

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

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: 12/2015

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1 FULL PRESCRIBING INFORMATION

2 **WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND** 3 **HEALING COMPLICATIONS, and HEMORRHAGE**

4 **Gastrointestinal Perforations**

5 **The incidence of gastrointestinal perforation, some fatal, in Avastin-treated patients ranges**
6 **from 0.3 to 3.2%. Discontinue Avastin in patients with gastrointestinal perforation.**

7 *[See Dosage and Administration (2.4), Warnings and Precautions (5.1).]*

8 **Surgery and Wound Healing Complications**

9 **The incidence of wound healing and surgical complications, including serious and fatal**
10 **complications, is increased in Avastin-treated patients. Discontinue Avastin in patients with**
11 **wound dehiscence. The appropriate interval between termination of Avastin and subsequent**
12 **elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has**
13 **not been determined. Discontinue at least 28 days prior to elective surgery. Do not initiate**
14 **Avastin for at least 28 days after surgery and until the surgical wound is fully healed.**

15 *[See Dosage and Administration (2.4), Warnings and Precautions (5.3), Adverse Reactions (6.1).]*

16 **Hemorrhage**

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

23 1 INDICATIONS AND USAGE

24 1.1 Metastatic Colorectal Cancer (mCRC)

25 Avastin is indicated for the first- or second-line treatment of patients with metastatic carcinoma of
26 the colon or rectum in combination with intravenous 5-fluorouracil-based chemotherapy.
27 Avastin, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based
28 chemotherapy, is indicated for the second-line treatment of patients with metastatic colorectal cancer
29 who have progressed on a first-line Avastin-containing regimen.

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

32 1.2 Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

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

35 1.3 Glioblastoma

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

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

41 1.4 Metastatic Renal Cell Carcinoma (mRCC)

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

44 1.5 Persistent, Recurrent, or Metastatic Carcinoma of the Cervix

45 Avastin in combination with paclitaxel and cisplatin or paclitaxel and topotecan is indicated for
46 the treatment of persistent, recurrent, or metastatic carcinoma of the cervix. *[See Clinical Studies*
47 *(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.

95 **2.4 Dose Modifications**

96 There are no recommended dose reductions.

97 Discontinue Avastin for:

- 98 • Gastrointestinal perforations (gastrointestinal perforations, fistula formation in the
- 99 gastrointestinal tract, intra-abdominal abscess), fistula formation involving an internal organ
- 100 [See *Boxed Warning, Warnings and Precautions (5.1, 5.2).*]
- 101 • Wound dehiscence and wound healing complications requiring medical intervention
- 102 [See *Warnings and Precautions (5.3).*]
- 103 • Serious hemorrhage (i.e., requiring medical intervention) [See *Boxed Warning, Warnings and*
- 104 *Precautions (5.4).*]
- 105 • Severe arterial thromboembolic events [See *Warnings and Precautions (5.5).*]
- 106 • Life-threatening (Grade 4) venous thromboembolic events, including pulmonary embolism [See
- 107 *Warnings and Precautions (5.6).*]
- 108 • Hypertensive crisis or hypertensive encephalopathy [See *Warnings and Precautions (5.7).*]
- 109 • Posterior Reversible Encephalopathy Syndrome (PRES) [See *Warnings and Precautions*
- 110 *(5.8).*]
- 111 • Nephrotic syndrome [See *Warnings and Precautions (5.9).*]

112 Temporarily suspend Avastin for:

- 113 • At least 4 weeks prior to elective surgery [See *Warnings and Precautions (5.3).*]
- 114 • Severe hypertension not controlled with medical management [See *Warnings and Precautions*
- 115 *(5.7).*]
- 116 • Moderate to severe proteinuria [See *Warnings and Precautions (5.9).*]
- 117 • Severe infusion reactions [See *Warnings and Precautions (5.10).*]

118

119 **3 DOSAGE FORMS AND STRENGTHS**

- 120 • 100 mg per 4 mL single-use vial
- 121 • 400 mg per 16 mL single-use vial

122

123 **4 CONTRAINDICATIONS**

124 None.

125

126 **5 WARNINGS AND PRECAUTIONS**

127 **5.1 Gastrointestinal Perforations and Fistulae**

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

137 The typical presentation may include abdominal pain, nausea, emesis, constipation, and fever.
138 Perforation can be complicated by intra-abdominal abscess, fistula formation, and the need for
139 diverting ostomies. The majority of cases occurred within the first 50 days of initiation of Avastin.
140 Avoid use of Avastin in patients with ovarian cancer who have evidence of recto-sigmoid
141 involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of
142 bowel obstruction. Permanently discontinue Avastin in patients with gastrointestinal perforation.

143 In Avastin clinical trials, gastrointestinal fistulae have been reported with an incidence of up to
144 2% in patients with metastatic colorectal cancer and ovarian cancer. In a cervical cancer trial (Study
145 9), the incidence of gastrointestinal-vaginal fistulae was 8.3% in Avastin-treated patients and 0.9%

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

149 **5.2 Non-Gastrointestinal Fistulae**

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

156 From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (Study 9),
157 1.8% of Avastin-treated patients and 1.4% of control patients were reported to have had non-
158 gastrointestinal vaginal, vesical, or female genital tract fistulae.

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

162 **5.3 Surgery and Wound Healing Complications**

163 Avastin impairs wound healing in animal models. [See *Nonclinical Toxicology (13.2).*] In
164 clinical trials, administration of Avastin was not allowed until at least 28 days after surgery. In a
165 controlled clinical trial, the incidence of wound healing complications, including serious and fatal
166 complications, in patients with mCRC who underwent surgery during the course of Avastin
167 treatment was 15% and in patients who did not receive Avastin, was 4%. [See *Adverse Reactions*
168 *(6.1).*]

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

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

176 Necrotizing fasciitis including fatal cases, has been reported in patients treated with Avastin;
177 usually secondary to wound healing complications, gastrointestinal perforation or fistula formation.
178 Discontinue Avastin therapy in patients who develop necrotizing fasciitis. [See *Adverse Reactions*
179 *(6.3).*]

180 **5.4 Hemorrhage**

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

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

191 In clinical studies in non-small cell lung cancer where patients with CNS metastases who
192 completed radiation and surgery more than 4 weeks prior to the start of Avastin were evaluated with
193 serial CNS imaging, symptomatic Grade 2 CNS hemorrhage was documented in one of
194 83 Avastin-treated patients (rate 1.2%, 95% CI 0.06%–5.93%).

