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)
Solution for intravenous infusion
Initial U.S. Approval: 2004

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

See full prescribing information for complete boxed warning.

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

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

Indications and Usage (1.6)	11/2014
Dosage and Administration (2.2)	11/2014
Warnings and Precautions, Gastrointestinal Perforations and Fistulae (5.1)	11/2014
Warnings and Precautions, Non-Gastrointestinal Fistulae (5.2)	11/2014
Warnings and Precautions, Embryo-fetal Toxicity (5.11)	05/2015

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

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

- Metastatic colorectal cancer, with intravenous 5-fluorouracil–based chemotherapy for first- or second-line treatment. (1.1)
- Metastatic colorectal cancer, with fluoropyrimidine- irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line Avastin-containing regimen. (1.1)
- Non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease. (1.2)
- Glioblastoma, as a single agent for adult patients with progressive disease following prior therapy. (1.3)
  -Effectiveness based on improvement in objective response rate. No data available demonstrating improvement in disease-related symptoms or survival with Avastin.
- Metastatic renal cell carcinoma with interferon alfa (1.4)
- Cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease. (1.5)
- Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan (1.6)

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

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

- Do not administer as an IV push or bolus. (2.1)
- Do not initiate Avastin for 28 days following major surgery and until surgical wound is fully healed. (2.1)

Metastatic colorectal cancer (2.2)
- 5 mg/kg IV every 2 weeks with bolus-IFL
- 10 mg/kg IV every 2 weeks with FOLFOX4
- 5 mg/kg IV every 2 weeks or 7.5 mg/kg IV every 3 weeks with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy after progression on a first-line Avastin containing regimen

Non–squamous non–small cell lung cancer (2.2)
- 15 mg/kg IV every 3 weeks with carboplatin/paclitaxel

Glioblastoma (2.2)
- 10 mg/kg IV every 2 weeks

Metastatic renal cell carcinoma (mRCC) (2.2)
- 10 mg/kg IV every 2 weeks with interferon alfa

Persistent, recurrent, or metastatic carcinoma of the cervix (2.2)
- 15 mg/kg IV every 3 weeks with paclitaxel/cisplatin or paclitaxel/topotecan

Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer (2.2)
- 10 mg/kg IV every 2 weeks with paclitaxel, pegylated liposomal doxorubicin or weekly topotecan
- 15 mg/kg IV every 3 weeks with topotecan given every 3 weeks

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

- 100 mg/4 mL, single use vial (3)
- 400 mg/16 mL, single use vial (3)

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

None (4)

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

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

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

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

To report SUSPECTED ADVERSE REACTIONS, contact Genentech, Inc. at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Lactation: Not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 9/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

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

Gastrointestinal Perforations

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

Surgery and Wound Healing Complications

The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients. Discontinue Avastin in patients with wound dehiscence. The appropriate interval between termination of Avastin and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined. Discontinue at least 28 days prior to elective surgery. Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. [*See Dosage and Administration (2.4), Warnings and Precautions (5.2), Adverse Reactions (6.1)*.]

Hemorrhage

Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, central nervous systems (CNS) hemorrhage, epistaxis, and vaginal bleeding occur up to five-fold more frequently in patients receiving Avastin. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis. [*See Dosage and Administration (2.4), Warnings and Precautions (5.3), Adverse Reactions (6.1)*.]

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer (mCRC)

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

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

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

1.3 Glioblastoma

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

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

1.4 Metastatic Renal Cell Carcinoma (mRCC)

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

1.5 Persistent, Recurrent, or Metastatic Carcinoma of the Cervix

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

1.6 Platinum-Resistant 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.

2 DOSAGE AND ADMINISTRATION

2.1 Administration

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

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

2.2 Recommended Doses and Schedules

Patients should continue treatment until disease progression or unacceptable toxicity.

Metastatic Colorectal Cancer (mCRC)

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

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

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

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

Glioblastoma

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

Metastatic Renal Cell Carcinoma (mRCC)

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

Cervical Cancer

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

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

The recommended dose is 10mg/kg every 2 weeks in combination with one of the following intravenous chemotherapy regimens: paclitaxel, pegylated liposomal doxorubicin, or topotecan (weekly); or 15 mg/kg every 3 weeks in combination with topotecan (every 3 weeks).

2.3 Preparation for Administration

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Withdraw necessary amount of Avastin and dilute in a total volume of 100 mL of 0.9% Sodium Chloride Injection, USP. Discard any unused portion left in a vial, as the product contains no preservatives.

DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.

2.4 Dose Modifications

There are no recommended dose reductions.

Discontinue Avastin for:

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

Temporarily suspend Avastin for:

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

3 DOSAGE FORMS AND STRENGTHS

- 100 mg per 4 mL single-use vial
- 400 mg per 16 mL single-use vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Perforations and Fistulae

Serious and sometimes fatal gastrointestinal perforation occurs at a higher incidence in Avastin treated patients compared to controls. The incidence of gastrointestinal perforation ranged from 0.3 to 3.2% across clinical studies. [*See Adverse Reactions (6.1)*.] From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (Study 9), gastrointestinal perforations were reported in 3.2% of Avastin treated patients, all of whom had a history of prior pelvic radiation. Fatal outcome was reported in <1% of Avastin-treated patients. In a platinum-resistant ovarian cancer trial (Study 10), the incidence of GI perforation was 1.7% (3/179). In this trial, patients with evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction were excluded.

