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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

**AVASTIN® (bevacizumab) injection, for intravenous use**
**Initial U.S. Approval: 2004**

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

- **Gastrointestinal Perforations: Discontinue for gastrointestinal perforation. (5.1)**
- **Surgery and Wound Healing Complications: Discontinue in patients who develop wound healing complications that require medical intervention. Withhold for at least 28 days prior to elective surgery. Do not administer Avastin for at least 28 days after surgery and until the wound is fully healed. (5.2)**
- **Hemorrhage: Severe or fatal hemorrhages have occurred. Do not administer for recent hemoptysis. Discontinue for Grade 3-4 hemorrhage (5.3)**

**----------RECENT MAJOR CHANGES----------**

| | |
|---|---|
| Indications and Usage, Recurrent Glioblastoma (1.3) | 12/2017 |
| Dosage and Administration, Recurrent Glioblastoma (2.4) | 12/2017 |
| Warnings and Precautions, Congestive Heart Failure (5.12) | 12/2017 |

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

Avastin is a vascular endothelial growth factor directed antibody indicated for the treatment of:

- Metastatic colorectal cancer, in combination with intravenous 5-fluorouracil-based chemotherapy for first- or second-line treatment. (1.1)
- Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin-containing regimen. (1.1)

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

- Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment. (1.2)
- Recurrent glioblastoma in adults. (1.3)
- Metastatic renal cell carcinoma in combination with interferon alfa. (1.4)
- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan. (1.5)
- Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that is:
  - platinum-resistant in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan
  - platinum-sensitive in combination with carboplatin and paclitaxel or carboplatin and gemcitabine followed by Avastin as a single agent (1.6)

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

Do not administer Avastin for 28 days following major surgery and until surgical wound is fully healed. (2.1)
Metastatic colorectal cancer (2.2)
- 5 mg/kg every 2 weeks with bolus-IFL
- 10 mg/kg every 2 weeks with FOLFOX4
- 5 mg/ kg every 2 weeks or 7.5 mg/kg every 3 weeks with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy after progression on a first-line Avastin containing regimen

First-Line Non–squamous non–small cell lung cancer (2.3)
- 15 mg/kg every 3 weeks with carboplatin and paclitaxel

Recurrent glioblastoma (2.4)
- 10 mg/kg every 2 weeks

Metastatic renal cell cancer (2.5)
- 10 mg/kg every 2 weeks with interferon alfa

Persistent, recurrent, or metastatic cervical cancer (2.6)
- 15 mg/kg every 3 weeks with paclitaxel and cisplatin, or paclitaxel and topotecan

Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer (2.7)
- 10 mg/kg every 2 weeks with paclitaxel, pegylated liposomal doxorubicin, or topotecan given every week
- 15 mg/kg every 3 weeks with topotecan given every 3 weeks

Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (2.7)
- 15 mg/kg every 3 weeks with carboplatin and paclitaxel for 6-8 cycles, followed by 15 mg/kg every 3 weeks as a single agent
- 15 mg/kg every 3 weeks with carboplatin and gemcitabine for 6-10 cycles, followed by 15 mg/kg every 3 weeks as a single agent

Administer as an intravenous infusion. (2.8)

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

Injection: 100 mg/4 mL or 400 mg/16 mL, single dose vial (3)

**----------CONTRAINDICATIONS----------**

None (4)

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

- Perforation or Fistula: Discontinue for tracheoesophageal fistula, grade 4 fistula, or necrotizing fasciitis. (5.1)
- Arterial Thromboembolic Events (ATE): Discontinue for severe ATE. (5.4)
- Venous Thromboembolic Events (VTE): Discontinue for Grade 4 VTE. (5.5)
- Hypertension: Monitor blood pressure and treat hypertension. Withhold if not medically controlled; resume once controlled. Discontinue for hypertensive crisis or hypertensive encephalopathy. (5.6)
- Posterior Reversible Encephalopathy Syndrome (PRES): Discontinue. (5.7)
- Renal Injury and Proteinuria: Monitor urine protein. Discontinue for nephrotic syndrome. Withhold until less than 2 grams of protein in urine. (5.8)
- Infusion Reactions: Decrease rate for infusion reactions. Discontinue for severe infusion reactions and administer medical therapy. (5.9)
- Embryo-fetal Toxicity: Advise females of potential risk to fetus and need for use of effective contraception. (5.10, 8.1, 8.3)
- Ovarian Failure: Advise females of the potential risk. (5.11, 8.3)
- Congestive Heart Failure (CHF): Discontinue if CHF (5.12).

**----------ADVERSE REACTIONS----------**

Most common adverse reactions incidence (incidence > 10%) 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 Genentech, Inc. at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

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

- Lactation: Advise not to breast feed. (8.2)

**See 17 for PATIENT COUNSELING INFORMATION.**

**Revised: 12/2017**

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# FULL PRESCRIBING INFORMATION

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

**Gastrointestinal Perforations: The incidence of gastrointestinal perforation, some fatal, in patients receiving Avastin ranges from 0.3% to 3%. Discontinue Avastin in patients who develop gastrointestinal perforation *[see 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 patients receiving Avastin. Discontinue Avastin in patients who develop wound healing complications that require medical intervention. Withhold Avastin at least 28 days prior to elective surgery. Do not administer Avastin for at least 28 days after surgery, and until the wound is fully healed *[see Warnings and Precautions (5.2)]*.**

**Hemorrhages: Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occur up to 5-fold more frequently in patients receiving Avastin. Do not administer Avastin to patients with a recent history of hemoptysis. Discontinue in patients who develop Grade 3-4 hemorrhage *[see Warnings and Precautions (5.3)]*.**

## 1 INDICATIONS AND USAGE

### 1.1 Metastatic Colorectal Cancer (mCRC)

Avastin, in combination with intravenous 5-fluorouracil-based chemotherapy, is indicated for the first- or second-line treatment of patients with metastatic colorectal cancer.

Avastin, 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 Avastin-containing regimen.

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

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

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

### 1.3 Recurrent Glioblastoma (GBM)

Avastin is indicated for the treatment of recurrent glioblastoma in adults.

### 1.4 Metastatic Renal Cell Carcinoma (mRCC)

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

### 1.5 Persistent, Recurrent, or Metastatic Cervical Cancer

Avastin, in combination with paclitaxel and cisplatin or paclitaxel and topotecan, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.

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### 1.6 Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Avastin, in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan, is indicated for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than 2 prior chemotherapy regimens.

Avastin, in combination with carboplatin and paclitaxel, or with carboplatin and gemcitabine, followed by Avastin as a single agent, is indicated for the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Important Administration Information

Do not administer Avastin until at least 28 days following surgery and the wound is fully healed.

### 2.2 Metastatic Colorectal Cancer (mCRC)

The recommended dose when Avastin is administered in combination with intravenous 5-fluorouracil-based chemotherapy is:

- 5 mg/kg every 2 weeks intravenously in combination with bolus-IFL.
- 10 mg/kg every 2 weeks intravenously 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 Avastin-containing regimen.

### 2.3 First-Line Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

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

### 2.4 Recurrent Glioblastoma (GBM)

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

### 2.5 Metastatic Renal Cell Carcinoma (mRCC)

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

### 2.6 Persistent, Recurrent, or Metastatic Cervical Cancer

The recommended dose of Avastin is 15 mg/kg intravenously every 3 weeks in combination with paclitaxel and cisplatin or in combination with paclitaxel and topotecan.

### 2.7 Recurrent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

*Platinum Resistant*

The recommended dose is 10 mg/kg intravenously every 2 weeks in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan (every week).

The recommended dose is 15 mg/kg intravenously every 3 weeks in combination with topotecan (every 3 weeks).

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*Platinum Sensitive*
The recommended dose is 15 mg/kg intravenously every 3 weeks, in combination with carboplatin and paclitaxel for 6 to 8 cycles, followed by Avastin 15 mg/kg every 3 weeks as a single agent until disease progression.

The recommended dose is 15 mg/kg intravenously every 3 weeks, in combination with carboplatin and gemcitabine for 6 to 10 cycles, followed by Avastin 15 mg/kg every 3 weeks as a single agent until disease progression.

### 2.8 Dose Modifications for Adverse Reactions
Table 1 describes dose modifications for specific adverse reactions *[see Warnings and Precautions (5)]*. No dose reductions for Avastin are recommended.

**Table 1: Dose Modifications for Adverse Reactions**

| Adverse Reaction | Severity | Dose Modification |
|---|---|---|
| Gastrointestinal Perforation and fistulae *[see Warnings and Precautions (5.1)]*. | • Gastrointestinal perforation, any grade<br>• Tracheoesophageal fistula, any grade<br>• Fistula, Grade 4<br>• Fistula formation involving any internal organ | Discontinue Avastin |
| Wound Healing Complications *[see Warnings and Precautions (5.2)]*. | • Wound healing complications requiring medical intervention<br>• Necrotizing fasciitis | Discontinue Avastin |
| Hemorrhage *[see Warnings and Precautions (5.3)]*. | • Grade 3 or 4 | Discontinue Avastin |
| | • Recent history of hemoptysis of 1/2 teaspoon (2.5 mL) or more | Withhold Avastin |
| Thromboembolic Events *[see Warnings and Precautions (5.4, 5.5)]*. | • Arterial thromboembolism, severe | Discontinue Avastin |
| | • Venous thromboembolism, Grade 4 | Discontinue Avastin |
| Hypertension *[see Warnings and Precautions (5.6)]*. | • Hypertensive crisis<br>• Hypertensive encephalopathy | Discontinue Avastin |
| | • Hypertension, severe | Withhold Avastin if not controlled with medical management; resume once controlled |
| Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (5.7)]*. | • Any | Discontinue Avastin |
| Renal Toxicity and Proteinuria *[see Warnings and Precautions (5.8)]*. | • Nephrotic syndrome | Discontinue Avastin |
| | • Proteinuria greater than or equal to 2 grams per 24 hours in absence of nephrotic syndrome | Withhold Avastin until proteinuria less than 2 grams per 24 hours |



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| Adverse Reaction | Severity | Dose Modification |
|---|---|---|
| Infusion Reaction *[see Warnings and Precautions (5.10)]*. | • Severe infusion reaction | Discontinue Avastin |
| | • Clinically significant | Interrupt infusion; resume at a decreased rate of infusion after symptoms resolve |
| | • Mild, clinically insignificant | Decrease infusion rate |
| Congestive Heart Failure *[see Warnings and Precautions (5.12)]*. | Any | Discontinue Avastin |

### 2.9 Preparation and Administration

*Administration*

- Administer as an intravenous infusion.
- 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 second infusion over 60 minutes is tolerated.