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

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

200 **5.5 Arterial Thromboembolic Events**

201 Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction,
202 transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a
203 higher incidence in patients receiving Avastin compared to those in the control arm. Across
204 indications, the incidence of Grade ≥ 3 ATE in the Avastin containing arms was 2.6% compared to
205 0.8% in the control arms. Among patients receiving Avastin in combination with chemotherapy, the
206 risk of developing ATE during therapy was increased in patients with a history of arterial
207 thromboembolism, diabetes, or age greater than 65 years. [See *Use in Specific Populations (8.5).*]

208 The safety of resumption of Avastin therapy after resolution of an ATE has not been studied.
209 Discontinue Avastin in patients who experience a severe ATE. [See *Dosage and Administration*
210 *(2.4).*]

211 **5.6 Venous Thromboembolic Events**

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

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

219 **5.7 Hypertension**

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

222 Monitor blood pressure every two to three weeks during treatment with Avastin. Treat with
223 appropriate anti-hypertensive therapy and monitor blood pressure regularly. Continue to monitor
224 blood pressure at regular intervals in patients with Avastin-induced or -exacerbated hypertension
225 after discontinuation of Avastin.

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

229 **5.8 Posterior Reversible Encephalopathy Syndrome (PRES)**

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

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

239 **5.9 Proteinuria**

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

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

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

248 Suspend Avastin administration for ≥ 2 grams of proteinuria/24 hours and resume when
249 proteinuria is < 2 gm/24 hours. Discontinue Avastin in patients with nephrotic syndrome. [*See*
250 *Dosage and Administration (2.4).*] Data from a postmarketing safety study showed poor correlation
251 between UPCR (Urine Protein/Creatinine Ratio) and 24 hour urine protein (Pearson Correlation 0.39
252 (95% CI 0.17, 0.57). [*See Use in Specific Populations (8.5).*]

253 **5.10 Infusion Reactions**

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

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

261 **5.11 Embryo-fetal Toxicity**

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

270 **5.12 Ovarian Failure**

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

276

277 **6 ADVERSE REACTIONS**

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

- 280 • Gastrointestinal Perforations and Fistulae [*See Boxed Warning, Dosage and Administration*
281 *(2.4), Warnings and Precautions (5.1).*]
- 282 • Non-Gastrointestinal Fistulae [*See Dosage and Administration (2.4), Warnings and Precautions*
283 *(5.2).*]
- 284 • Surgery and Wound Healing Complications [*See Boxed Warning, Dosage and Administration*
285 *(2.4), Warnings and Precautions (5.3).*]
- 286 • Hemorrhage [*See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions*
287 *(5.4).*]
- 288 • Arterial Thromboembolic Events [*See Dosage and Administration (2.4), Warnings and*
289 *Precautions (5.5).*]
- 290 • Venous Thromboembolic Events [*See Dosage and Administration (2.4), Warnings and*
291 *Precautions (5.6).*]
- 292 • Hypertensive Crisis [*See Dosage and Administration (2.4), Warnings and Precautions (5.7).*]

- 293 • Posterior Reversible Encephalopathy Syndrome [*See Dosage and Administration (2.4),*
- 294 *Warnings and Precautions (5.8).*]
- 295 • Proteinuria [*See Dosage and Administration (2.4), Warnings and Precautions (5.9).*]
- 296 • Infusion Reactions [*See Dosage and Administration (2.4), Warnings and Precautions (5.10).*]
- 297 • Ovarian Failure [*See Warnings and Precautions (5.12), Use in Specific Populations (8.3).*]

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

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

307 **6.1 Clinical Trial Experience**

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

311 The data below reflect exposure to Avastin in 4996 patients with CRC, non-squamous NSCLC,
312 glioblastoma, mCRC, or cervical cancer or platinum-resistant recurrent epithelial ovarian, fallopian
313 tube or primary peritoneal cancer including controlled (Studies 1, 2, 4, 5, 8 9 and 10) or
314 uncontrolled, single arm trials (Study 6) treated at the recommended dose and schedule for a median
315 of 6 to 23 doses of Avastin. [*See Clinical Studies (14).*] The population was aged 18-89 years
316 (median 60 years), 42% male and 86% White. The population included 2184 first- and second-line
317 mCRC patients who received a median of 10 doses of Avastin, 480 first-line metastatic NSCLC
318 patients who received a median of 8 doses of Avastin, 163 glioblastoma patients who received a
319 median of 9 doses of Avastin, 337 mCRC patients who received a median of 16 doses of Avastin,
320 218 cervical cancer patients who received a median of 6 doses of Avastin and 179 platinum-resistant
321 recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer patients who received a
322 median of 6 doses of Avastin. These data also reflect exposure to Avastin in 363 patients with
323 metastatic breast cancer (MBC) who received a median of 9.5 doses of Avastin, 1338 adjuvant CRC
324 patients, including 669 female patients, who received a median of 23 doses of Avastin, and 403
325 previously untreated patients with diffuse large B-cell lymphoma (DLBCL) who received a median
326 of 8 doses of Avastin. Avastin is not approved for use in MBC, adjuvant CRC, or DLBCL.

327 *Surgery and Wound Healing Complications*

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

333 In Study 6, events of post-operative wound healing complications (craniotomy site wound
334 dehiscence and cerebrospinal fluid leak) occurred in patients with previously treated glioblastoma:
335 3/84 patients in the Avastin alone arm and 1/79 patients in the Avastin plus irinotecan arm.
336 [*See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.3).*]

337 *Hemorrhage*

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

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

345 *Venous Thromboembolic Events*

346 The overall incidence of Grade 3–4 venous thromboembolic events in Study 1 was 15.1% in
347 patients receiving bolus-IFL plus Avastin and 13.6% in patients receiving bolus-IFL plus placebo.
348 In Study 1, more patients in the Avastin containing arm experienced deep venous thrombosis (34 vs.
349 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

350 The risk of developing a second thromboembolic event while on Avastin and oral anticoagulants
351 was evaluated in two randomized studies. In Study 1, 53 patients (14%) on the bolus-IFL plus
352 Avastin arm and 30 patients (8%) on the bolus-IFL plus placebo arm received full dose warfarin
353 following a venous thromboembolic event (VTE). Among these patients, an additional
354 thromboembolic event occurred in 21% (11/53) of patients receiving bolus-IFL plus Avastin and 3%
355 (1/30) of patients receiving bolus-IFL alone.

356 In a second, randomized, 4-arm study in 1401 patients with mCRC, prospectively evaluating the
357 incidence of VTE (all grades), the overall incidence of first VTE was higher in the Avastin
358 containing arms (13.5%) than the chemotherapy alone arms (9.6%). Among the 116 patients treated
359 with anticoagulants following an initial VTE event (73 in the Avastin plus chemotherapy arms and
360 43 in the chemotherapy alone arms), the overall incidence of subsequent VTEs was also higher
361 among the Avastin treated patients (31.5% vs. 25.6%). In this subgroup of patients treated with
362 anticoagulants, the overall incidence of bleeding, the majority of which were Grade 1, was higher in
363 the Avastin treated arms than the chemotherapy arms (27.4% vs. 20.9%).