The typical presentation may include abdominal pain, nausea, emesis, constipation, and fever. Perforation can be complicated by intra-abdominal abscess, fistula formation, and the need for diverting ostomies. The majority of cases occurred within the first 50 days of initiation of Avastin. Avoid use of 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. Permanently discontinue Avastin in patients with gastrointestinal perforation.

In Avastin clinical trials, gastrointestinal fistulae have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer and ovarian cancer. In a cervical cancer trial (Study 9), the incidence of gastrointestinal-vaginal fistulae was 8.3% in Avastin-treated patients and 0.9%

in control patients, all of whom had a history of prior pelvic radiation. Patients who develop GI vaginal fistulas may also have bowel obstructions and require surgical intervention as well as diverting ostomies. [*See Boxed Warning, Dosage and Administration (2.4)*.]

5.2 Non-Gastrointestinal Fistulae

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

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

Permanently discontinue Avastin in patients with tracheoesophageal (TE) fistula or any Grade 4 fistula. Discontinue Avastin in patients with fistula formation involving an internal organ. [*See Dosage and Administration (2.4)*.]

5.3 Surgery and Wound Healing Complications

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

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

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

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

5.4 Hemorrhage

Avastin can result in two distinct patterns of bleeding: minor hemorrhage, most commonly Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin compared to patients receiving only chemotherapy. Across indications, the incidence of Grade ≥ 3 hemorrhagic events among patients receiving Avastin ranged from 0.4 to 6.9 %. [*See Adverse Reactions (6.1)*.]

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

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

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

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

5.5 Arterial Thromboembolic Events

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

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

5.6 Venous Thromboembolic Events

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

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

5.7 Hypertension

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

Monitor blood pressure every two to three weeks during treatment with 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 discontinuation of Avastin.

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

5.8 Posterior Reversible Encephalopathy Syndrome (PRES)

PRES has been reported with an incidence of <0.5% in clinical studies. The onset of symptoms occurred from 16 hours to 1 year after initiation of Avastin. PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging (MRI) is necessary to confirm the diagnosis of PRES.

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

5.9 Proteinuria

The incidence and severity of proteinuria is increased in patients receiving Avastin as compared to controls. Nephrotic syndrome occurred in <1% of patients receiving Avastin in clinical trials, in some instances with fatal outcome. [*See Adverse Reactions (6.1)*.] In a published case series,

kidney biopsy of six patients with proteinuria showed findings consistent with thrombotic microangiopathy.

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

Suspend Avastin administration for ≥2 grams of proteinuria/24 hours and resume when proteinuria is <2 gm/24 hours. Discontinue Avastin in patients with nephrotic syndrome. [*See Dosage and Administration (2.4)*.] 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). [*See Use in Specific Populations (8.5)*.]

5.10 Infusion Reactions

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

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

5.11 Embryo-fetal Toxicity

Avastin may cause fetal harm based on the drug's mechanism of action and findings from animal studies. Congenital malformations were observed with the administration of bevacizumab to pregnant rabbits during organogenesis every 3 days at a dose as low as a clinical dose of 10 mg/kg. Furthermore, animal models link angiogenesis and VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryo-fetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with and for 6 months after the last dose of Avastin. [*See Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1).*]

5.12 Ovarian Failure

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

6 ADVERSE REACTIONS

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

- Gastrointestinal Perforations and Fistulae [*See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.1)*.]
- Non-Gastrointestinal Fistulae [*See Dosage and Administration (2.4), Warnings and Precautions (5.2)*.]
- Surgery and Wound Healing Complications [*See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.3)*.]
- Hemorrhage [*See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.4)*.]
- Arterial Thromboembolic Events [*See Dosage and Administration (2.4), Warnings and Precautions (5.5)*.]
- Venous Thromboembolic Events [*See Dosage and Administration (2.4), Warnings and Precautions (5.6)*.]
- Hypertensive Crisis [*See Dosage and Administration (2.4), Warnings and Precautions (5.7)*.]

- Posterior Reversible Encephalopathy Syndrome [*See Dosage and Administration (2.4), Warnings and Precautions (5.8)*.]
- Proteinuria [*See Dosage and Administration (2.4), Warnings and Precautions (5.9)*.]
- Infusion Reactions [*See Dosage and Administration (2.4), Warnings and Precautions (5.10).*]
- Ovarian Failure [*See Warnings and Precautions (5.12), Use in Specific Populations (8.1)*.]

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

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

6.1 Clinical Trial Experience

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

The data below reflect exposure to Avastin in 4996 patients with CRC, non-squamous NSCLC, glioblastoma, mRCC, or cervical cancer or platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer including controlled (Studies 1, 2, 4, 5, 8 9 and 10) or uncontrolled, single arm trials (Study 6) treated at the recommended dose and schedule for a median of 6 to 23 doses of Avastin. [*See Clinical Studies (14)*.] The population was aged 18-89 years (median 60 years), 42% male and 86% White. The population included 2184 first- and second-line mCRC patients who received a median of 10 doses of Avastin, 480 first-line metastatic NSCLC patients who received a median of 8 doses of Avastin, 163 glioblastoma patients who received a median of 9 doses of Avastin, 337 mRCC patients who received a median of 16 doses of Avastin, 218 cervical cancer patients who received a median of 6 doses of Avastin and 179 platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer patients who received a median of 6 doses of Avastin. These data also reflect exposure to Avastin in 363 patients with metastatic breast cancer (MBC) who received a median of 9.5 doses of Avastin, 1338 adjuvant CRC patients, including 669 female patients, who received a median of 23 doses of Avastin, and 403 previously untreated patients with diffuse large B-cell lymphoma (DLBCL) who received a median of 8 doses of Avastin. Avastin is not approved for use in MBC, adjuvant CRC, or DLBCL.