*Preparation*

- Use appropriate aseptic technique.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.
- Withdraw necessary amount of Avastin and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.
- Discard any unused portion left in a vial, as the product contains no preservatives.
- Store diluted Avastin solution at 2–8°C (36–46°F) for up to 8 hours.
- No incompatibilities between Avastin and polyvinylchloride or polyolefin bags have been observed.

## 3 DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/4 mL (25 mg/mL) or 400 mg/16 mL (25 mg/mL) as a clear to slightly opalescent, colorless to pale brown solution in single-dose vial

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Gastrointestinal Perforations and Fistulae

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

Serious fistulae (including, tracheoesophageal, bronchopleural, biliary, vaginal, renal and bladder sites) occur at a higher incidence in patients receiving Avastin compared to patients receiving chemotherapy. The incidence ranged from < 1% to 1.8% across clinical studies, with the highest incidence in patients with cervical cancer. The majority of fistulae occurred within 6 months of the

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first dose. Patients who develop a gastrointestinal vaginal fistula may also have a bowel obstruction and require surgical intervention, as well as a diverting ostomy.

Avoid Avastin in patients with ovarian cancer who have evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction. Discontinue in patients who develop gastrointestinal perforation, tracheoesophageal fistula or any Grade 4 fistula. Discontinue in patients with fistula formation involving any internal organ *[see Adverse Reactions (6.1)]*.

### 5.2 Surgery and Wound Healing Complications

In a controlled clinical study in which Avastin was not administered within 28 days of major surgical procedures, the incidence of wound healing complications, including serious and fatal complications, was 15% in patients with mCRC who underwent surgery while receiving Avastin and 4% in patients who did not receive Avastin. In a controlled clinical study in patients with relapsed or recurrent GBM, the incidence of wound healing events was 5% in patients who received Avastin and 0.7% in patients who did not receive Avastin *[see Adverse Reactions (6.1)]*.

Discontinue Avastin in patients with wound healing complications requiring medical intervention. Withhold for at least 28 days prior to elective surgery. Do not administer for at least 28 days following surgery and until the wound is fully healed.

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

### 5.3 Hemorrhage

Avastin can result in two distinct patterns of bleeding: minor hemorrhage, most commonly Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhage. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin compared to patients receiving chemotherapy alone. Across clinical studies, the incidence of Grades 3-5 hemorrhagic events ranged from 0.4% to 7% in patients receiving Avastin *[see Adverse Reactions (6.1)]*.

Serious or fatal pulmonary hemorrhage occurred in 31% of patients with squamous NSCLC and 4% of patients with non-squamous NSCLC receiving Avastin with chemotherapy compared to none of the patients receiving chemotherapy alone.

Do not administer Avastin to patients with recent history of hemoptysis of 1/2 teaspoon or more of red blood. Discontinue in patients who develop a Grade 3-4 hemorrhage.

### 5.4 Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, and angina, occurred at a higher incidence in patients receiving Avastin compared to patients receiving chemotherapy. Across clinical studies, the incidence of Grades 3-5 ATE was 5% in patients receiving Avastin with chemotherapy compared to ≤ 2% in patients receiving chemotherapy alone; the highest incidence occurred in patients with GBM. The risk of developing ATE was increased in patients with a history of arterial thromboembolism, diabetes, or greater than 65 years old *[see Use in Specific Populations (8.5)]*.

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Discontinue in patients who develop a severe ATE. The safety of reinitiating Avastin after an ATE is resolved is not known.

### 5.5 Venous Thromboembolic Events

An increased risk of venous thromboembolic events (VTE) was observed across clinical studies. In Study GOG-0240, Grade 3-4 VTE was reported in 11% of patients receiving Avastin with chemotherapy compared with 5% of patients receiving chemotherapy alone. In EORTC 26101, the incidence of Grade 3-4 VTE was 5% in patients receiving Avastin with chemotherapy compared to 2% in patients receiving chemotherapy alone.

Discontinue Avastin in patients with a Grade 4 VTE, including pulmonary embolism *[see Adverse Reactions (6.1)]*.

### 5.6 Hypertension

The incidence of severe hypertension is increased in patients receiving Avastin as compared to patients receiving chemotherapy alone. Across clinical studies, the incidence of Grade 3-4 hypertension ranged from 5% to 18%.

Monitor blood pressure every two to three weeks during treatment with Avastin. Treat with appropriate anti-hypertensive therapy and monitor blood pressure regularly. Continue to monitor blood pressure at regular intervals in patients with Avastin-induced or -exacerbated hypertension after discontinuing Avastin. Withhold Avastin in patients with severe hypertension that is not controlled with medical management; resume once controlled with medical management. Discontinue in patients who develop hypertensive crisis or hypertensive encephalopathy.

### 5.7 Posterior Reversible Encephalopathy Syndrome (PRES)

PRES was reported in < 0.5% of patients across clinical studies. The onset of symptoms occurred from 16 hours to 1 year after the first dose. PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of PRES.

Discontinue Avastin in patients who develop PRES. Symptoms usually resolve or improve within days after discontinuing Avastin, although some patients have experienced ongoing neurologic sequelae. The safety of reinitiating Avastin in patients who developed PRES is not known.

### 5.8 Renal Injury and Proteinuria

The incidence and severity of proteinuria is higher in patients receiving Avastin as compared to patients receiving chemotherapy. Grade 3 (defined as urine dipstick 4+ or > 3.5 grams of protein per 24 hours) to Grade 4 (defined as nephrotic syndrome) ranged from 0.7% to 7% in clinical studies. The overall incidence of proteinuria (all grades) was only adequately assessed in Study BO17705, in which the incidence was 20%. Median onset of proteinuria was 5.6 months (15 days to 37 months) after initiating Avastin. Median time to resolution was 6.1 months (95% CI: 2.8, 11.3). Proteinuria did not resolve in 40% of patients after median follow-up of 11.2 months and required discontinuation of Avastin in 30% of the patients who developed proteinuria.

In an exploratory, pooled analysis of patients from seven randomized clinical studies, 5% of patients receiving Avastin with chemotherapy experienced Grades 2-4 (defined as urine dipstick 2+ or greater or > 1 gram of protein per 24 hours or nephrotic syndrome) proteinuria. Grades 2-4

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proteinuria resolved in 74% of patients. Avastin was reinitiated in 42% of patients. Of the 113 patients who reinitiated Avastin, 48% experienced a second episode of Grade 2-4 proteinuria.

Nephrotic syndrome occurred in <1% of patients receiving Avastin across clinical studies, in some instances with fatal outcome. In a published case series, kidney biopsy of 6 patients with proteinuria showed findings consistent with thrombotic microangiopathy. Results of a retrospective analysis of 5805 patients who received Avastin with chemotherapy and 3713 patients who received chemotherapy alone, showed higher rates of elevated serum creatinine levels (between 1.5 to 1.9 times baseline levels) in patients who received Avastin. Serum creatinine levels did not return to baseline in approximately one-third of patients who received Avastin.

Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria with serial urinalyses during Avastin therapy. Patients with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection. Withhold for proteinuria greater than or equal to 2 grams per 24 hours and resume when less than 2 grams per 24 hours. Discontinue in patients who develop nephrotic syndrome.

Data from a postmarketing 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)].

### 5.9 Infusion Reactions

Infusion reactions reported across clinical studies 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 occurred in <3% of patients and severe reactions occurred in 0.2% of patients.

Decrease the rate of infusion for mild, clinically insignificant infusion reactions. Interrupt the infusion in patients with clinically significant infusion reactions and consider resuming at a slower rate following resolution. Discontinue in patients who develop a severe infusion reaction and administer appropriate medical therapy (e.g., epinephrine, corticosteroids, intravenous antihistamines, bronchodilators and/or oxygen).

### 5.10 Embryo-Fetal Toxicity

Avastin may cause fetal harm based on its 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 VEGFR 2 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 Avastin *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)]*.

### 5.11 Ovarian Failure

The incidence of ovarian failure was 34% vs. 2% in premenopausal women receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone for adjuvant treatment of a solid tumor. After discontinuing Avastin, recovery of ovarian function at all time points during the post-treatment period was demonstrated in 22% of women receiving Avastin. 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 Avastin on fertility are

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unknown. Inform females of reproductive potential of the risk of ovarian failure prior to initiating Avastin *[see Adverse Reactions (6.1), Use in Specific Populations (8.3)]*.