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

368 *Neutropenia and Infection*

369 The incidences of neutropenia and febrile neutropenia are increased in patients receiving Avastin
370 plus chemotherapy compared to chemotherapy alone. In Study 1, the incidence of Grade 3 or 4
371 neutropenia was increased in mCRC patients receiving IFL plus Avastin (21%) compared to patients
372 receiving IFL alone (14%). In Study 5, the incidence of Grade 4 neutropenia was increased in
373 NSCLC patients receiving paclitaxel/carboplatin (PC) plus Avastin (26.2%) compared with patients
374 receiving PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC plus Avastin vs.
375 1.8% for PC alone). There were 19 (4.5%) infections with Grade 3 or 4 neutropenia in the PC plus
376 Avastin arm of which 3 were fatal compared to 9 (2%) neutropenic infections in patients receiving
377 PC alone, of which none were fatal. During the first 6 cycles of treatment, the incidence of serious
378 infections including pneumonia, febrile neutropenia, catheter infections and wound infections was
379 increased in the PC plus Avastin arm [58 patients (13.6%)] compared to the PC alone arm
380 [29 patients (6.6%)].

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

384 *Proteinuria*

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

391 In an exploratory, pooled analysis of 8,273 patients treated in 7 randomized clinical trials, 5.4%
392 (271 of 5037) of patients receiving Avastin in combination with chemotherapy experienced
393 Grade ≥ 2 proteinuria. The Grade ≥ 2 proteinuria resolved in 74.2% (201 of 271) of patients.
394 Avastin was re-initiated in 41.7% (113 of 271) of patients. Of the 113 patients who re-initiated
395 Avastin, 47.8% (54 of 113) experienced a second episode of Grade ≥ 2 proteinuria. [*See Warnings*
396 *and Precautions (5.9).*]

397 *Renal Injury*

398 A retrospective analysis across clinical trials where 5805 patients had received Avastin and
399 chemotherapy and 3713 had received chemotherapy alone has shown higher rates of elevated serum
400 creatinine levels (ranging between 1.5 – 1.9 times baseline levels) in patients who had received
401 Avastin. Creatinine levels did not return to baseline in approximately one-third of patients who
402 received Avastin.

403 *Congestive Heart Failure (CHF)*

404 The incidence of Grade ≥ 3 left ventricular dysfunction was 1.0% in patients receiving Avastin
405 compared to 0.6% in the control arm across indications. In patients with metastatic breast cancer
406 (MBC), an indication for which Avastin is not approved, the incidence of Grade 3–4 CHF was
407 increased in patients in the Avastin plus paclitaxel arm (2.2%) as compared to the control arm
408 (0.3%). Among patients receiving prior anthracyclines for MBC, the rate of CHF was 3.8% for
409 patients receiving Avastin as compared to 0.6% for patients receiving paclitaxel alone. The safety of
410 continuation or resumption of Avastin in patients with cardiac dysfunction has not been studied.

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

423 *Ovarian Failure*

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

435 *Post-Treatment Vascular Events*

436 In an open-label, randomized, controlled trial of Avastin in adjuvant colorectal cancer, an indication
437 for which Avastin is not approved, the overall incidence rate of post-treatment Grade ≥ 3 vascular
438 events was 3.1% (41 of 1338) among patients receiving mFOLFOX6 plus Avastin, compared to
439 1.6% (21 of 1349) among patients receiving mFOLFOX6 alone. Post-treatment vascular events

440 included arterial and venous thromboembolic events, ischemic events, and vascular aneurysms.

441 *Metastatic Colorectal Cancer (mCRC)*

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

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

449

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

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

450

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

455

Table 2
 NCI-CTC Grade 1-4 Adverse Events in Study 1
 (Occurring at Higher Incidence [$\geq 5\%$] 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)
<u>Body as a Whole</u>			
Pain	55%	61%	62%
Abdominal Pain	55%	61%	50%
Headache	19%	26%	26%
<u>Cardiovascular</u>			
Hypertension	14%	23%	34%
Hypotension	7%	15%	7%
Deep Vein Thrombosis	3%	9%	6%
<u>Digestive</u>			
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%
<u>Hemic/Lymphatic</u>			
Thrombocytopenia	0%	5%	5%
<u>Nervous</u>			
Dizziness	20%	26%	19%
<u>Respiratory</u>			
Upper Respiratory Infection	39%	47%	40%
Epistaxis	10%	35%	32%
Dyspnea	15%	26%	25%
Voice Alteration	2%	9%	6%
<u>Skin/Appendages</u>			
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 [$\geq 5\%$] 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)
<u>Special Senses</u>			
Taste Disorder	9%	14%	21%
<u>Urogenital</u>			
Proteinuria	24%	36%	36%

457

458 *Avastin in Combination with FOLFOX4 in Second-line mCRC*

459 Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events related to treatment
 460 were collected in Study 2. The most frequent adverse events (selected Grade 3-5 non-hematologic
 461 and Grade 4-5 hematologic adverse events) occurring at a higher incidence ($\geq 2\%$) in 287 patients
 462 receiving FOLFOX4 plus Avastin compared to 285 patients receiving FOLFOX4 alone were fatigue
 463 (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%),
 464 vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8%
 465 vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache
 466 (3% vs. 0%). These data are likely to under-estimate the true adverse event rates due to the reporting
 467 mechanisms used in Study 2.

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

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

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

475 Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected in
 476 Study 5. Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events (occurring at a
 477 higher incidence ($\geq 2\%$) in 427 patients receiving PC plus Avastin compared with 441 patients
 478 receiving PC alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs.
 479 0.7%), infection without neutropenia (7% vs. 3%), venous thrombus/embolism (5% vs. 3%), febrile
 480 neutropenia (5% vs. 2%), pneumonitis/pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or
 481 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3%
 482 vs. 0%).

483 *Glioblastoma*

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

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

493 In patients receiving Avastin alone or Avastin plus irinotecan (N= 163), the incidence of
494 Avastin-related adverse events (Grade 1–4) were bleeding/hemorrhage (40%), epistaxis (26%), CNS
495 hemorrhage (5%), hypertension (32%), venous thromboembolic event (8%), arterial thromboembolic
496 event (6%), wound-healing complications (6%), proteinuria (4%), gastrointestinal perforation (2%),
497 and PRES (1%). The incidence of Grade 3–5 events in these 163 patients were bleeding/hemorrhage
498 (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic event (7%), arterial
499 thromboembolic event (3%), wound-healing complications (3%), proteinuria (1%), and
500 gastrointestinal perforation (2%).

