, active-controlled, open-label, multicenter study.

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 = 6.0, by IV on day 1 (PC) or PC in combination with bevacizumab 15 mg/kg by IV on day 1 (PC plus bevacizumab). After completion or upon discontinuation of chemotherapy, patients in the PC plus bevacizumab arm continued to receive bevacizumab alone until disease progression or until unacceptable toxicity. Patients with predominant squamous histology (mixed cell type tumors only), central nervous system (CNS) metastasis, gross hemoptysis (≥1/2 tsp of red blood), unstable angina, or receiving therapeutic anticoagulation were excluded. The main outcome measure was duration of survival.

Of the 878 patients randomized, the median age was 63, 46% were female, 43% were ≥age 65, and 28% had ≥5% weight loss at study entry. Eleven percent had recurrent disease and of the 89% with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had Stage IV disease.

The results are presented in Figure 3. OS was statistically significantly higher among patients receiving PC plus bevacizumab compared with those receiving PC alone; median OS was 12.3 months vs. 10.3 months [hazard ratio 0.80 (repeated 95% CI 0.68, 0.94), final p-value 0.013, stratified log-rank test]. Based on investigator assessment which was not independently verified, patients were reported to have longer PFS with bevacizumab in combination with PC compared to PC alone.

Figure 3: Duration of Survival in Study 5



In an exploratory analyses across patient subgroups, the impact of bevacizumab on OS was less robust in the following: women [HR = 0.99 (95% CI: 0.79, 1.25)], age ≥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)]. 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, three-arm study of bevacizumab in combination with cisplatin and gemcitabine (CG) versus placebo and CG. A total of 1043 patients were randomized 1:1:1 to receive placebo plus CG, bevacizumab 7.5 mg/kg plus CG or bevacizumab 15.0 mg/kg plus CG. The median age was 58 years, 36% were female, and 29% were ≥ age 65. Eight percent had recurrent disease and 77% had Stage IV disease. Progression-free survival, the main efficacy outcome measure, was significantly higher in both bevacizumab containing arms compared to the placebo arm [HR 0.75 (95% CI 0.62, 0.91), p = 0.0026 for the bevacizumab 7.5 mg/kg plus CG arm and HR 0.82 (95% CI 0.68; 0.98), p = 0.0301 for the bevacizumab 15.0 mg/kg plus CG arm]. The addition of bevacizumab to CG chemotherapy failed to demonstrate an improvement in the duration of overall survival, an additional efficacy outcome measure, [HR 0.93 (95% CI 0.78; 1.11), p = 0.4203 for the bevacizumab 7.5 mg/kg plus CG arm and HR 1.03 (95% CI 0.86; 1.23), p = 0.7613 for the bevacizumab 15.0 mg/kg plus CG arm].

14.4 Glioblastoma

Study 6

The efficacy and safety of bevacizumab was evaluated in Study 6, an open-label, multicenter, randomized, non-comparative study of patients with previously treated glioblastoma. Patients received bevacizumab (10 mg/kg IV) alone or bevacizumab plus irinotecan every 2 weeks until disease progression or until unacceptable toxicity. All patients received prior radiotherapy (completed at least 8 weeks prior to receiving bevacizumab) and temozolomide. Patients with active brain hemorrhage were excluded.

Of the 85 patients randomized to the bevacizumab arm, the median age was 54 years, 32% were female, 81% were in first relapse, Karnofsky performance status was 90-100 for 45% and 70-80 for 55%.

The efficacy of bevacizumab was demonstrated using response assessment based on both WHO radiographic criteria and by stable or decreasing corticosteroid use, which occurred in 25.9% (95%

CI 17.0%, 36.1%) of the patients. Median duration of response was 4.2 months (95% CI 3.0, 5.7). Radiologic assessment was based on MRI imaging (using T1 and T2/FLAIR). MRI does not necessarily distinguish between tumor, edema, and radiation necrosis.

Study 7
Study 7, was a single-arm, single institution trial with 56 patients with glioblastoma. All patients had documented disease progression after receiving temozolomide and radiation therapy. Patients received bevacizumab 10 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity.

The median age was 54, 54% were male, 98% Caucasian, and 68% had a Karnofsky Performance Status of 90-100.

The efficacy of bevacizumab was supported by an objective response rate of 19.6% (95% CI 10.9%, 31.3%) using the same response criteria as in Study 6. Median duration of response was 3.9 months (95% CI 2.4, 17.4).