### 5.12 Congestive Heart Failure (CHF)

Avastin is not indicated for use with anthracycline-based chemotherapy. The incidence of Grade ≥ 3 left ventricular dysfunction was 1% in patients receiving Avastin compared to 0.6% of patients receiving chemotherapy alone. Among patients who received prior anthracycline treatment, the rate of CHF was 4% for patients receiving Avastin with chemotherapy as compared to 0.6% for patients receiving chemotherapy alone.

In previously untreated patients with a hematological malignancy, the incidence of CHF and decline in left ventricular ejection fraction (LVEF) were increased in patients receiving Avastin with anthracycline-based chemotherapy compared to patients receiving placebo with the same chemotherapy regimen. The proportion of patients with a decline in LVEF from baseline of ≥ 20% or a decline from baseline of 10% to < 50%, was 10% in patients receiving Avastin with chemotherapy compared to 5% in patients receiving chemotherapy alone. Time to onset of left-ventricular dysfunction or CHF was 1 to 6 months after the first dose in at least 85% of the patients and was resolved in 62% of the patients who developed CHF in the Avastin arm compared to 82% in the placebo arm. Discontinue Avastin in patients who develop CHF.

## 6 ADVERSE REACTIONS

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

- Gastrointestinal Perforations and Fistulae *[see Warnings and Precautions (5.1)]*.
- Surgery and Wound Healing Complications *[see Warnings and Precautions (5.2)]*
- Hemorrhage *[see Warnings and Precautions (5.3)]*.
- Arterial Thromboembolic Events *[see Warnings and Precautions (5.4)]*.
- Venous Thromboembolic Events *[see Warnings and Precautions (5.5)]*.
- Hypertension *[see Warnings and Precautions (5.6)]*.
- Posterior Reversible Encephalopathy Syndrome *[see Warnings and Precautions (5.7)]*.
- Renal Injury and Proteinuria *[see Warnings and Precautions (5.8)]*.
- Infusion Reactions *[see Warnings and Precautions (5.9)]*.
- Ovarian Failure *[see Warnings and Precautions (5.11)]*.
- Congestive Heart Failure *[see Warnings and Precautions (5.12).]*.

### 6.1 Clinical Trial Experience

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

The most common adverse reactions observed in patients receiving Avastin as a single agent or in combination with chemotherapy at a rate > 10%, are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis.

The safety data below reflect exposure to Avastin in 2919 patients with mCRC, non-squamous NSCLC, glioblastoma, mRCC, cervical cancer, platinum-resistant or platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, including controlled studies

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(AVF2107g, E3200, E4599, EORTC 26101, BO17705, GOG-0240, MO22224, AVF4095, GOG-0213) at the recommended dose and schedule for a median of 6 to 23 doses.

Across clinical studies, Avastin was discontinued in 8% to 22% of patients because of adverse reactions *[see Clinical Studies (14)]*.

*Platinum-Resistant Recurrent Epithelia Ovarian, Fallopian Tube, or Primary Peritoneal Cancer*
The safety of Avastin was evaluated in 179 patients who received at least one dose of Avastin in a multicenter, open-label study (MO22224) in which patients were randomized (1:1) to Avastin with chemotherapy or 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. Patients were randomized to receive Avastin (10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks). Patients had received no more than 2 prior chemotherapy regimens. The trial excluded patients with evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction. Patients were treated until disease progression or unacceptable toxicity. Forty percent of patients on the chemotherapy alone arm received Avastin alone upon progression. The demographics of the safety population were similar to the demographics of the efficacy population. Adverse reactions are presented in Table 2.

**Table 2: Grade 2−4 Adverse Reactions Occurring at Higher Incidence (≥5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in Study MO22224**

| Adverse Reaction[a] | Avastin with Chemotherapy (N=179) | Chemotherapy (N=181) |
|---|---|---|
| **Blood and lymphatic system disorders** | | |
| Neutropenia | 31% | 25% |
| **General disorders** | | |
| Mucosal inflammation | 13% | 6% |
| **Infections** | | |
| Infection | 11% | 4% |
| **Nervous system disorders** | | |
| Peripheral sensory neuropathy | 18% | 7% |
| **Renal and urinary disorders** | | |
| Proteinuria | 12% | 0.6% |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Epistaxis | 5% | 0% |
| **Skin and subcutaneous tissue disorders** | | |
| Palmar-plantar erythrodysaesthesia | 11% | 5% |
| **Vascular disorders** | | |
| Hypertension | 19% | 6% |

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Grade 3-4 adverse reactions occurring at a higher incidence ( ≥ 2%) in 179 patients receiving Avastin with chemotherapy compared to 181 patients receiving chemotherapy alone were hypertension (6.7% vs. 1.1%) and palmar-plantar erythrodysaesthesia syndrome (4.5% vs. 1.7%).
*Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer*
The safety of Avastin was evaluated in 247 patients who received at least one dose of Avastin in a double-blind study (AVF4095g) in patients with platinum sensitive recurrent epithelial ovarian,

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fallopian tube or primary peritoneal cancer. Patients were randomized (1:1) to receive Avastin (15 mg/kg) or placebo every 3 weeks with carboplatin and gemcitabine for 6 to 10 cycles followed by Avastin or placebo alone until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population. Adverse reactions are presented in Table 3.

**Table 3: Grade 1−5 Adverse Reactions Occurring at a Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Placebo with Chemotherapy in Study AVF4095g**

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



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| Adverse Reaction[a] | Avastin with Carboplatin and Gemcitabine (N=247) | Placebo with Carboplatin and Gemcitabine (N=233) |
|---|---|---|
| **Vascular disorders** | | |
| Hypertension | 42% | 9% |

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Grade 3–4 adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving Avastin with chemotherapy compared to placebo with chemotherapy were: thrombocytopenia (40% vs. 34%), nausea (4% vs. 1.3%), fatigue (6% vs. 4%), headache (4% vs. 0.9%), proteinuria (10% vs. 0.4%), dyspnea (4% vs. 1.7%), epistaxis (5% vs. 0.4%), and hypertension (17% vs. 0.9%).

The safety of Avastin was evaluated in an open-label, controlled study, GOG-0213, in 325 patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have not received more than one previous regimen of chemotherapy. Patients were randomized (1:1) to receive carboplatin and paclitaxel for 6 to 8 cycles or Avastin (15 mg/kg every 3 weeks) with carboplatin and paclitaxel for 6 to 8 cycles followed by Avastin as a single agent until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population. Adverse reactions are presented in Table 4.

**Table 4: Grade 1−5 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in Study GOG-0213**

| Adverse Reaction[a] | Avastin with Carboplatin and Paclitaxel (N=325) | Carboplatin and Paclitaxel (N=332) |
|---|---|---|
| **Gastrointestinal disorders** | | |
| Diarrhea | 39% | 32% |
| Abdominal pain | 33% | 28% |
| Vomiting | 33% | 25% |
| Stomatitis | 33% | 16% |
| **Metabolism and nutrition disorders** | | |
| Decreased appetite | 35% | 25% |
| Hyperglycemia | 31% | 24% |
| Hypomagnesemia | 27% | 17% |
| Hyponatremia | 17% | 6% |
| Weight decreased | 15% | 4% |
| Hypocalcemia | 12% | 5% |
| Hypoalbuminemia | 11% | 6% |
| Hyperkalemia | 9% | 3% |
| **Musculoskeletal and connective tissue disorders** | | |
| Arthralgia | 45% | 30% |
| Myalgia | 29% | 18% |
| Pain in extremity | 25% | 14% |
| Back pain | 17% | 10% |
| Muscular weakness | 13% | 8% |
| Neck pain | 9% | 0% |



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| Adverse Reaction[a] | Avastin with Carboplatin and Paclitaxel (N=325) | Carboplatin and Paclitaxel (N=332) |
|---|---|---|
| **Respiratory, thoracic and mediastinal disorders** | | |
| Epistaxis | 33% | 2% |
| Dyspnea | 30% | 25% |
| Cough | 30% | 17% |
| Rhinitis allergic | 17% | 4% |
| Nasal mucosal disorder | 14% | 3% |
| **Nervous system disorders** | | |
| Headache | 38% | 20% |
| Dysarthria | 14% | 2% |
| Dizziness | 13% | 8% |
| **Hepatic Disorders** | | |
| Aspartate aminotransferase increased | 15% | 9% |
| **Skin and subcutaneous tissue disorders** | | |
| Exfoliative rash | 23% | 16% |
| Nail disorder | 10% | 2% |
| Dry skin | 7% | 2% |
| **Vascular disorders** | | |
| Hypertension | 42% | 3% |
| **Renal and urinary disorders** | | |
| Proteinuria | 17% | 1% |
| Blood creatinine increased | 13% | 5% |
| **General disorders** | | |
| Chest pain | 8% | 2% |
| **Infections** | | |
| Sinusitis | 7% | 2% |

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Grade 3–4 adverse reactions occurring at a higher incidence (≥ 2%) in patients receiving Avastin with chemotherapy compared to chemotherapy alone were: hypertension (11% vs. 0.6%), fatigue (8% vs. 3%), febrile neutropenia (6% vs. 3%), proteinuria (8% vs. 0%), abdominal pain (6% vs. 0.9%), hyponatremia (4% vs. 0.9%), headache (3% vs. 0.9%), and pain in extremity (3% vs. 0%).

*Metastatic Renal Cell Carcinoma (mRCC)*
The safety of Avastin was evaluated in 337 patients who received at least one dose of Avastin in a multicenter, double-blind study (BO17705) in patients with metastatic renal cell carcinoma. Patients who had undergone a nephrectomy were randomized (1:1) to receive either Avastin (10 mg/kg every 2 weeks) or placebo with interferon alfa. Patients were treated until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population.