Surgery and Wound Healing Complications

The incidence of post-operative wound healing and/or bleeding complications was increased in patients with mCRC receiving Avastin as compared to patients receiving only chemotherapy. Among patients requiring surgery on or within 60 days of receiving study treatment, wound healing and/or bleeding complications occurred in 15% (6/39) of patients receiving bolus-IFL plus Avastin as compared to 4% (1/25) of patients who received bolus-IFL alone.

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

Hemorrhage

The incidence of epistaxis was higher (35% vs. 10%) in patients with mCRC receiving bolus-IFL plus Avastin compared with patients receiving bolus-IFL plus placebo. All but one of these events were Grade 1 in severity and resolved without medical intervention. Grade 1 or 2 hemorrhagic events were more frequent in patients receiving bolus-IFL plus Avastin when compared to those receiving bolus-IFL plus placebo and included gastrointestinal hemorrhage (24% vs. 6%), minor

gum bleeding (2% vs. 0), and vaginal hemorrhage (4% vs. 2%). [*See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.4)*.]

Venous Thromboembolic Events

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

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

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

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

Neutropenia and Infection

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

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

Proteinuria

Grade 3–4 proteinuria ranged from 0.7 to 7.4% in Studies 1, 2, 4, 5, 8 and 10. The overall incidence of proteinuria (all grades) was only adequately assessed in Study 8, in which the incidence was 20%. Median onset of proteinuria was 5.6 months (range 15 days to 37 months) after initiation of Avastin. Median time to resolution was 6.1 months (95% CI 2.8 months, 11.3 months). Proteinuria did not resolve in 40% of patients after median follow up of 11.2 months and required permanent discontinuation of Avastin in 30% of the patients who developed proteinuria (Study 8).

In an exploratory, pooled analysis of 8,273 patients treated in 7 randomized clinical trials, 5.4% (271 of 5037) of patients receiving Avastin in combination with chemotherapy experienced Grade ≥ 2 proteinuria. The Grade ≥ 2 proteinuria resolved in 74.2% (201 of 271) of patients. Avastin was re-initiated in 41.7% (113 of 271) of patients. Of the 113 patients who re-initiated Avastin, 47.8% (54 of 113) experienced a second episode of Grade ≥ 2 proteinuria. [*See Warnings and Precautions (5.9)*.]

Congestive Heart Failure (CHF)

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

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

Ovarian Failure

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

Post-Treatment Vascular Events

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

Metastatic Colorectal Cancer (mCRC)

The data in Table 1 and Table 2 were obtained in Study 1, a randomized, double-blind, controlled trial comparing chemotherapy plus Avastin with chemotherapy plus placebo. Avastin was administered at 5 mg/kg every 2 weeks.

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

Table 1

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

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

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

Grade 1–4 adverse events which occurred at a higher incidence (≥5%) in patients receiving bolus-IFL plus Avastin as compared to the bolus-IFL plus placebo arm are presented in Table 2. Grade 1–4 adverse events were collected for the first approximately 100 patients in each of the three treatment arms who were enrolled until enrollment in Arm 3 (5-FU/LV + Avastin) was discontinued.

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

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

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

	Arm 1 IFL+Placebo (n=98)	Arm 2 IFL+Avastin (n=102)	Arm 3 5-FU/LV+Avastin (n=109)
Special Senses			
Taste Disorder	9%	14%	21%
Urogenital			
Proteinuria	24%	36%	36%

Avastin in Combination with FOLFOX4 in Second-line mCRC

Only Grade 3-5 non-hematologic and Grade 4–5 hematologic adverse events related to treatment were collected in Study 2. The most frequent adverse events (selected Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events) occurring at a higher incidence (≥2%) in 287 patients receiving FOLFOX4 plus Avastin compared to 285 patients receiving FOLFOX4 alone were fatigue (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%), vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8% vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache (3% vs. 0%). These data are likely to under-estimate the true adverse event rates due to the reporting mechanisms used in Study 2.

Avastin in Combination with Fluoropyrimidine-Irinotecan or Fluoropyrimidine-Oxaliplatin Based Chemotherapy in Second-line mCRC Patients who have Progressed on an Avastin Containing Regimen in First-line mCRC:

No new safety signals were observed in Study 4 when Avastin was administered in second line mCRC patients who progressed on an Avastin containing regimen in first line mCRC. The safety data was consistent with the known safety profile established in first and second line mCRC.

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

Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected in Study 5. Grade 3–5 non-hematologic and Grade 4–5 hematologic adverse events (occurring at a higher incidence (≥2%) in 427 patients receiving PC plus Avastin compared with 441 patients receiving PC alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs. 0.7%), infection without neutropenia (7% vs. 3%), venous thrombus/embolism (5% vs. 3%), febrile neutropenia (5% vs. 2%), pneumonitis/pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3% vs. 0%).

Glioblastoma

All adverse events were collected in 163 patients enrolled in Study 6 who either received Avastin alone or Avastin plus irinotecan. All patients received prior radiotherapy and temozolomide. Avastin was administered at 10 mg/kg every 2 weeks alone or in combination with irinotecan. Avastin was discontinued due to adverse events in 4.8% of patients treated with Avastin alone.