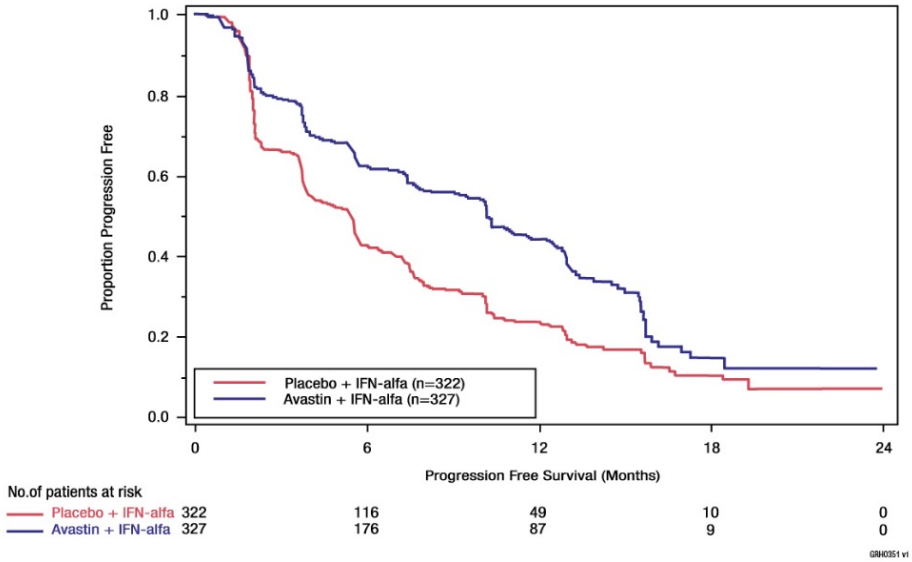
14.5 Metastatic Renal Cell Carcinoma (mRCC)

Study 8
Patients with treatment-naïve mRCC were evaluated in a multicenter, randomized, double-blind, international study comparing bevacizumab plus interferon alfa 2a (IFN-α2a) versus placebo plus IFN-α2a. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to receive either bevacizumab (10 mg/kg IV infusion every 2 weeks; n = 327) or placebo (IV every 2 weeks; n = 322) in combination with IFN-α2a (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 of the study was investigator-assessed PFS. Secondary outcome measures were ORR and OS.

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

The results are presented in Figure 4. PFS was statistically significantly prolonged among patients receiving bevacizumab plus IFN-α2a compared to those receiving IFN-α2a alone; 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 <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 bevacizumab plus IFN-α2a arm and 21 months in the IFN-α2a plus placebo arm [HR 0.86, (95% CI 0.72, 1.04)].

Figure 4: Progression-Free Survival in Study 8



14.6 Persistent, Recurrent, or Metastatic Carcinoma of the Cervix

Study 9

Patients with persistent, recurrent, or metastatic carcinoma of the cervix were evaluated in a randomized, four-arm, multi-center trial comparing bevacizumab plus chemotherapy versus chemotherapy alone (Study 9; GOG-0240). 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 IV over 24 hours, Day 2: cisplatin 50 mg/m^2 IV plus bevacizumab; or Day 1: paclitaxel 175 mg/m^2 IV over 3 hours, Day 2: cisplatin 50 mg/m^2 IV plus bevacizumab; or Day 1: paclitaxel 175 mg/m^2 IV over 3 hours plus cisplatin 50 mg/m^2 IV plus bevacizumab
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours plus bevacizumab, Days 1-3: topotecan 0.75 mg/m^2 over 30 minutes

Patients were treated until disease progression or unacceptable adverse events precluded further therapy. The main outcome measure of the study was overall survival (OS). Response rate (ORR) was a secondary outcome measure.

The median age was 48 years (range: 20-85). Of the 452 patients randomized at baseline, 78% of patients were Caucasian, 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 (PS) of 0 (58%) or 1 (42%). Demographic and disease characteristics were balanced across arms.

The study results for OS in patients who received chemotherapy plus bevacizumab as compared to chemotherapy alone are presented in Table 7 and Figure 5.