Grade 3-5 adverse reactions occurring at a higher incidence ( >2%) were fatigue (13% vs. 8%), asthenia (10% vs. 7%), proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis), and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, hemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma). Adverse reactions are presented in Table 5.

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**Table 5: Grades 1-5 Adverse Reactions Occurring at Higher Incidence (≥ 5%) of Patients Receiving Avastin vs. Placebo with Interferon Alfa in Study BO17705**

| Adverse Reaction[a] | Avastin with Interferon Alfa (N=337) | Placebo with Interferon Alfa (N=304) |
|---|---|---|
| **Gastrointestinal disorders** | | |
| Diarrhea | 21% | 16% |
| **General disorders and administration site conditions** | | |
| Fatigue | 33% | 27% |
| **Metabolism and nutrition disorders** | | |
| Decreased appetite | 36% | 31% |
| Weight decreased | 20% | 15% |
| **Musculoskeletal and connective tissue disorders** | | |
| Myalgia | 19% | 14% |
| Back pain | 12% | 6% |
| **Nervous system disorders** | | |
| Headache | 24% | 16% |
| **Renal and urinary disorders** | | |
| Proteinuria | 20% | 3% |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Epistaxis | 27% | 4% |
| Dysphonia | 5% | 0% |
| **Vascular disorders** | | |
| Hypertension | 28% | 9% |

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The following adverse reactions were reported at a 5-fold greater incidence in patients receiving Avastin with interferon-alfa compared to patients receiving placebo with interferon-alfa and not represented in Table 3: gingival bleeding (13 patients vs. 1 patient); rhinitis (9 vs. 0); blurred vision (8 vs. 0); gingivitis (8 vs. 1); gastroesophageal reflux disease (8 vs. 1); tinnitus (7 vs. 1); tooth abscess (7 vs. 0); mouth ulceration (6 vs. 0); acne (5 vs. 0); deafness (5 vs. 0); gastritis (5 vs. 0); gingival pain (5 vs. 0) and pulmonary embolism (5 vs. 1).

*Persistent, Recurrent, or Metastatic Cervical Cancer*
The safety of Avastin was evaluated in 218 patients who received at least one dose of Avastin in a multicenter study (GOG-0240) in patients with persistent, recurrent, or metastatic cervical cancer. Patients were randomized (1:1:1:1) to receive paclitaxel and cisplatin with or without Avastin (15 mg/kg every 3 weeks), or paclitaxel and topotecan with or without Avastin (15 mg/kg every 3 weeks). The demographics of the safety population were similar to the demographics of the efficacy population. Adverse reactions are presented in Table 6.



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**Table 6: Grades 1-4 Adverse Reactions Occurring at Higher Incidence (≥ 5%) in Patients Receiving Avastin with Chemotherapy vs. Chemotherapy Alone in Study GOG-0240**

| Adverse Reaction[a] | Avastin with Chemotherapy (N=218) | Chemotherapy (N=222) |
|---|---|---|
| **Metabolism and nutrition disorders** | | |
| Decreased appetite | 34% | 26% |
| Hyperglycemia | 26% | 19% |
| Hypomagnesemia | 24% | 15% |
| Weight Decreased | 21% | 7% |
| Hyponatremia | 19% | 10% |
| Hypoalbuminemia | 16% | 11% |
| **General disorders** | | |
| Fatigue | 80% | 75% |
| Edema Peripheral | 15% | 22% |
| **Infections and infestations** | | |
| Urinary Tract Infection | 22% | 14% |
| Infection | 10% | 5% |
| **Vascular disorders** | | |
| Hypertension | 29% | 6% |
| Thrombosis | 10% | 3% |
| **Nervous system disorders** | | |
| Headache | 22% | 13% |
| Dysarthria | 8% | 1% |
| **Gastrointestinal disorders** | | |
| Stomatitis | 15% | 10% |
| Proctalgia | 6% | 1% |
| Anal fistula | 6% | 0.0% |
| **Blood and lymphatic system disorders** | | |
| Neutropenia | 12% | 6% |
| Lymphopenia | 12% | 5% |
| **Psychiatric disorders** | | |
| Anxiety | 17% | 10% |
| **Reproductive system and breast disorders** | | |
| Pelvic pain | 14% | 8% |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Epistaxis | 17% | 1% |
| **Renal and urinary disorders** | | |
| Blood Creatinine Increased | 16% | 10% |
| Proteinuria | 10% | 3% |

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

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*Metastatic Colorectal Cancer (mCRC)*
The safety of Avastin was evaluated in 392 patients who received at least one dose of Avastin in a double-blind, active-controlled study (AVF2107g), which compared Avastin (5 mg/kg every 2 weeks) with bolus-IFL to placebo with bolus IFL in patients with mCRC. Patients were randomized (1:1:1) to placebo with bolus IFL, Avastin with bolus IFL, or Avastin with 5 fluorouracil and leucovorin. The demographics of the safety population were similar to the demographics of the efficacy population.

All Grade 3–4 adverse reactions and selected Grade 1–2 adverse reactions (i.e., hypertension, proteinuria, thromboembolic events) were collected in the entire study population. Adverse reactions are presented in Table 7.

**Table 7: Grade 3–4 Adverse Reactions Occurring at Higher Incidence (≥2%) in Patients Receiving Avastin vs. Placebo in Study AVF2107g**

| Adverse Reaction[a] | Avastin with IFL (N=392) | Placebo with IFL (N=396) |
|---|---|---|
| **General disorders** | | |
| Asthenia | 10% | 7% |
| Pain | 8% | 5% |
| **Vascular disorders** | | |
| Hypertension | 12% | 2% |
| Deep Vein Thrombosis | 9% | 5% |
| Intra-Abdominal Thrombosis | 3% | 1% |
| Syncope | 3% | 1% |
| **Gastrointestinal disorders** | | |
| Diarrhea | 34% | 25% |
| Abdominal Pain | 8% | 5% |
| Constipation | 4% | 2% |
| **Blood and lymphatic disorders** | | |
| Leukopenia | 37% | 31% |
| Neutropenia | 21% | 14% |

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The safety of Avastin was evaluated in 521 patients in an open-label, active-controlled study (E3200). Patients who were previously treated with irinotecan and fluorouracil for initial therapy for metastatic colorectal cancer. Patients were randomized (1:1:1) to FOLFOX4, Avastin (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1) with FOLFOX4, or Avastin alone (10 mg/kg every 2 weeks). Avastin was continued until disease progression or unacceptable toxicity.

The demographics of the safety population were similar to the demographics of the efficacy population. The most frequent adverse reactions (selected Grade 3–5 non-hematologic and Grade 4–5 hematologic) occurring at a higher incidence (≥2%) in patients receiving Avastin with FOLFOX4 compared to FOLFOX4 alone were fatigue (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%), vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8% vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache (3% vs. 0%). These data are likely to under-estimate the true adverse event rates due to the reporting mechanisms.

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*First-Line Non Squamous Non Small Cell Lung Cancer (NSCLC)*
The safety of Avastin was evaluated as first-line treatment in 422 patients with unresectable NSCLC who received at least one dose of Avastin in an active-controlled, open-label, multicenter trial (E4599). Chemotherapy naïve patients with locally advanced, metastatic or recurrent non–squamous NSCLC were randomized (1:1) to receive six 21 day cycles of paclitaxel and carboplatin with or without Avastin (15 mg/kg every 3 weeks). After completion or upon discontinuation of chemotherapy, patients randomized to receive Avastin continued to receive Avastin 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 demographics of the safety population were similar to the demographics of the efficacy population.

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

*Recurrent Glioblastoma*
EORTC 26101 was a multicenter, randomized, open-label study in patients with recurrent GBM following radiotherapy and temozolomide of whom 278 patients received at least one dose of Avastin and are considered safety evaluable. Patients were randomized (2:1) to receive Avastin (10 mg/kg every 2 weeks) with lomustine or lomustine alone until disease progression or unacceptable toxicity. The demographics of the safety population were similar to the demographics of the efficacy population. In the Avastin with lomustine arm, 22% of patients discontinued treatment due to adverse reactions compared with 10% of patients in the lomustine arm. In patients receiving Avastin with lomustine, the adverse reaction profile was similar to that observed in other approved indications.

### 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 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 to bevacizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In clinical studies for adjuvant treatment of a solid tumor, 0.6% (14/2323) of patients tested positive for treatment-emergent anti-bevacizumab antibodies as 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-bevacizumab antibodies is not known.


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### 6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Avastin. 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, Mesenteric venous occlusion
*Gastrointestinal:* Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration
*Hemic and lymphatic:* Pancytopenia
*Hepatobiliary disorders:* Gallbladder perforation
*Musculoskeletal and Connective Tissue Disorders:* Osteonecrosis of the jaw
*Renal:* Renal thrombotic microangiopathy (manifested as severe proteinuria)
*Respiratory:* Nasal septum perforation

## 7 DRUG INTERACTIONS

No clinically meaningful effect on the pharmacokinetics of irinotecan or its active metabolite SN38, interferon alfa, carboplatin or paclitaxel was observed when Avastin was administered in combination with these drugs; however, 3 of the 8 patients receiving Avastin with paclitaxel and carboplatin had lower paclitaxel exposure after four cycles of treatment (at Day 63) than those at Day 0, while patients receiving paclitaxel and carboplatin alone had a greater paclitaxel exposure at Day 63 than at Day 0.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

*Risk Summary*

Avastin may cause fetal harm based on findings from animal studies and its mechanism of action. *[see Clinical Pharmacology (12.1)]*. Limited postmarketing reports describe cases of fetal malformations with use of Avastin 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 VEGFR-2 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% to 4% and 15% to 20%, respectively.