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

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

Metastatic Renal Cell Carcinoma (mRCC)

All grade adverse events were collected in Study 8. Grade 3–5 adverse events occurring at a higher incidence (≥ 2%) in 337 patients receiving interferon alfa (IFN-α) plus Avastin compared to 304 patients receiving IFN-α plus placebo arm were fatigue (13% vs. 8%), asthenia (10% vs. 7%), proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis), and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, haemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma).

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

Table 3

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

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

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

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

Persistent, Recurrent, or Metastatic Carcinoma of the Cervix

All grade adverse reactions were collected in Study 9.

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

Table 4

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

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

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

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

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

Patients with evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction were excluded in this study.

Grade 2-4 adverse events occurring at a higher incidence (≥5%) in patients receiving Avastin plus chemotherapy compared to patients receiving chemotherapy alone are presented in Table 5.

Table 5

Grade 2−4 Adverse Events Occurring at Higher Incidence [≥5%] in Chemo + Avastin vs. Chemo Safety−Evaluable Patients

System Organ Class Preferred Term	Chemo (n=181)	Chemo+Avastin (n=179)
Blood And Lymphatic System Disorders		
Neutropenia	25.4%	30.7%
General Disorders And Administration Site Conditions		
Mucosal Inflammation	5.5%	12.8%
Infections And Infestations		
Infection	4.4%	10.6%
Nervous System Disorders		
Peripheral Sensory Neuropathy	7.2%	17.9%
Renal And Urinary Disorders		
Proteinuria	0.6%	12.3%
Respiratory, Thoracic and Mediastinal Disorders		
Epistaxis	0.0%	5.0%
Skin And Subcutaneous Tissue Disorders		
Palmar−Plantar Erythrodysaesthesia Syndrome	5.0%	10.6%
Vascular Disorders		
Hypertension	5.5%	19.0%

Grade 3–4 adverse events occurring at a higher incidence (≥2%) in 179 patients receiving Avastin plus 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%).

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

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response to Avastin.

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

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the test method and may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Avastin with the incidence of antibodies to other products may be misleading.

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, PRES, Mesenteric venous occlusion
Eye disorders (from unapproved intravitreal use for treatment of various ocular disorders): Permanent loss of vision; Endophthalmitis (infectious and sterile); Intraocular inflammation; Retinal detachment; Increased intraocular pressure; Hemorrhage including conjunctival, vitreous hemorrhage or retinal hemorrhage; Vitreous floaters; Ocular hyperemia; Ocular pain or discomfort
Gastrointestinal: Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration
Hemic and lymphatic: Pancytopenia
Hepatobiliary disorders: Gallbladder perforation
Infections and infestations: Necrotizing fasciitis, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation
Musculoskeletal and Connective Tissue Disorders: Osteonecrosis of the jaw; Non-mandibular osteonecrosis (cases have been observed in pediatric patients who have received Avastin)
Neurological: Posterior Reversible Encephalopathy Syndrome (PRES)
Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)
Respiratory: Nasal septum perforation, dysphonia
Systemic Events (from unapproved intravitreal use for treatment of various ocular disorders): Arterial thromboembolic events, Hypertension, Gastrointestinal perforation, Hemorrhage

7 DRUG INTERACTIONS

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

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Avastin may cause fetal harm based on findings from animal studies and the drug's mechanism of action. [*See Clinical Pharmacology (12.1).*] Limited postmarketing reports describe cases of fetal malformations with use of 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 VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus.

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

Data

Animal Data

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

8.2 Lactation

No data are available regarding the presence of bevacizumab 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 a nursing woman that breastfeeding is not recommended during treatment with Avastin.

8.3 Females and Males of Reproductive Potential

Contraception

Females

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

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 starting treatment with Avastin. Long term effects of Avastin exposure on fertility are unknown.

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

8.4 Pediatric Use

The safety, effectiveness and pharmacokinetic profile 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 children with relapsed glioblastoma treated with bevacizumab and irinotecan. There is insufficient information to determine the safety and efficacy of Avastin in children with glioblastoma.

Animal Data

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

8.5 Geriatric Use

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

In Study 2, patients aged ≥65 years receiving Avastin plus FOLFOX4 had a greater relative risk as compared to younger patients for the following adverse events: nausea, emesis, ileus, and fatigue.

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

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

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

10 OVERDOSAGE

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

11 DESCRIPTION

Avastin (bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay systems. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Avastin has an approximate molecular weight of 149 kD. 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 is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous infusion. Avastin is supplied in 100 mg and 400 mg preservative-free, single-use 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 weekly, every 2 weeks, or every 3 weeks, the estimated half-life of bevacizumab was approximately 20 days (range 11–50 days). The predicted time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg of bevacizumab every 2 weeks was 2.8.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity studies of bevacizumab have been conducted.

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 1

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

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

The addition of Avastin resulted in an improvement in survival across subgroups defined by age (<65 yrs, ≥ 65 yrs) and gender. Results are presented in Table 6 and Figure 1.