501 *Metastatic Renal Cell Carcinoma (mRCC)*

502 All grade adverse events were collected in Study 8. Grade 3–5 adverse events occurring at a
503 higher incidence ($\geq 2\%$) in 337 patients receiving interferon alfa (IFN- α) plus Avastin compared to
504 304 patients receiving IFN- α plus placebo arm were fatigue (13% vs. 8%), asthenia (10% vs. 7%),
505 proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis),
506 and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured,
507 gastric ulcer hemorrhage, gingival bleeding, haemoptysis, hemorrhage intracranial, large intestinal
508 hemorrhage, respiratory tract hemorrhage, and traumatic hematoma).

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

511

Table 3
 NCI-CTC Grades 1–5 Adverse Events in Study 8 (Occurring at
 Higher Incidence [$\geq 5\%$] in IFN- α + Avastin vs. IFN- α + Placebo)

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

^a Adverse events were encoded using MedDRA, Version 10.1.

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

523

524 Grade 3 or 4 adverse reactions occurring at a higher incidence ($\geq 2\%$) in 218 patients receiving
 525 chemotherapy plus Avastin compared to 222 patients receiving chemotherapy alone were abdominal
 526 pain (11.9% vs. 9.9%), diarrhea (5.5% vs. 2.7%), anal fistula (3.7% vs. 0%), proctalgia (2.8% vs.
 527 0%), urinary tract infection (8.3% vs. 6.3%), cellulitis (3.2% vs. 0.5%), fatigue (14.2% vs. 9.9%),
 528 hypokalemia (7.3% vs. 4.5%), hyponatremia (3.7% vs. 1.4%), dehydration (4.1% vs. 0.5%),
 529 neutropenia (7.8% vs. 4.1%), lymphopenia (6.0% vs. 3.2%), back pain (5.5% vs. 3.2%), and pelvic
 530 pain (5.5% vs. 1.4%).

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

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

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

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

538

539

Table 5

540 Grade 2–4 Adverse Events Occurring at Higher Incidence [$\geq 5\%$] in Chemo + Avastin vs. Chemo
 541 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 Erythrodysesthesia Syndrome	5.0%	10.6%
Vascular Disorders		
Hypertension	5.5%	19.0%

542

543 Grade 3–4 adverse events occurring at a higher incidence ($\geq 2\%$) in 179 patients receiving Avastin
 544 plus chemotherapy compared to 181 patients receiving chemotherapy alone were hypertension (6.7%
 545 vs. 1.1%) and palmar-plantar erythrodysesthesia syndrome (4.5% vs. 1.7%).

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

548 6.2 Immunogenicity

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

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

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

560 **6.3 Postmarketing Experience**

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

564 *Body as a Whole:* Polyserositis

565 *Cardiovascular:* Pulmonary hypertension, PRES, Mesenteric venous occlusion

566 *Eye disorders (from unapproved intravitreal use for treatment of various ocular disorders):*

567 Permanent loss of vision; Endophthalmitis (infectious and sterile); Intraocular inflammation; Retinal
568 detachment; Increased intraocular pressure; Hemorrhage including conjunctival, vitreous

569 hemorrhage or retinal hemorrhage; Vitreous floaters; Ocular hyperemia; Ocular pain or discomfort

570 *Gastrointestinal:* Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration

571 *Hemic and lymphatic:* Pancytopenia

572 *Hepatobiliary disorders:* Gallbladder perforation

573 *Infections and infestations:* Necrotizing fasciitis, usually secondary to wound healing complications,
574 gastrointestinal perforation or fistula formation

575 *Musculoskeletal and Connective Tissue Disorders:* Osteonecrosis of the jaw; Non-mandibular
576 osteonecrosis (cases have been observed in pediatric patients who have received Avastin)

577 *Neurological:* Posterior Reversible Encephalopathy Syndrome (PRES)

578 *Renal:* Renal thrombotic microangiopathy (manifested as severe proteinuria)

579 *Respiratory:* Nasal septum perforation, dysphonia

580 *Systemic Events (from unapproved intravitreal use for treatment of various ocular disorders):*

581 Arterial thromboembolic events, Hypertension, Gastrointestinal perforation, Hemorrhage

582

583 **7 DRUG INTERACTIONS**

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

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

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

595

596 **8 USE IN SPECIFIC POPULATIONS**

597 **8.1 Pregnancy**

598 *Risk Summary*

599 Avastin may cause fetal harm based on findings from animal studies and the drug's mechanism of
600 action. [See *Clinical Pharmacology (12.1)*.] Limited postmarketing reports describe cases of fetal
601 malformations with use of Avastin in pregnancy; however, these reports are insufficient to determine
602 drug associated risks. In animal reproduction studies, intravenous administration of bevacizumab to
603 pregnant rabbits every 3 days during organogenesis at doses approximately 1 to 10 times the clinical

604 dose of 10 mg/kg produced fetal resorptions, decreased maternal and fetal weight gain and multiple
605 congenital malformations including corneal opacities and abnormal ossification of the skull and
606 skeleton including limb and phalangeal defects [see Data]. Furthermore, animal models link
607 angiogenesis and VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction,
608 embryofetal development, and postnatal development. Advise pregnant women of the potential risk
609 to a fetus.

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

613 *Data*

614 Animal Data

615 Pregnant rabbits dosed with 10 to 100 mg/kg bevacizumab (approximately 1 to 10 times the
616 clinical dose of 10 mg/kg) every three days during the period of organogenesis (gestation day 6–18)
617 exhibited decreases in maternal and fetal body weights and increased number of fetal resorptions.
618 There were dose-related increases in the number of litters containing fetuses with any type of
619 malformation (42.1% for the 0 mg/kg dose, 76.5% for the 30 mg/kg dose, and 95% for the 100
620 mg/kg dose) or fetal alterations (9.1% for the 0 mg/kg dose, 14.8% for the 30 mg/kg dose, and
621 61.2% for the 100 mg/kg dose). Skeletal deformities were observed at all dose levels, with some
622 abnormalities including meningocele observed only at the 100 mg/kg dose level. Teratogenic effects
623 included: reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws;
624 fontanel, rib and hindlimb deformities; corneal opacity; and absent hindlimb phalanges.

625 **8.2 Lactation**

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

632 **8.3 Females and Males of Reproductive Potential**

633 *Contraception*

634 Females

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

638 *Infertility*

639 Females

640 Avastin increases the risk of ovarian failure and may impair fertility. Inform females of
641 reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin. Long
642 term effects of Avastin exposure on fertility are unknown.