*Data*

Animal Data

Pregnant rabbits dosed with 10 mg/kg 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% for the 0 mg/kg dose, 76% for the 30 mg/kg dose, and 95% for the 100 mg/kg dose) or fetal alterations (9% for the 0 mg/kg dose, 15% for the 30 mg/kg dose, and 61% 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:

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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

*Risk Summary*

No data are available regarding the presence of bevacizumab 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, advise women not to breastfeed during treatment with Avastin and for 6 months following the final dose.

### 8.3 Females and Males of Reproductive Potential

*Contraception*

Females

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

*Infertility*

Females

Avastin increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to the first-dose of Avastin. Long-term effects of Avastin on fertility are not known.

In a clinical study of 179 premenopausal women randomized to receive chemotherapy with or without Avastin, the incidence of ovarian failure was higher in patients who received Avastin with chemotherapy (34%) compared patients who received chemotherapy alone (2%). After discontinuing Avastin with chemotherapy, recovery of ovarian function occurred in 22% of these patients. *[see Warnings and Precautions (5.11), Adverse Reactions (6.1*).]

### 8.4 Pediatric Use

The safety and effectiveness of Avastin 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 Avastin. Avastin is not approved for use in patients under the age of 18 years.

Antitumor activity was not observed among eight pediatric patients with relapsed glioblastoma receiving bevacizumab and irinotecan.

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 an exploratory, pooled analysis of 1745 patients from five randomized, controlled studies, 35% patients were ≥65 years old. The overall incidence of arterial thromboembolic events was increased in all patients receiving Avastin with chemotherapy as compared to those receiving chemotherapy

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alone, regardless of age; however, the increase in the incidence of ATE was greater in patients ≥ 65 years (8% vs. 3%) as compared to patients < 65 years (2% vs. 1%) *[see Warnings and Precautions (5.4)]*.

## 10 OVERDOSAGE

No information is available concerning Avastin overdosage.

## 11 DESCRIPTION

Bevacizumab is vascular endothelial growth factor directed antibody. Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that contains human framework regions and murine complementarity-determining regions. Bevacizumab has an approximate molecular weight of 149 kDa. Bevacizumab is produced in a mammalian cell (Chinese Hamster Ovary) expression system in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

Avastin (bevacizumab) Injection for intravenous use is a sterile, clear to slightly opalescent, colorless to pale brown solution. Avastin is supplied in 100 mg and 400 mg preservative-free, single-dose vials to deliver 4 mL or 16 mL of Avastin (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 binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

### 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 Avastin every week, every 2 weeks, or every 3 weeks, bevacizumab pharmacokinetics are linear and the predicted time to reach more than 90% of steady state concentration is 84 days. The accumulation ratio following a dose of 10 mg/kg once every 2 weeks is 2.8.

Population simulations of bevacizumab exposures provide a median trough concentration of 80.3 mcg/mL on Day 84 ($10^{th}$, $90^{th}$ percentile: 45, 128) following a dose of 5 mg/kg once every two weeks.

*Distribution*

The mean (% coefficient of variation [CV%]) central volume of distribution is 2.9 (22%) L.

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*Elimination*
The mean (CV%) clearance is 0.23 (33) L/day. The estimated half-life is 20 days (11 to 50 days).

*Specific Populations*
The clearance of bevacizumab varied by body weight, sex, and tumor burden. After correcting for body weight, males had a higher bevacizumab clearance (0.26 L/day vs. 0.21 L/day) and a larger central volume of distribution (3.2 L vs. 2.7 L) than females. Patients with higher tumor burden (at or above median value of tumor surface area) had a higher bevacizumab clearance (0.25 L/day vs. 0.20 L/day) than patients with tumor burdens below the median. In AVF2107g, there was no evidence of lesser efficacy (hazard ratio for overall survival) in males or patients with higher tumor burden treated with Avastin as compared to females and patients with low tumor burden. Based on data in specific populations, no dose adjustments for Avastin are needed.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to assess potential of bevacizumab for carcinogenicity or mutagenicity.

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

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

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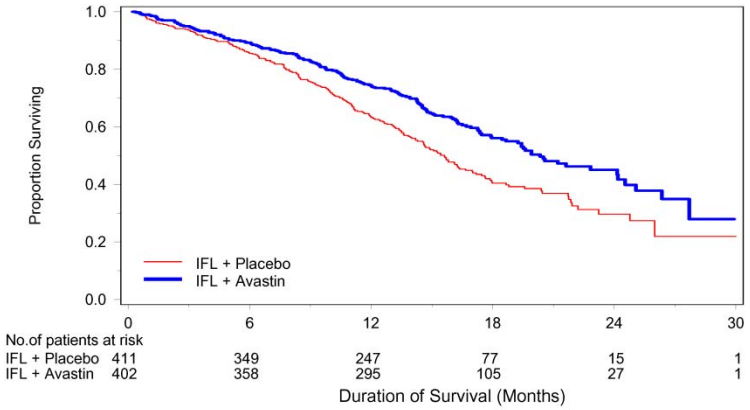
The addition of Avastin improved survival across subgroups defined by age (<65 years, ≥65 years) and sex. Results are presented in Table 8 and Figure 1.

**Table 8: Efficacy Results in Study AVF2107g**

| Efficacy Parameter | Avastin with bolus-IFL (N=402) | Placebo with bolus-IFL (N=411) |
|---|---|---|
| **Overall Survival** | | |
| Median (months) | 20.3 | 15.6 |
| Hazard ratio (95% CI) | 0.66 (0.54, 0.81) | |
| p-value[a] | < 0.001 | |
| **Progression Free Survival** | | |
| Median (months) | 10.6 | 6.2 |
| Hazard ratio (95% CI) | 0.54 (0.45, 0.66) | |
| p-value[a] | < 0.0001 | |
| **Overall Response Rate** | | |
| Rate (%) | 45% | 35% |
| p-value[b] | < 0.01 | |
| **Duration of Response** | | |
| Median (months) | 10.4 | 7.1 |

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

**Figure 1: Kaplan-Meier Curves for Duration of Survival in Metastatic Colorectal Cancer in Study AVF2107g**




Among the 110 patients randomized to Avastin with 5-fluorouracil and leucovorin, median OS was 18.3 months, median progression-free survival (PFS) was 8.8 months, overall response rate (ORR) was 39%, and median duration of response was 8.5 months.

*Study E3200*

E3200 (NCT00025337) was a randomized, open-label, active-controlled study in 829 patients who were previously treated with irinotecan and 5-fluorouracil for initial therapy for metastatic disease or as adjuvant therapy. Patients were randomized (1:1:1) to FOLFOX4 (Day 1: oxaliplatin 85 mg/m$^2$ and leucovorin 200 mg/m$^2$ concurrently, then 5-fluorouracil 400 mg/m$^2$ bolus followed by 600 mg/m$^2$ continuously; Day 2: leucovorin 200 mg/m$^2$, then 5-fluorouracil 400 mg/m$^2$ bolus followed by 600 mg/m$^2$ continuously; every 2 weeks), Avastin (10 mg/kg every 2 weeks prior to

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FOLFOX4 on Day 1) with FOLFOX4, or Avastin alone (10 mg/kg every 2 weeks). Avastin was continued until disease progression or unacceptable toxicity. The main outcome measure was OS.

The Avastin 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 5-fluorouracil for metastatic disease, and 1% received prior irinotecan and 5-fluorouracil as adjuvant therapy.

The addition of Avastin 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 Avastin with FOLFOX4.

*Study TRC-0301*
The activity of Avastin with 5-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 5-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*
ML18147 (NCT00700102) was a prospective, randomized, open-label, multinational, controlled study in 820 patients with histologically confirmed mCRC who had progressed on a first-line Avastin containing regimen. Patients were excluded if they progressed within 3 months of initiating first-line chemotherapy and if they received Avastin for less than 3 consecutive months in the first-line setting. Patients were randomized (1:1) within 3 months after discontinuing Avastin as first-line therapy to receive fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy with or without Avastin (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. Second-line therapy 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 Avastin as first-line treatment within 42 days of being randomized. Second-line chemotherapy regimens were generally balanced between each arm.

The addition of Avastin 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 9 and Figure 2.

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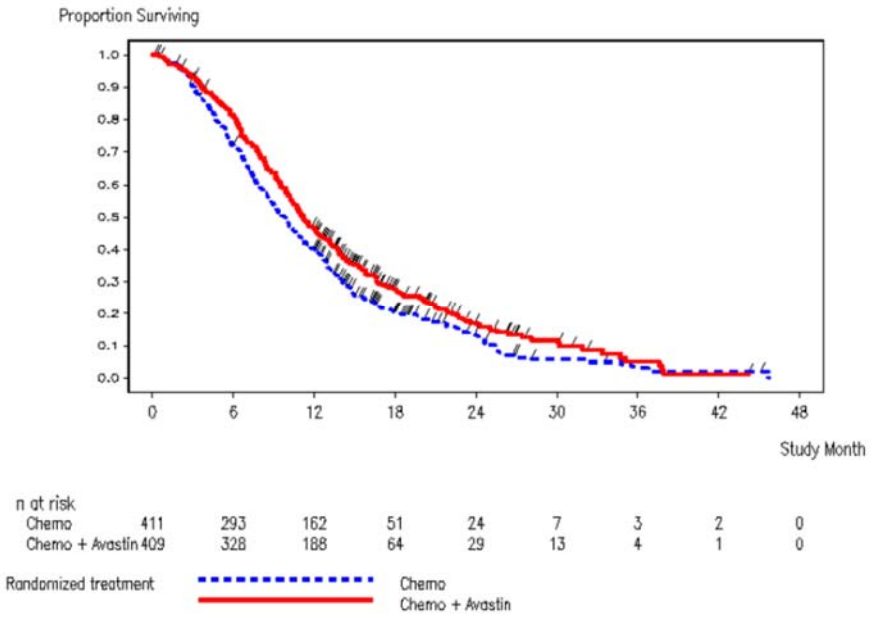
**Table 9: Efficacy Results in Study ML18147**

| Efficacy Parameter | Avastin with Chemotherapy (N=409) | Chemotherapy (N=411) |
|---|---|---|
| | | |
| **Overall Survival**[a] | | |
| Median (months) | 11.2 | 9.8 |
| Hazard ratio (95% CI) | 0.81 (0.69, 0.94) | |
| **Progression-Free Survival**[b] | | |
| Median (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.