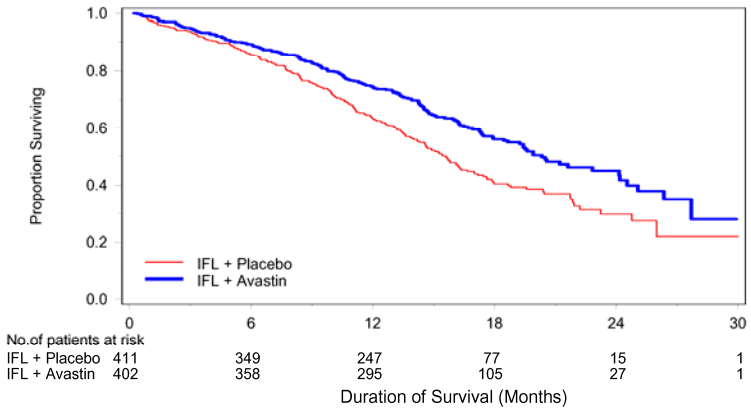
Table 6
Study 1 Efficacy Results

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

[a] $p<0.001$ by stratified log rank test.

[b] $p<0.01$ by χ^2 test.

Figure 1
Duration of Survival in Study 1



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

Study 2

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

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

Of the 829 patients randomized to the three arms, the median age was 61 years, 40% were female, 87% were Caucasian, 49% had an ECOG performance status of 0, 26% received prior radiation therapy, and 80% received prior adjuvant chemotherapy, 99% received prior irinotecan, with or without 5-FU as therapy for metastatic disease, and 1% received prior irinotecan and 5-FU as adjuvant therapy.

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

Study 3

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

Study 4

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

Of the 820 patients randomized, the majority of patients were male (64%) and the median age was 63.0 years (range 21 to 84 years). At baseline, 52% of patients were ECOG performance status (PS) 1, 44% were ECOG PS 0, 58% received irinotecan-based therapy as first-line treatment, 55% progressed on first-line treatment within 9 months, and 77% received their last dose of Avastin as first-line treatment within 42 days of being randomized. Second-line chemotherapy regimens were generally balanced between each treatment arm.

The addition of Avastin to fluoropyrimidine-based chemotherapy resulted in a statistically significant prolongation of survival and PFS; there was no significant difference in overall response rate, a key secondary outcome measure. Results are presented in Table 7 and Figure 2.

Table 7
Study 4 Efficacy Results

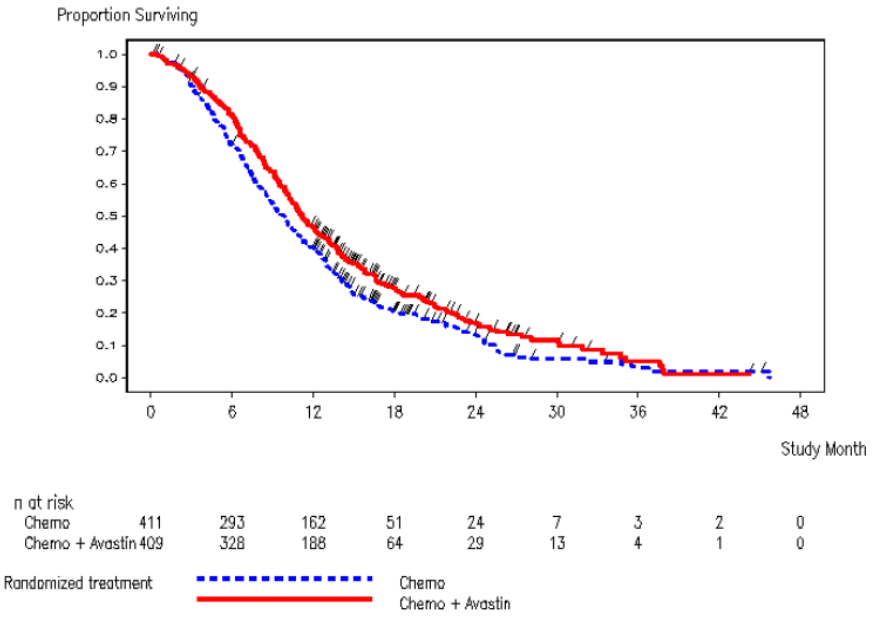
	Chemotherapy	Avastin + Chemotherapy
Number of Patients	411	409
Overall Survival[a]		
Median (months)	9.8	11.2
Hazard ratio (95% CI)	0.81 (0.69, 0.94)	
Progression-Free Survival[b]		
Median (months)	4.0	5.7
Hazard ratio (95% CI)	0.68 (0.59, 0.78)	

[a] $p = 0.0057$ by unstratified log rank test.

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

Figure 2

Duration of Survival in Study 4



14.2 Lack of Efficacy in Adjuvant Treatment of Colon Cancer

Lack of efficacy of Avastin as an adjunct to standard chemotherapy for the adjuvant treatment of colon cancer was determined in two randomized, open-label, multicenter clinical trials.

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

The main efficacy outcome of the study was disease free survival (DFS) in patients with stage III colon cancer. Addition of Avastin to chemotherapy did not improve DFS. As compared to the control arm, the proportion of stage III patients with disease recurrence or with death due to disease progression were numerically higher in the FOLFOX4 plus Avastin and in the XELOX plus Avastin arms. The hazard ratios for DFS were 1.17 (95% CI: 0.98–1.39) for the FOLFOX4 plus Avastin versus FOLFOX4 and 1.07 (95% CI: 0.90–1.28) for the XELOX plus Avastin versus FOLFOX4. The hazard ratios for overall survival were 1.31 (95% CI=1.03, 1.67) and 1.27 (95% CI=1.00, 1.62) for the comparison of Avastin plus FOLFOX4 versus FOLFOX4 and Avastin plus XELOX versus FOLFOX4, respectively. Similar lack of efficacy for DFS were observed in the Avastin-containing arms compared to control in the high-risk stage II cohort.