Figure 5: Study 9: Overall Survival for Chemotherapy vs. Chemotherapy plus bevacizumab

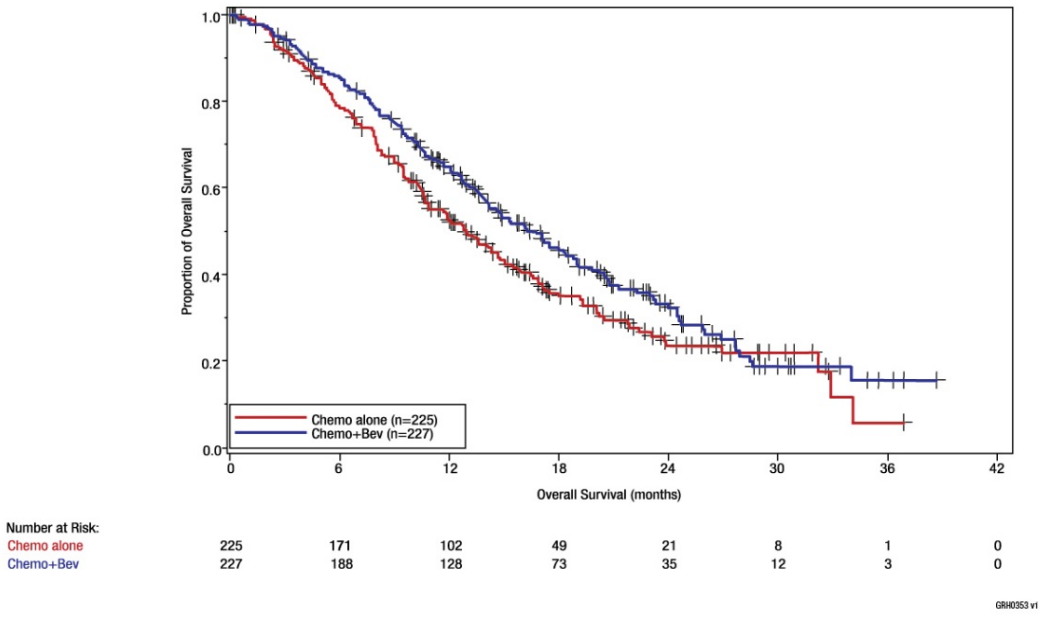


Table 7: Study 9 Efficacy Results: Chemotherapy versus Chemotherapy + Bevacizumab

	Chemotherapy (n = 225)	Chemotherapy + Bevacizumab (n = 227)
Overall Survival		
Median (months)[a]	12.9	16.8
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 overall response rate was also higher in patients who received chemotherapy plus bevacizumab [45% (95% CI: 39, 52)] than in patients who received chemotherapy alone [34% (95% CI: 28, 40)].

Table 8: Study 9 Efficacy Results: Platinum Doublet versus Nonplatinum Doublet

	Topotecan + Paclitaxel +/- bevacizumab (n = 223)	Cisplatin + Paclitaxel +/- bevacizumab (n = 229)
Overall Survival		
Median (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 hazard ratio for OS with Cisplatin + Paclitaxel + bevacizumab as compared to Cisplatin + Paclitaxel alone was 0.72 (95% CI: 0.51, 1.02). The hazard ratio for OS with Topotecan + Paclitaxel + bevacizumab as compared to Topotecan + Paclitaxel alone was 0.76 (95% CI: 0.55,

1.06).

16 HOW SUPPLIED/STORAGE AND HANDLING

MVASI (bevacizumab-awwb) injection is supplied as a sterile, colorless to pale yellow, preservative-free solution containing 25 mg/mL bevacizumab-awwb in a single-dose vial. The vial stopper contains dry natural rubber.

MVASI is provided as one vial per carton. Each single dose vial contains:

- 100 mg of bevacizumab-awwb in 4 mL (25 mg/mL) (NDC 55513-206-01).
- 400 mg of bevacizumab-awwb in 16 mL (25 mg/mL) (NDC 55513-207-01).

Store at 2-8°C (36-46°F) in the original carton until time of use. MVASI vials should be protected from light. **Do not freeze or shake.** Discard any unused portion remaining in the vial.

17 PATIENT COUNSELING INFORMATION

Advise patients:

- To undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated.
- To immediately contact their health care provider for unusual bleeding, high fever, rigors, sudden onset of worsening neurological function, or persistent or severe abdominal pain, severe constipation, or vomiting.
- Of increased risk of wound healing complications during and following MVASI.
- Of increased risk of an arterial thromboembolic event.
- Of the increased risk for ovarian failure following MVASI treatment.

Embryo-fetal Toxicity

- Advise female patients that MVASI may cause fetal harm and to inform their healthcare provider with a known or suspected pregnancy *[see Warnings and Precautions (5.11), Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment with MVASI and for 6 months after the last dose of MVASI *[see Use in Specific Populations (8.3)]*.

Lactation

- Advise nursing women that breastfeeding is not recommended during treatment with MVASI *[see Use in Specific Populations (8.2)]*.

MVASI (bevacizumab-awwb)

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Marketed by Amgen Inc.

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