**Figure 2: Kaplan-Meier Curves for Duration of Survival in Metastatic Colorectal Cancer in Study ML18147**




## 14.2 Lack of Efficacy in Adjuvant Treatment of Colon Cancer

Lack of efficacy of Avastin 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 Avastin at a dose equivalent to 2.5 mg/kg/week on either a 2-weekly schedule with FOLFOX4 (N=1155), or on a 3-weekly schedule with XELOX (N=1145) or FOLFOX4 alone (N=1151). The main outcome measure was disease free survival (DFS) in patients with stage III colon cancer.

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

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The addition of Avastin 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 Avastin with FOLFOX4 or with XELOX. The hazard ratios for DFS were 1.17 (95% CI: 0.98,1.39) for Avastin with FOLFOX4 versus FOLFOX4 alone and 1.07 (95% CI: 0.90, 1.28) for Avastin 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 Avastin with FOLFOX4 versus FOLFOX4 alone and Avastin with XELOX versus FOLFOX4 alone, respectively. Similar lack of efficacy for DFS were observed in the Avastin-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 Avastin 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 efficacy 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 Avastin to mFOLFOX6 [HR 0.96 (95% CI: 0.75,1.22)].

### 14.3 First-Line Non–Squamous Non–Small Cell Lung Cancer (NSCLC)

*Study E4599*

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

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

OS was statistically significantly longer for patients receiving Avastin with paclitaxel and carboplatin compared with those receiving chemotherapy alone. Median OS was 12.3 months vs. 10.3 months [HR 0.80 (95% CI: 0.68, 0.94), final p-value of 0.013, stratified log-rank test]. Based on investigator assessment which was not independently verified, patients were reported to have longer PFS with Avastin with paclitaxel and carboplatin compared to chemotherapy alone. Results are presented in Figure 3.

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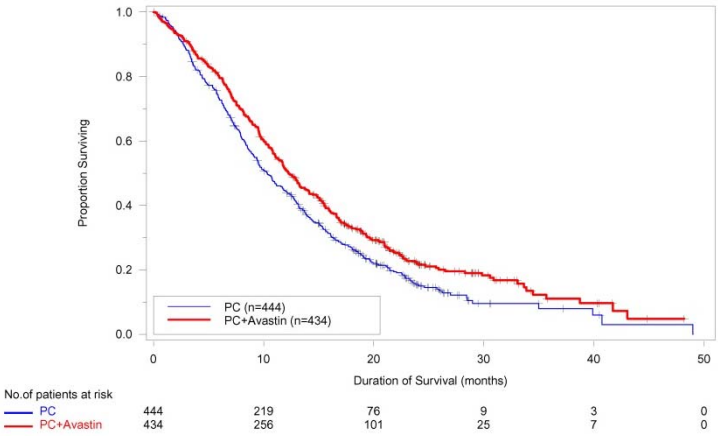
**Figure 3: Kaplan-Meier Curves for Duration of Survival in First-Line Non-Squamous Non-Small Cell Lung Cancer in Study E4599**




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

*Study BO17704*
The safety and efficacy of Avastin in patients with locally advanced, metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy was studied in another randomized, double-blind, placebo controlled study [BO17704 (NCT00806923)]. A total of 1043 patients were randomized (1:1:1) to receive cisplatin and gemcitabine with placebo, Avastin 7.5 mg/kg or Avastin 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 Avastin-containing arms compared to the placebo arm [HR 0.75 (95% CI 0.62, 0.91), p-value of 0.0026 for Avastin 7.5 mg/kg and HR 0.82 (95% CI 0.68; 0.98), p-value of 0.0301 for Avastin 15 mg/kg]. The addition of Avastin 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 Avastin 7.5 mg/kg and HR 1.03 (95% CI: 0.86, 1.23), p-value of 0.761 for Avastin 15 mg/kg].

### 14.4 Recurrent Glioblastoma (GBM)

*Study EORTC 26101*
The safety and efficacy of Avastin 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 Avastin (10 mg/kg every 2 weeks) with lomustine (90 mg/m$^2$ every 6 weeks) or lomustine (110 mg/m$^2$ every 6 weeks) alone until disease progression or unacceptable toxicity. Randomization was stratified by World Health Organization performance status (0 vs. >0), steroid use (yes vs. no), largest tumor diameter (≤ 40 vs. > 40 mm), and institution. The main outcome measure was OS. Secondary outcome measures were investigator-assessed PFS and ORR per the modified Response Assessment

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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 Avastin 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 Avastin 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 Avastin with lomustine arm [HR 0.52 (95% CI: 0.41, 0.64)] with a median PFS of 4.2 months in the Avastin 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 Avastin with lomustine arm discontinued corticosteroids (23% vs. 12%).

*Study AVF3708g and Study NCI 06-C-0064E*
One single arm single center study (NCI 06-C-0064E) and a randomized noncomparative multicenter study [AVF3708g (NCT00345163)] evaluated the efficacy and safety of Avastin 10 mg/kg every 2 weeks in patients with previously treated GBM. 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).

### 14.5 Metastatic Renal Cell Carcinoma (mRCC)

*Study BO17705*
Patients with treatment-naïve mRCC were evaluated in a multicenter, randomized, double-blind, international study [BO17705 (NCT00738530)] comparing interferon alfa Avastin versus placebo. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to receive either Avastin (10 mg/kg every 2 weeks; N=327) or placebo (every 2 weeks; N=322) with interferon alfa (9 MIU subcutaneously three times weekly for a maximum of 52 weeks). Patients were treated until disease progression or unacceptable toxicity. The main outcome measure was investigator-assessed PFS. Secondary outcome measures were ORR and OS.

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

PFS was statistically significantly prolonged among patients receiving Avastin compared to placebo; median PFS was 10.2 months vs. 5.4 months [HR 0.60 (95% CI: 0.49, 0.72), p-value <0.0001, stratified log-rank test]. Among the 595 patients with measurable disease, ORR was also significantly higher (30% vs. 12%, p-value <0.0001, stratified CMH test). There was no improvement in OS based on the final analysis conducted after 444 deaths, with a median OS of 23 months in the patients receiving Avastin with interferon alfa and 21 months in patients receiving interferon alone [HR 0.86, (95% CI 0.72, 1.04)]. Results are presented in Figure 4.


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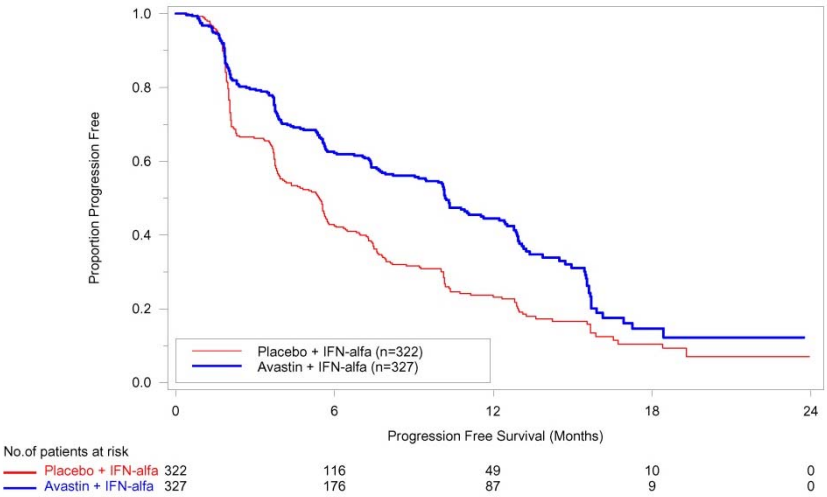
**Figure 4: Kaplan-Meier Curves for Progression-Free Survival in Metastatic Renal Cell Carcinoma in Study BO17705**




## 14.6 Persistent, Recurrent, or Metastatic Cervical Cancer

*Study GOG-0240*

Patients with persistent, recurrent, or metastatic cervical cancer were evaluated in a randomized, four-arm, multi-center study comparing Avastin 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 Avastin, or paclitaxel and topotecan with or without Avastin.

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

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

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

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

Results are presented in Table 10 and Figure 5.