In a second study, 2710 patients with stage II and III colon cancer who had undergone surgery with curative intent, were randomized to receive either Avastin administered at a dose equivalent to 2.5 mg/kg/week in combination with mFOLFOX6 (N=1354) or mFOLFOX6 alone (N=1356). The median age was 57 years, 50% were male and 87% Caucasian. Seventy-five percent had stage III disease. The main efficacy outcome was DFS among stage III patients. The hazard ratio for DFS was 0.92 (95% CI: 0.77, 1.10). Overall survival, an additional efficacy outcome, was not significantly improved with the addition of Avastin to mFOLFOX6 (HR=0.96, 95% CI=[0.75,1.22].

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

Study 5

The safety and efficacy of 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.

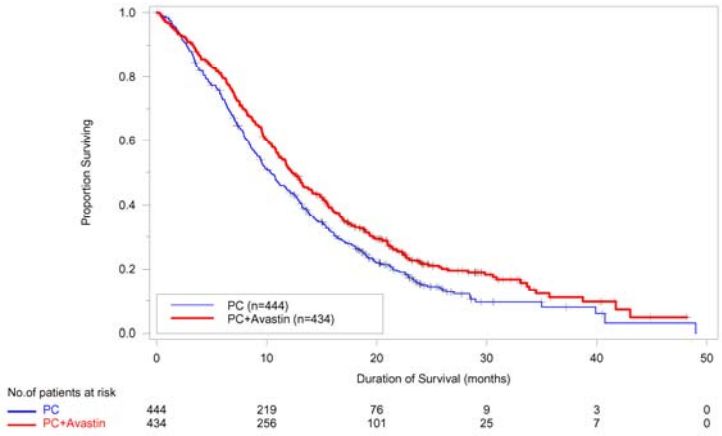
Chemotherapy-naïve patients with locally advanced, metastatic or recurrent non–squamous NSCLC were randomized (1:1) to receive six 21-day cycles of paclitaxel 200 mg/m^2 and carboplatin AUC = 6.0, by IV on day 1 (PC) or PC in combination with Avastin 15 mg/kg by IV on day 1 (PC plus Avastin). After completion or upon discontinuation of chemotherapy, patients in the PC plus Avastin arm continued to receive Avastin alone until disease progression or until unacceptable toxicity. Patients with predominant squamous histology (mixed cell type tumors only), central nervous system (CNS) metastasis, gross hemoptysis (≥ 1/2 tsp of red blood), unstable angina, or receiving therapeutic anticoagulation were excluded. The main outcome measure was duration of survival.

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

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

Figure 3

Duration of Survival in Study 5



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

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

14.4 Glioblastoma

Study 6

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

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

The efficacy of Avastin was demonstrated using response assessment based on both WHO radiographic criteria and by stable or decreasing corticosteroid use, which occurred in 25.9% (95% CI 17.0%, 36.1%) of the patients. Median duration of response was 4.2 months (95% CI 3.0, 5.7). Radiologic assessment was based on MRI imaging (using T1 and T2/FLAIR). MRI does not necessarily distinguish between tumor, edema, and radiation necrosis.

Study 7

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

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

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

14.5 Metastatic Renal Cell Carcinoma (mRCC)

Study 8

Patients with treatment-naïve mRCC were evaluated in a multicenter, randomized, double-blind, international study comparing Avastin plus interferon alfa 2a (IFN-α2a) versus placebo plus IFN-α2a. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to receive either Avastin (10 mg/kg IV infusion every 2 weeks; n=327) or placebo (IV every 2 weeks; n=322) in combination with IFN-α2a (9 MIU subcutaneously three times weekly, for a maximum of 52 weeks). Patients were treated until disease progression or unacceptable toxicity. The main

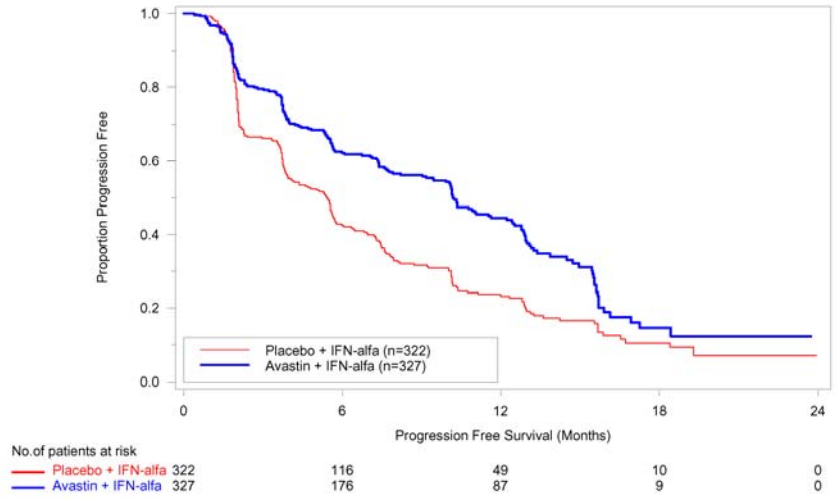
outcome measure of the study was investigator-assessed PFS. Secondary outcome measures were ORR and OS.