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

648 **8.4 Pediatric Use**

649 The safety, effectiveness and pharmacokinetic profile of Avastin in pediatric patients have not
650 been established. In published literature reports, cases of non-mandibular osteonecrosis have been
651 observed in patients under the age of 18 years who have received Avastin. Avastin is not approved
652 for use in patients under the age of 18 years.

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

656 Animal Data

657 Juvenile cynomolgus monkeys with open growth plates exhibited physal dysplasia following 4 to
658 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure).
659 The incidence and severity of physal dysplasia were dose-related and were partially reversible upon
660 cessation of treatment.

661 **8.5 Geriatric Use**

662 In Study 1, severe adverse events that occurred at a higher incidence ($\geq 2\%$) in patients aged
663 ≥ 65 years as compared to younger patients were asthenia, sepsis, deep thrombophlebitis,
664 hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhea, constipation,
665 anorexia, leukopenia, anemia, dehydration, hypokalemia, and hyponatremia. The effect of Avastin
666 on overall survival was similar in elderly patients as compared to younger patients.

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

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

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

676 In an exploratory, pooled analysis of 1745 patients treated in five randomized, controlled studies,
677 there were 618 (35%) patients aged ≥ 65 years and 1127 patients < 65 years of age. The overall
678 incidence of arterial thromboembolic events was increased in all patients receiving Avastin with
679 chemotherapy as compared to those receiving chemotherapy alone, regardless of age. However, the
680 increase in arterial thromboembolic events incidence was greater in patients aged ≥ 65 years (8.5%
681 vs. 2.9%) as compared to those < 65 years (2.1% vs. 1.4%). [See *Warnings and Precautions* (5.5).]
682

683 **10 OVERDOSAGE**

684 The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of
685 16 patients and with severe headache in three of 16 patients.
686

687 **11 DESCRIPTION**

688 Avastin (bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that binds to and
689 inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in *in vitro* and
690 *in vivo* assay systems. Bevacizumab contains human framework regions and the
691 complementarity-determining regions of a murine antibody that binds to VEGF. Avastin has an
692 approximate molecular weight of 149 kD. Bevacizumab is produced in a mammalian cell (Chinese
693 Hamster Ovary) expression system in a nutrient medium containing the antibiotic gentamicin.
694 Gentamicin is not detectable in the final product.

695 Avastin is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for
696 intravenous infusion. Avastin is supplied in 100 mg and 400 mg preservative-free, single-use vials
697 to deliver 4 mL or 16 mL of Avastin (25 mg/mL). The 100 mg product is formulated in 240 mg
698 α, α -trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium
699 phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The 400 mg
700 product is formulated in 960 mg α, α -trehalose dihydrate, 92.8 mg sodium phosphate (monobasic,

701 monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water
702 for Injection, USP.

703

704 **12 CLINICAL PHARMACOLOGY**

705 **12.1 Mechanism of Action**

706 Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR)
707 on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial
708 cell proliferation and new blood vessel formation in *in vitro* models of angiogenesis. Administration
709 of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction
710 of microvascular growth and inhibition of metastatic disease progression.

711 **12.3 Pharmacokinetics**

712 The pharmacokinetic profile of bevacizumab was assessed using an assay that measures total
713 serum bevacizumab concentrations (i.e., the assay did not distinguish between free bevacizumab and
714 bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of
715 491 patients who received 1 to 20 mg/kg of Avastin weekly, every 2 weeks, or every 3 weeks, the
716 estimated half-life of bevacizumab was approximately 20 days (range 11–50 days). The predicted
717 time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg of
718 bevacizumab every 2 weeks was 2.8.

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

727

728 **13 NONCLINICAL TOXICOLOGY**

729 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

740 **13.2 Animal Toxicology and/or Pharmacology**

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

745

746 **14 CLINICAL STUDIES**

747 **14.1 Metastatic Colorectal Cancer (mCRC)**

748 *Study 1*

749 In this double-blind, active-controlled study, patients were randomized (1:1:1) to IV bolus-IFL
 750 (irinotecan 125 mg/m², 5-FU 500 mg/m², and leucovorin (LV) 20 mg/m² given once weekly for
 751 4 weeks every 6 weeks) plus placebo (Arm 1), bolus-IFL plus Avastin (5 mg/kg every 2 weeks)
 752 (Arm 2), or 5-FU/LV plus Avastin (5 mg/kg every 2 weeks) (Arm 3). Enrollment in Arm 3 was
 753 discontinued, as pre-specified, when the toxicity of Avastin in combination with the bolus-IFL
 754 regimen was deemed acceptable. The main outcome measure was overall survival (OS).

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

759 The addition of Avastin resulted in an improvement in survival across subgroups defined by age
 760 (<65 yrs, ≥65 yrs) and gender. Results are presented in Table 6 and Figure 1.

761

Table 6
 Study 1 Efficacy Results

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

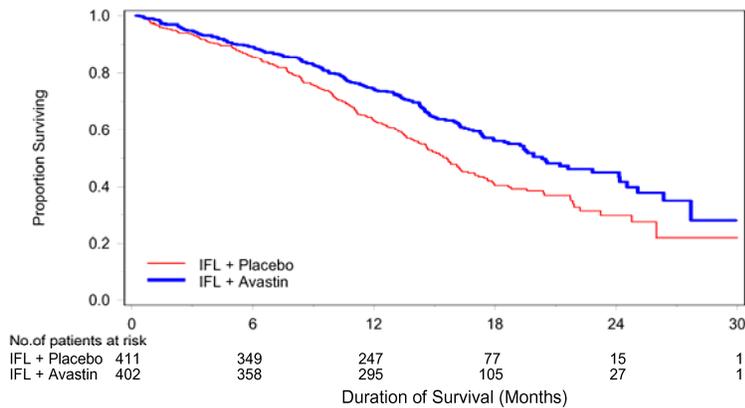
^a p<0.001 by stratified log rank test.

^b p<0.01 by χ^2 test.

762

763
764

Figure 1
Duration of Survival in Study 1



765
766

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.

770 *Study 2*

771 Study 2 was a randomized, open-label, active-controlled trial in patients who were previously
772 treated with irinotecan ± 5-FU for initial therapy for metastatic disease or as adjuvant therapy.
773 Patients were randomized (1:1:1) to IV FOLFOX4 (Day 1: oxaliplatin 85 mg/m² and LV 200 mg/m²
774 concurrently, then 5-FU 400 mg/m² bolus followed by 600 mg/m² continuously; Day 2: LV
775 200 mg/m², then 5-FU 400 mg/m² bolus followed by 600 mg/m² continuously; repeated every
776 2 weeks), FOLFOX4 plus Avastin (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1), or
777 Avastin monotherapy (10 mg/kg every 2 weeks). The main outcome measure was OS.