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**Figure 5: Kaplan-Meier Curves for Overall Survival in Persistent, Recurrent, or Metastatic Cervical Cancer in Study GOG-0240**

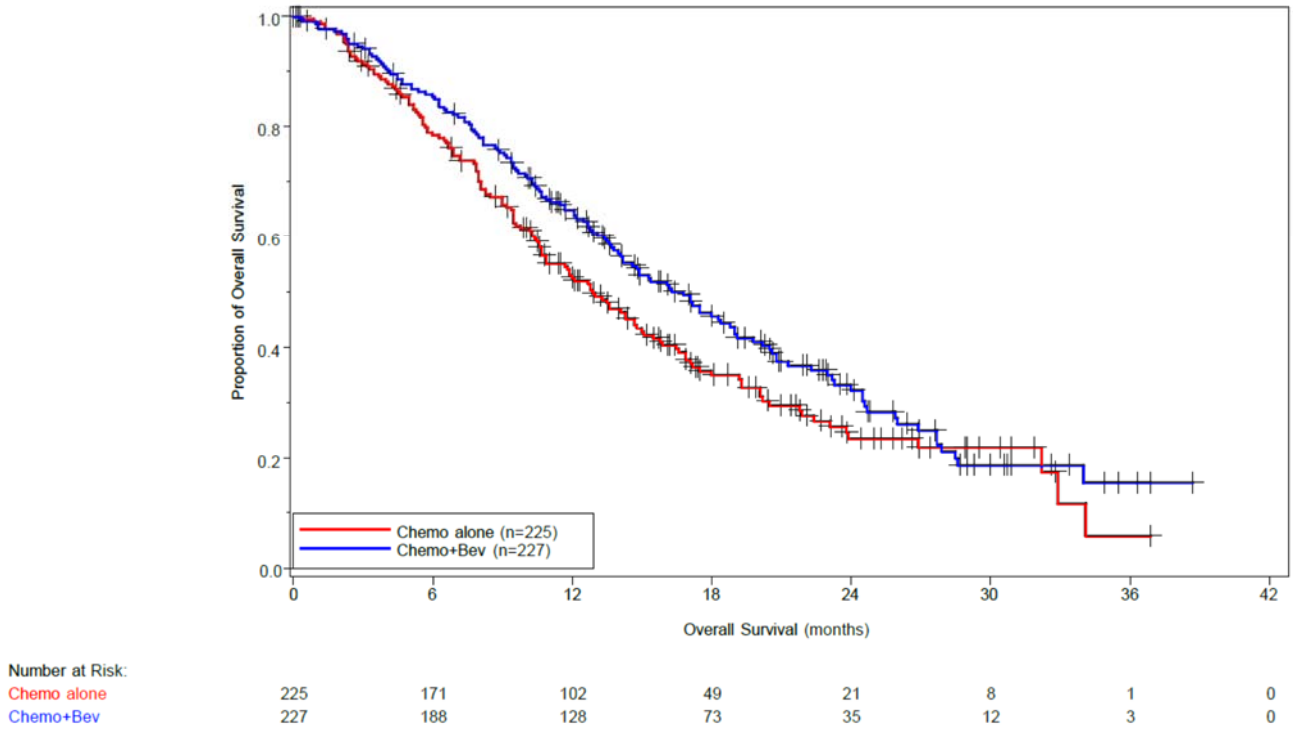


**Table 10: Efficacy Results in Study GOG-0240**

| Efficacy Parameter | Avastin with Chemotherapy (N=227) | Chemotherapy (N=225) |
|---|---|---|
| **Overall Survival** | | |
| Median (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 Avastin with chemotherapy [45% (95% CI: 39, 52)] compared to patients who received chemotherapy alone [34% (95% CI: 28,40)].



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**Table 11: Efficacy Results in Study GOG-0240**

| Efficacy Parameter | Topotecan and Paclitaxel with or without Avastin (N=223) | Cisplatin and Paclitaxel with or without Avastin (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 HR for OS with Avastin 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 Avastin with topotecan and paclitaxel as compared to topotecan and paclitaxel alone was 0.76 (95% CI: 0.55, 1.06).

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

*Study MO22224*

Avastin was evaluated in a multicenter, open-label, randomized study [MO22224 (NCT00976911)] comparing Avastin 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/m$^2$ on days 1, 8, 15 and 22 every 4 weeks; pegylated liposomal doxorubicin 40 mg/m$^2$ on day 1 every 4 weeks; or topotecan 4 mg/m$^2$ on days 1, 8 and 15 every 4 weeks or 1.25 mg/m$^2$ 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 Avastin 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 Avastin 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 12 and Figure 6. Results for the separate chemotherapy cohorts are presented in Table 13.



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**Table 12: Efficacy Results in Study MO22224**

| Efficacy Parameter | Avastin with Chemotherapy (N=179) | Chemotherapy (N=182) |
|---|---|---|
| **PFS 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

**Figure 6: Kaplan-Meier Curves for Investigator-Assessed Progression-Free Survival in Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study MO22224**

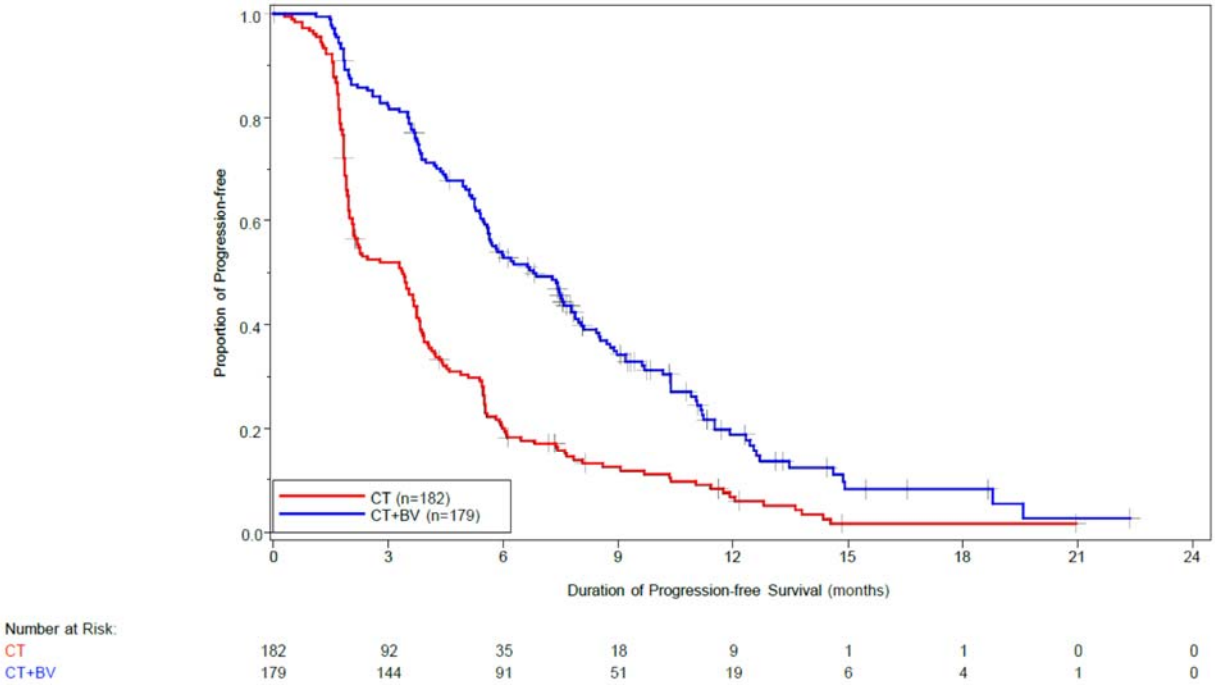

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**Table 13: Efficacy Results in Study MO22224 by Chemotherapy**

| Efficacy Parameter | Paclitaxel | | Topotecan | | Pegylated Liposomal Doxorubicin | |
|---|---|---|---|---|---|---|
| | Avastin with Chemotherapy (N=60) | Chemotherapy (N=55) | Avastin with Chemotherapy (N=57) | Chemotherapy (N=63) | Avastin with Chemotherapy (N=62) | Chemotherapy (N=64) |
| **Progression-Free Survival** *(per Investigator)* | | | | | | |
| Median (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 (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 (months) | 11.6 | 6.8 | 5.2 | NE | 8.0 | 4.6 |

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

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

*Study AVF4095g*

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

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

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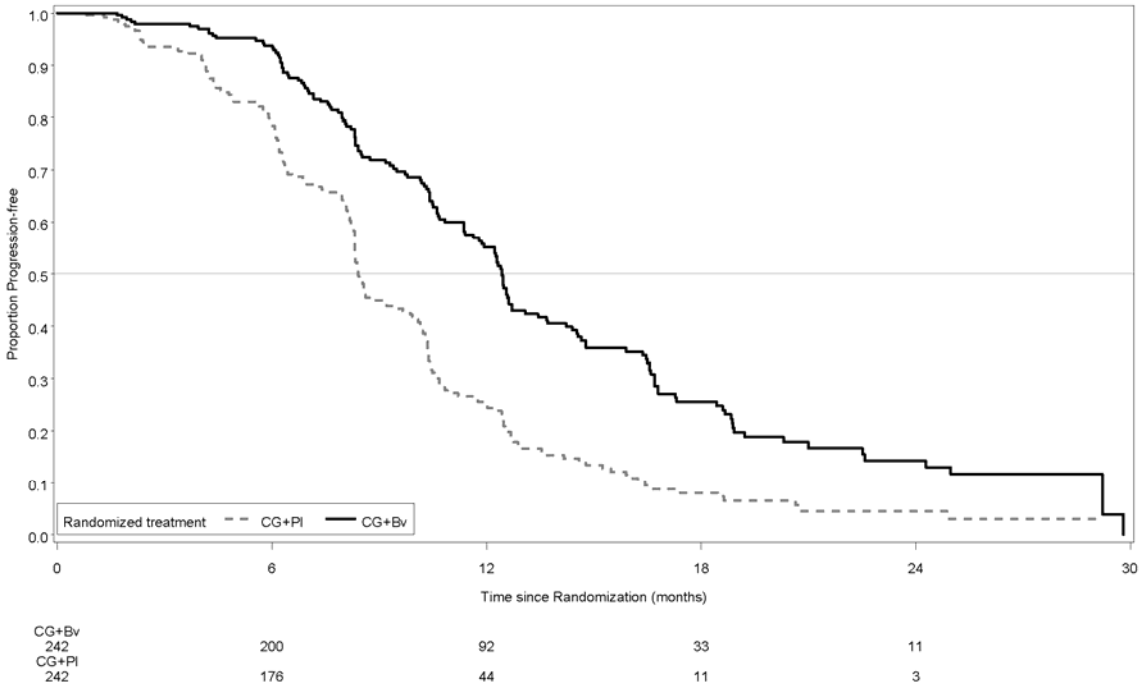
A statistically significant prolongation in PFS was demonstrated among patients receiving Avastin with chemotherapy compared to those receiving placebo with chemotherapy (Table 14 and Figure 7). Independent radiology review of PFS was consistent with investigator assessment [HR 0.45 (95% CI: 0.35, 0.58)]. OS was not significantly improved with the addition of Avastin to chemotherapy [HR 0.95 (95% CI: 0.77, 1.17)].