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

The results are presented in Figure 4. PFS was statistically significantly prolonged among patients receiving Avastin plus IFN-α2a compared to those receiving IFN-α2a alone; median PFS was 10.2 months vs. 5.4 months [HR 0.60 (95% CI 0.49, 0.72), p-value <0.0001, stratified log-rank test]. Among the 595 patients with measurable disease, ORR was also significantly higher (30% vs. 12%, $p<0.0001$, stratified CMH test). There was no improvement in OS based on the final analysis conducted after 444 deaths, with a median OS of 23 months in the Avastin plus IFN-α2a arm and 21 months in the IFN-α2a plus placebo arm [HR 0.86, (95% CI 0.72, 1.04)].

Figure 4

Progression-Free Survival in Study 8



14.6 Persistent, Recurrent, or Metastatic Carcinoma of the Cervix

Study 9

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

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

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

The study results for OS in patients who received chemotherapy plus Avastin as compared to chemotherapy alone are presented in Table 8 and Figure 5.

Figure 5

Study 9: Overall Survival for Chemotherapy vs. Chemotherapy plus Avastin

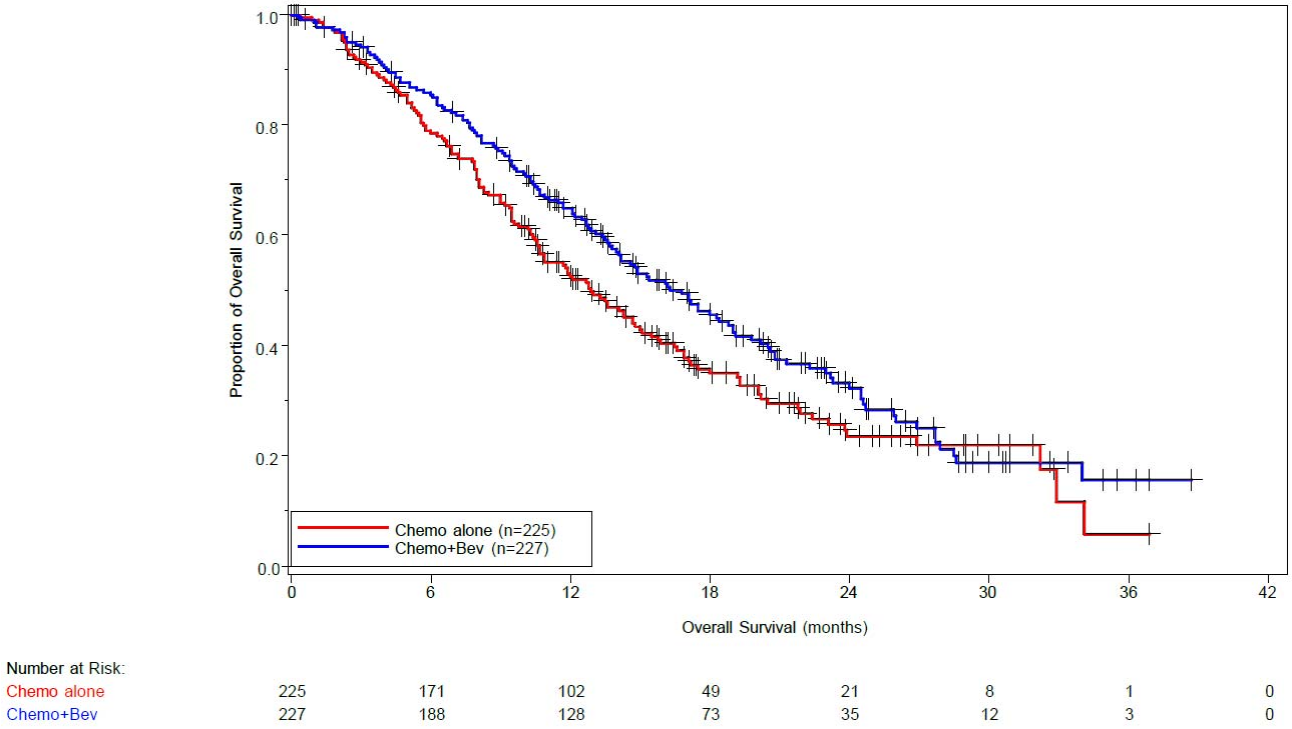


Table 8

Study 9 Efficacy Results: Chemotherapy versus Chemotherapy + Avastin

	Chemotherapy (n=225)	Chemotherapy + Avastin (n=227)
Overall Survival		
Median (months)[a]	12.9	16.8
Hazard ratio [95% CI]	0.74 [0.58;0.94] (p-value[b] = 0.0132)	

[a] Kaplan-Meier estimates.

[b] log-rank test (stratified).

The overall response rate was also higher in patients who received chemotherapy plus Avastin [45% (95% CI: 39, 52)] than in patients who received chemotherapy alone [34% (95% CI: 28,40)].

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

	Topotecan + Paclitaxel +/- Avastin (n=223)	Cisplatin + Paclitaxel +/- 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 hazard ratio for OS with Cisplatin +Paclitaxel + Avastin as compared to Cisplatin +Paclitaxel alone was 0.72 (95% CI: 0.51,1.02). The hazard ratio for OS with Topotecan +Paclitaxel +Avastin as compared to Topotecan +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 10

Avastin was evaluated in a multicenter, open-label, randomized, two-arm study (Study 10) comparing Avastin plus 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 intravenous chemotherapies at the discretion of the investigator: paclitaxel (80mg/m^2 on days 1, 8, 15 and 22 every 4 weeks; pegylated liposomal doxorubicin (PLD) 40mg/m^2 on day 1 every 4 weeks; or topotecan 4mg/m^2 on days 1, 8 and 15 every 4 weeks or 1.25mg/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 monotherapy upon progression.. The main outcome measure was investigator-assessed Progression-Free Survival (PFS). Secondary outcome measures were Objective Response Rate (ORR) and Overall Survival (OS).