778 The Avastin monotherapy arm was closed to accrual after enrollment of 244 of the planned
779 290 patients following a planned interim analysis by the data monitoring committee based on
780 evidence of decreased survival compared to FOLFOX4 alone.

781 Of the 829 patients randomized to the three arms, the median age was 61 years, 40% were female,
782 87% were Caucasian, 49% had an ECOG performance status of 0, 26% received prior radiation
783 therapy, and 80% received prior adjuvant chemotherapy, 99% received prior irinotecan, with or
784 without 5-FU as therapy for metastatic disease, and 1% received prior irinotecan and 5-FU as
785 adjuvant therapy.

786 The addition of Avastin to FOLFOX4 resulted in significantly longer survival as compared to
787 FOLFOX4 alone (median OS 13.0 months vs. 10.8 months; hazard ratio 0.75 [95% CI 0.63, 0.89],
788 p=0.001 stratified log rank test) with clinical benefit seen in subgroups defined by age (<65 yrs,
789 ≥65 yrs) and gender. PFS and ORR based on investigator assessment were higher in the Avastin
790 plus FOLFOX4 arm.

791 *Study 3*

792 The activity of Avastin in combination with bolus or infusional 5-FU/LV was evaluated in a
793 single arm study enrolling 339 patients with mCRC with disease progression following both
794 irinotecan- and oxaliplatin-containing chemotherapy regimens. Seventy-three percent of patients
795 received concurrent bolus 5-FU/LV. One objective partial response was verified in the first
796 100 evaluable patients for an overall response rate of 1% (95% CI 0–5.5%).

797 *Study 4*

798 Study 4 was a prospective, randomized, open-label, multinational, controlled trial in patients with
799 histologically confirmed metastatic colorectal cancer who had progressed on a first-line Avastin

800 containing regimen. Patients were excluded if they progressed within 3 months of initiating first-
801 line chemotherapy and if they received Avastin for less than 3 consecutive months in the first-line
802 setting.

803 Patients were randomized (1:1) within 3 months after discontinuation of Avastin as first-line
804 therapy to receive fluoropyrimidine/oxaliplatin- or fluoropyrimidine/irinotecan-based chemotherapy
805 with or without Avastin administered at 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks. The
806 choice of second line therapy was contingent upon first-line chemotherapy treatment. Second-line
807 treatment was administered until progressive disease or unacceptable toxicity. The main outcome
808 measure was OS defined as the time from randomization until death from any cause.

809 Of the 820 patients randomized, the majority of patients were male (64%) and the median age was
810 63.0 years (range 21 to 84 years). At baseline, 52% of patients were ECOG performance status (PS)
811 1, 44% were ECOG PS 0, 58% received irinotecan-based therapy as first-line treatment, 55%
812 progressed on first-line treatment within 9 months, and 77% received their last dose of Avastin as
813 first-line treatment within 42 days of being randomized. Second-line chemotherapy regimens were
814 generally balanced between each treatment arm.

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

818

819

820

821

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)	

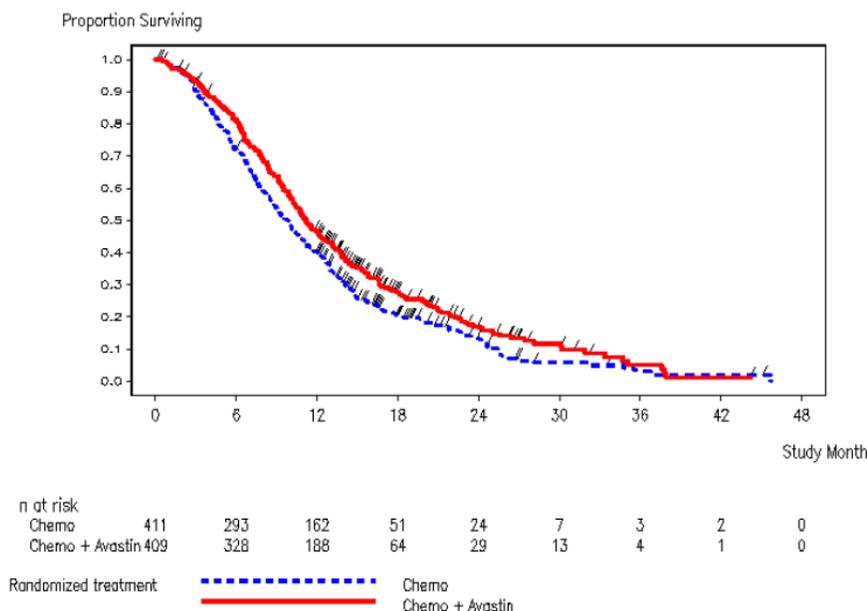
^a p = 0.0057 by unstratified log rank test.

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

822

823
824

Figure 2
Duration of Survival in Study 4



825
826

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 \geq 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]).

854 **14.3 Unresectable Non-Squamous Non-Small Cell Lung Cancer (NSCLC)**

855 *Study 5*

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

859 Chemotherapy-naïve patients with locally advanced, metastatic or recurrent non-squamous
860 NSCLC were randomized (1:1) to receive six 21-day cycles of paclitaxel 200 mg/m² and carboplatin
861 AUC=6.0, by IV on day 1 (PC) or PC in combination with Avastin 15 mg/kg by IV on day 1 (PC
862 plus Avastin). After completion or upon discontinuation of chemotherapy, patients in the PC plus
863 Avastin arm continued to receive Avastin alone until disease progression or until unacceptable
864 toxicity. Patients with predominant squamous histology (mixed cell type tumors only), central
865 nervous system (CNS) metastasis, gross hemoptysis (≥ 1/2 tsp of red blood), unstable angina, or
866 receiving therapeutic anticoagulation were excluded. The main outcome measure was duration of
867 survival.

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

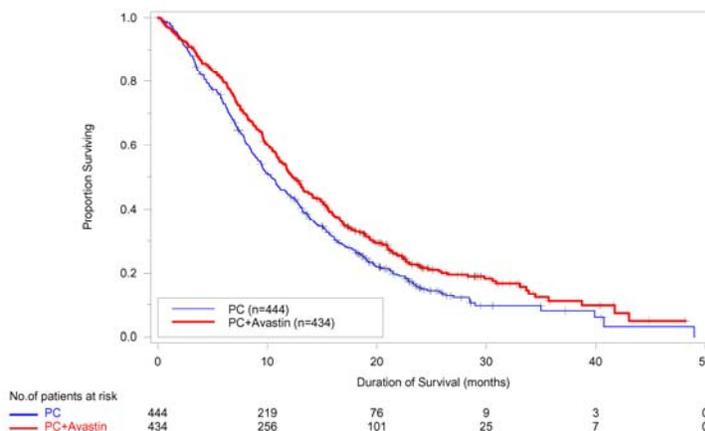
872 The results are presented in Figure 3. OS was statistically significantly higher among patients
873 receiving PC plus Avastin compared with those receiving PC alone; median OS was 12.3 months vs.
874 10.3 months [hazard ratio 0.80 (repeated 95% CI 0.68, 0.94), final p- value 0.013, stratified log-rank
875 test]. Based on investigator assessment which was not independently verified, patients were
876 reported to have longer PFS with Avastin in combination with PC compared to PC alone.