**Table 14: Efficacy Results in Study AVF4095g**

| Efficacy Parameter | Avastin with Gemcitabine and Carboplatin (N=242) | Placebo with Gemcitabine and Carboplatin (N=242) |
|---|---|---|
| **Progression Free Survival** | | |
| Median PFS (months) | 12.4 | 8.4 |
| Hazard ratio (95% CI) | 0.46 (0.37, 0.58) | |
| p-value | < 0.0001 | |
| **Overall Response Rate** | | |
| % patients with overall response | 78% | 57% |
| p-value | < 0.0001 | |

**Figure 7: Kaplan-Meier Curves for Progression Free Survival in Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study AVF4095g**




*Study GOG-0213*

Study GOG-0213 (NCT00565851) was a randomized, controlled, open-label study of Avastin with chemotherapy versus chemotherapy alone in the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have not received more than one previous regimen of chemotherapy (N=673). Patients were randomized (1:1) to receive carboplatin (AUC 5) and paclitaxel (175 mg/m$^2$ IV over 3 hours) every 3 weeks for 6 to 8 cycles (N=336) or Avastin (15 mg/kg) every 3 weeks with carboplatin (AUC 5) and paclitaxel (175 mg/m$^2$ IV over 3 hours) for 6 to 8 cycles followed by Avastin (15 mg/kg every 3 weeks) as a single

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agent until disease progression or unacceptable toxicity. The main outcome measure was OS. Other outcome measures were investigator-assessed PFS, and ORR.

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

Results are presented in Table 15 and Figure 8.

**Table 15: Efficacy Results in Study GOG-0213**

| **Efficacy Parameter** | **Avastin with Carboplatin and Paclitaxel (N=337)** | **Carboplatin and Paclitaxel (N=336)** |
|---|---|---|
| **Overall Survival** | | |
| Median OS (months) | 42.6 | 37.3 |
| Hazard ratio (95% CI) (IVRS)[a] | 0.84 (0.69, 1.01) | |
| Hazard ratio (95% CI) (eCRF)[b] | 0.82 (0.68, 0.996) | |
| **Progression-free Survival** | | |
| Median PFS (months) | 13.8 | 10.4 |
| Hazard ratio (95% CI) (IVRS)[a] | 0.61 (0.51, 0.72) | |
| **Overall Response Rate** | | |
| Number of patients with measurable disease at baseline | 274 | 286 |
| Rate, % | 213 (78%) | 159 (56%) |

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



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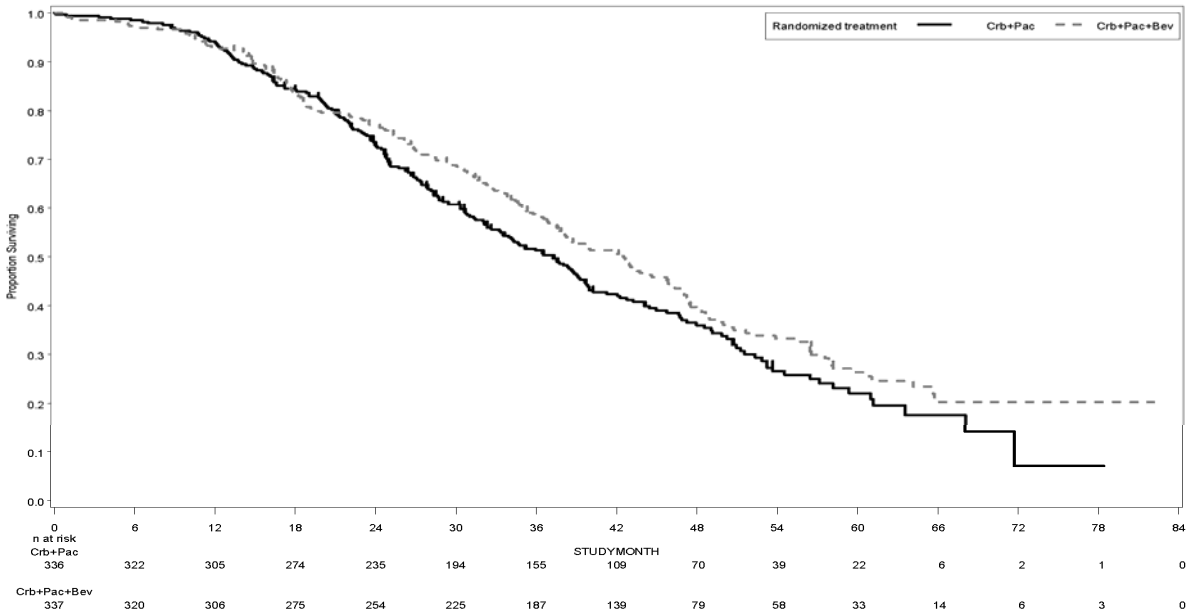
**Figure 8: Kaplan Meier Curves for Overall Survival in Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Study GOG-0213**




## 16 HOW SUPPLIED/STORAGE AND HANDLING

Avastin (bevacizumab) Injection is a clear to slightly opalescent, colorless to pale brown, sterile solution for intravenous infusion supplied as single-dose vials in the following strengths:
100 mg/4 mL (NDC 50242-060-01) and 400 mg/16 mL (NDC 50242-061-01). Each carton contains one vial.

Store refrigerated at 2–8°C (36–46°F) in the original carton until time of use to protect from light.

Do not freeze or shake the vial.

## 17 PATIENT COUNSELING INFORMATION

Gastrointestinal Perforations and Fistulae: Avastin may increase the risk of developing gastrointestinal perforations and fistulae. Advise patients to immediately contact their health care provider for high fever, rigors, persistent or severe abdominal pain, severe constipation, or vomiting *[see Warnings and Precautions (5.1)]*.

Surgery and Wound Healing Complications: Avastin can increase the risk of wound healing complications. Advise patients that Avastin should not be used for at least 28 days before or after surgery and until surgical wounds are fully healed *[see Warnings and Precautions (5.2)]*.

Hemorrhage: Avastin can increase the risk of hemorrhage. Advise patients to immediately contact their health care provider for signs and symptoms of serious or unusual bleeding including coughing or spitting blood *[see Warnings and Precautions (5.3)]*.

Arterial and Venous Thromboembolism: Avastin increases the risk of arterial and venous thromboembolic events. Advise patients to immediately contact their health care provider for signs and symptoms of arterial or venous thromboembolism *[see Warnings and Precautions (5.4, 5.5)]*.

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Hypertension: Avastin can increase blood pressure. Advise patients that they will undergo routine blood pressure monitoring and to contact their healthcare provider if they experience changes in blood pressure *[see Warnings and Precautions (5.6)]*.

Posterior Reversible Leukoencephalopathy Syndrome: Posterior reversible encephalopathy syndrome (PRES) has been associated with Avastin treatment. Advise patients to immediately contact their health care provider for new onset or worsening neurological function *[see Warnings and Precautions (5.7)]*.

Renal Injury and Proteinuria: Avastin increases the risk of proteinuria and renal injury, including nephrotic syndrome. Advise patients that treatment with Avastin requires regular monitoring of renal function and to contact their health care provider for proteinuria or signs and symptoms of nephrotic syndrome *[see Warnings and Precautions (5.8)]*.

Infusion Reactions: Avastin can cause infusion reactions. Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion reactions *[see Warnings and Precautions (5.9)]*.

Congestive Heart Failure: Avastin can increase the risk of developing congestive heart failure. Advise patients to contact their healthcare provider immediately for signs and symptoms of CHF *[see Warnings and Precautions (5.12)]*.

Embryo-Fetal Toxicity: Advise female patients that Avastin may cause fetal harm and to inform their healthcare provider with a known or suspected pregnancy *[see Warnings and Precautions (5.10), Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose of Avastin *[see Use in Specific Populations (8.3)]*.

Ovarian Failure: Avastin may lead to ovarian failure. Advise patients of potential options for preservation of ova prior to starting treatment *[see Warnings and Precautions (5.11)]*.

Lactation: Advise lactating women not to breastfeed while taking Avastin or within 6 months following their last dose of treatment *[see Use in Specific Populations (8.2)]*.

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**Avastin® (bevacizumab)**

Manufactured by:
**Genentech, Inc.**
A Member of the Roche Group
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