The median age was 61 years (range 25−84 years) and 37% of patients were ≥ age 65. Seventy-nine percent had measurable disease at baseline, 87% had baseline CA-125 levels ≥ 2 × ULN and 31% had ascites at baseline. Seventy-three percent had a platinum-free interval (PFI) of 3−6 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.

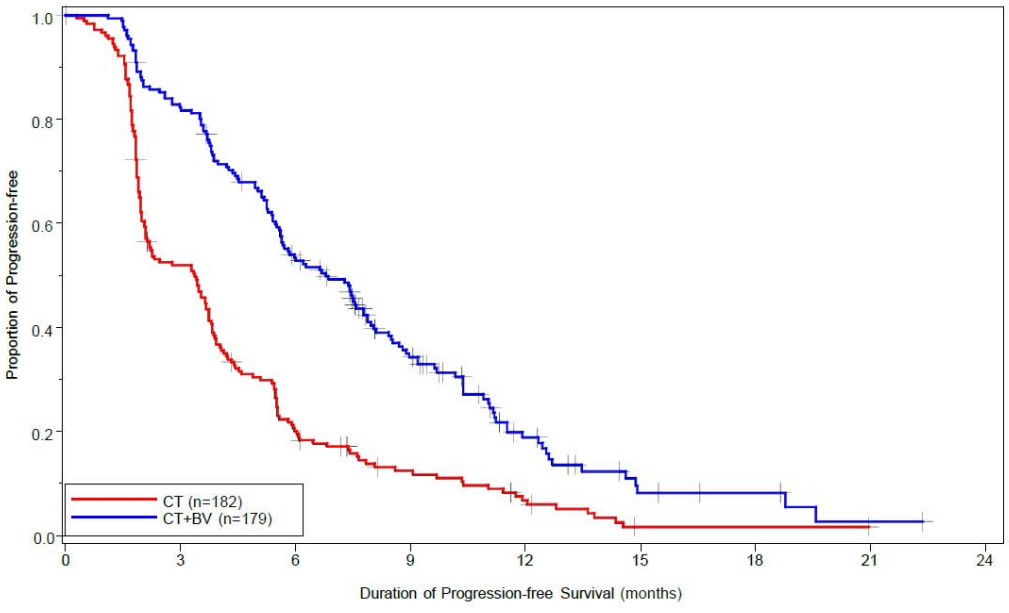
The addition of Avastin to chemotherapy demonstrated a statistically significant improvement in investigator-assessed PFS, which was supported by a retrospective independent review analysis. Study results for the intent to treat (ITT) population are presented in Table 10 and Figure 6. Results for the separate chemotherapy cohorts are presented in Table 11.

Table 10: Efficacy Results in Study 10 ITT Population

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

[a] per stratified Cox proportional hazards model
[b] per stratified logrank test
[c] chemotherapy

Figure 6
Investigator-Assessed Progression-Free Survival in Study 10 ITT Population



Number at Risk:

CT	182	92	35	18	9	1	1	0	0
CT+BV	179	144	91	51	19	6	4	1	0

Table 11 Study 10 Efficacy Results in Chemotherapy Cohorts

Efficacy Parameter	Paclitaxel		Topotecan		PLD	
	CT[b] (N=55)	CT[b]+Avastin (N=60)	CT[b] (N=63)	CT[b]+Avastin (N=57)	CT[b] (N=64)	CT[b]+Avastin (N=62)
PFS per Investigator						
Median (months) (95% CI)	3.9 (3.5, 5.5)	9.6 (7.8, 11.5)	2.1 (1.9, 2.3)	6.2 (5.3, 7.6)	3.5 (1.9, 3.9)	5.1 (3.9, 6.3)
HR (95% CI)[a]	0.47 (0.31, 0.72)		0.24 (0.15, 0.38)		0.47 (0.32, 0.71)	
Overall Survival						
Median (months) (95% CI)	13.2 (8.2, 19.7)	22.4 (16.7, 26.7)	13.3 (10.4, 18.3)	13.8 (11.0, 18.3)	14.1 (9.9, 17.8)	13.7 (11.0, 18.3)
HR (95% CI)[a]	0.64 (0.41, 1.01)		1.12 (0.73, 1.73)		0.94 (0.63, 1.42)	
Objective Response Rate						
Number of Patients with Measurable Disease at Baseline	43	45	50	46	51	51
Rate, % (95% CI)	30 (17, 44)	53 (39, 68)	2 (0, 6)	17 (6, 28)	8 (0, 15)	16 (6, 26)
Median of Response Duration (months)	6.8	11.6	NE	5.2	4.6	8.0

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

16 HOW SUPPLIED/STORAGE AND HANDLING

Avastin vials [100 mg (NDC 50242-060-01) and 400 mg (NDC 50242-061-01)] are stable at 2–8°C (36–46°F). Avastin vials should be protected from light. **Do not freeze or shake.**

Diluted Avastin solutions may be stored at 2–8°C (36–46°F) for up to 8 hours. Store in the original carton until time of use. No incompatibilities between Avastin and polyvinylchloride or polyolefin bags have been observed.

17 PATIENT COUNSELING INFORMATION

Advise patients:

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

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 (5.11), 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).*]

Lactation

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

Avastin® (bevacizumab)

Manufactured by:
Genentech, Inc.

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