877

878

879

Figure 3
Duration of Survival in Study 5



880

881

882 In an exploratory analyses across patient subgroups, the impact of Avastin on OS was less robust
883 in the following: women [HR=0.99 (95% CI: 0.79, 1.25)], age ≥ 65 years [HR=0.91 (95% CI:
884 0.72, 1.14)] and patients with ≥5% weight loss at study entry [HR=0.96 (95% CI: 0.73, 1.26)].

885 The safety and efficacy of Avastin in patients with locally advanced, metastatic or recurrent
886 non-squamous NSCLC, who had not received prior chemotherapy was studied in another
887 randomized, double-blind, placebo controlled, three-arm study of Avastin in combination with
888 cisplatin and gemcitabine (CG) versus placebo and CG. A total of 1043 patients were randomized
889 1:1:1 to receive placebo plus CG, Avastin 7.5 mg/kg plus CG or Avastin 15.0 mg/kg plus CG.
890 The median age was 58 years, 36% were female, and 29% were \geq age 65. Eight percent had
891 recurrent disease and 77% had Stage IV disease. Progression-free survival, the main efficacy
892 outcome measure, was significantly higher in both Avastin containing arms compared to the placebo
893 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
894 (95% CI 0.68; 0.98), $p=0.0301$ for the Avastin 15.0 mg/kg plus CG arm]. The addition of Avastin
895 to CG chemotherapy failed to demonstrate an improvement in the duration of overall survival, an
896 additional efficacy outcome measure, [HR 0.93 (95% CI 0.78; 1.11), $p=0.4203$ for the Avastin
897 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
898 plus CG arm].

899 **14.4 Glioblastoma**

900 *Study 6*

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

907 Of the 85 patients randomized to the Avastin arm, the median age was 54 years, 32% were
908 female, 81% were in first relapse, Karnofsky performance status was 90–100 for 45% and 70–80 for
909 55%.

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

915 *Study 7*

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

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

921 The efficacy of Avastin was supported by an objective response rate of 19.6% (95% CI 10.9%,
922 31.3%) using the same response criteria as in Study 6. Median duration of response was 3.9 months
923 (95% CI 2.4, 17.4).

924 **14.5 Metastatic Renal Cell Carcinoma (mRCC)**

925 *Study 8*

926 Patients with treatment-naïve mRCC were evaluated in a multicenter, randomized, double-blind,
927 international study comparing Avastin plus interferon alfa 2a (IFN- α 2a) versus placebo plus
928 IFN- α 2a. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to
929 receive either Avastin (10 mg/kg IV infusion every 2 weeks; $n=327$) or placebo (IV every 2 weeks;
930 $n=322$) in combination with IFN- α 2a (9 MIU subcutaneously three times weekly, for a maximum of
931 52 weeks). Patients were treated until disease progression or unacceptable toxicity. The main

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

934 The median age was 60 years (range 18–82), 96% were white, and 70% were male. The study
935 population was characterized by Motzer scores as follows: 28% favorable (0), 56% intermediate
936 (1-2), 8% poor (3–5), and 7% missing.

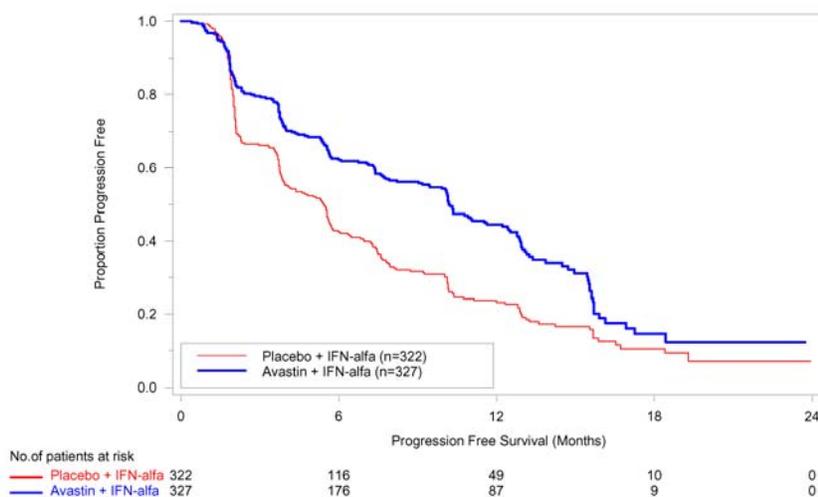
937 The results are presented in Figure 4. PFS was statistically significantly prolonged among
938 patients receiving Avastin plus IFN- α 2a compared to those receiving IFN- α 2a alone; median PFS
939 was 10.2 months vs. 5.4 months [HR 0.60 (95% CI 0.49, 0.72), p-value <0.0001, stratified log-rank
940 test]. Among the 595 patients with measurable disease, ORR was also significantly higher (30% vs.
941 12%, p <0.0001, stratified CMH test). There was no improvement in OS based on the final analysis
942 conducted after 444 deaths, with a median OS of 23 months in the Avastin plus IFN- α 2a arm and
943 21 months in the IFN- α 2a plus placebo arm [HR 0.86, (95% CI 0.72, 1.04)].

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Figure 4
Progression-Free Survival in Study 8



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949 **14.6 Persistent, Recurrent, or Metastatic Carcinoma of the Cervix**

950 *Study 9*

951 Patients with persistent, recurrent, or metastatic carcinoma of the cervix were evaluated in a
952 randomized, four-arm, multi-center trial comparing Avastin plus chemotherapy versus chemotherapy
953 alone. A total of 452 patients were randomized (1:1:1:1) to receive paclitaxel and Cisplatin with or
954 without Avastin, or paclitaxel and topotecan with or without Avastin.

955 The dosing regimens for Avastin, Paclitaxel, Cisplatin and Topotecan were as follows:

- 956 • Day 1: Paclitaxel 135 mg/m² IV over 24 hours, Day 2: cisplatin 50 mg/m² IV plus Avastin;
957 or Day 1: paclitaxel 175 mg/m² IV over 3 hours, Day 2: cisplatin 50 mg/m² IV plus Avastin ;
958 or Day 1: paclitaxel 175 mg/m² IV over 3 hours plus cisplatin 50 mg/m² IV plus Avastin
- 959 • Day 1: Paclitaxel 175 mg/m² over 3 hours plus Avastin, Days 1-3: topotecan 0.75 mg/m²
960 over 30 minutes

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

964 The median age was 48 years (range: 20–85). Of the 452 patients randomized at baseline, 78% of
965 patients were Caucasian, 80% had received prior radiation, 74% had received prior chemotherapy

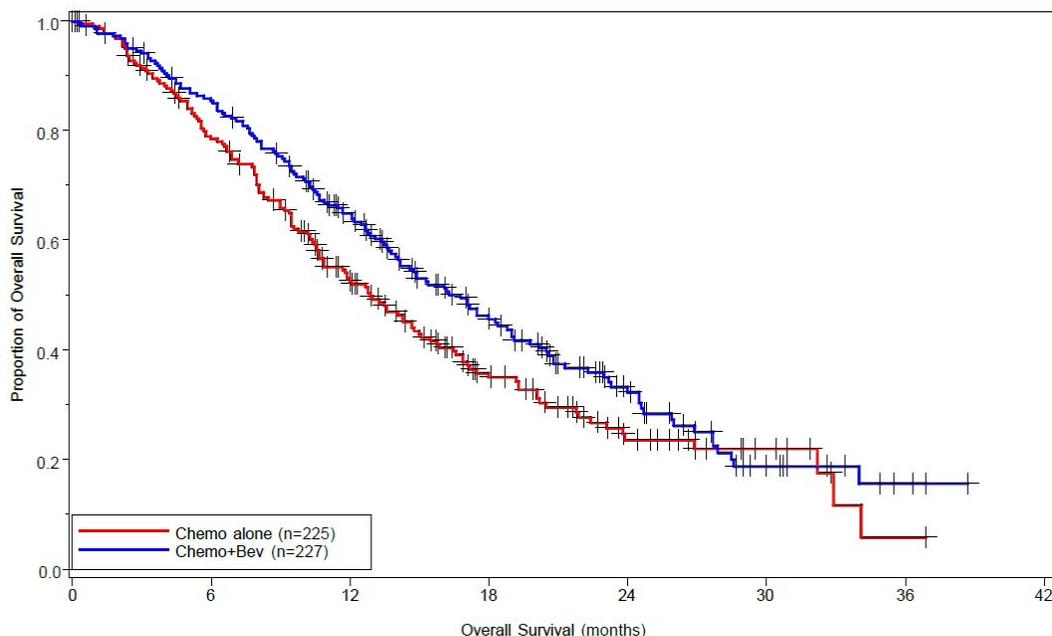
966 concurrent with radiation, and 32% had a platinum-free interval of less than 6 months. Patients had
 967 a GOG Performance Status (PS) of 0 (58%) or 1 (42%). Demographic and disease characteristics
 968 were balanced across arms.

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

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Figure 5

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



Number at Risk:

	0	6	12	18	24	30	36	42
Chemo alone	225	171	102	49	21	8	1	0
Chemo+Bev	227	188	128	73	35	12	3	0

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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).

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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/m² on days 1, 8, 15 and 22 every 4 weeks; pegylated liposomal doxorubicin (PLD) 40mg/m² on day 1 every 4 weeks; or topotecan 4mg/m² on days 1, 8 and 15 every 4 weeks or 1.25mg/m² on days 1-5 every 3 weeks). Patients were treated until disease progression, unacceptable toxicity, or withdrawal. Forty percent of patients on the chemotherapy alone arm received 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.

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Table 10: Efficacy Results in Study 10 ITT Population

Efficacy Parameter	CT ^c (N=182)	CT ^c +Avastin (N=179)
<u>PFS per Investigator</u>		
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	
<u>Overall Survival</u>		
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)	
<u>Objective Response Rate</u>		
Number of Patients with Measurable Disease at Baseline	144	142
Rate, % (95% CI)	13% (7%, 18%)	28% (21%, 36%)
<u>Median of Response Duration</u>		
in months	5.4	9.4

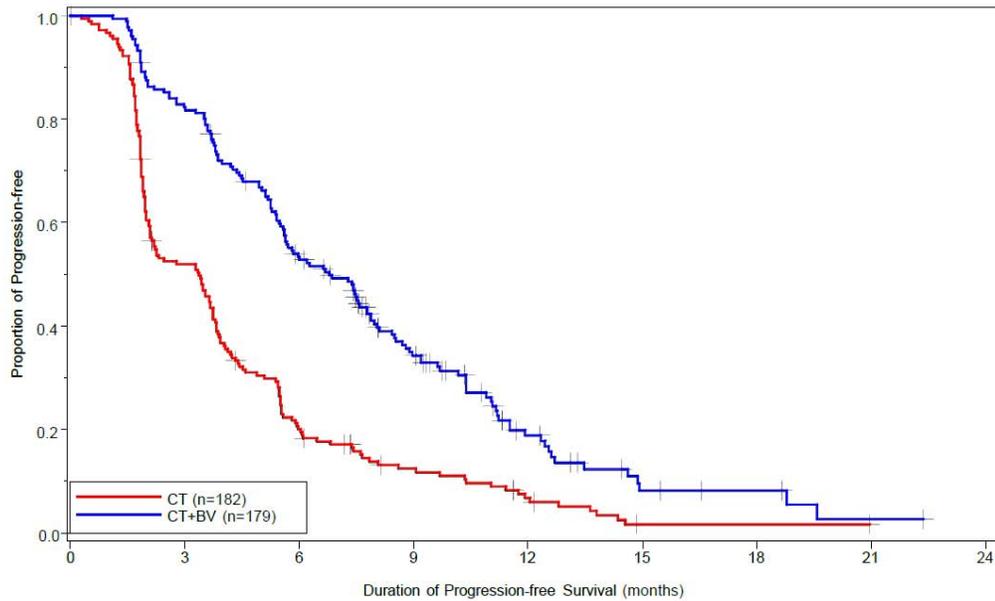
^a per stratified Cox proportional hazards model

^b per stratified logrank test

^c chemotherapy

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



Number at Risk:

	0	3	6	9	12	15	18	21	24
CT	182	92	35	18	9	1	1	0	0
CT+BV	179	144	91	51	19	6	4	1	0

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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)
<u>PFS per Investigator</u>						
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)	
<u>Overall Survival</u>						
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)	
<u>Objective Response Rate</u>						
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

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^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).*]

1050 Lactation

- 1051 • Advise nursing women that breastfeeding is not recommended during treatment with Avastin.
1052 [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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