

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, Arterial Thromboembolic Events (5.5)	12/2013
Warnings and Precautions, Proteinuria (5.8)	12/2013
Indications and Usage (1.5)	08/2014
Dosage and Administration (2.2)	08/2014
Warnings and Precautions, Gastrointestinal Perforations and Fistulae (5.1)	08/2014
Warnings and Precautions, Non-Gastrointestinal Fistulae (5.2)	08/2014
Warnings and Precautions, Hemorrhage (5.4)	08/2014
Warnings and Precautions, Venous Thromboembolic Events (5.6)	08/2014

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.
- Cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease. (1.5)
- Metastatic renal cell carcinoma with interferon alfa (1.4)

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

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)
- Ovarian Failure: Inform females of reproductive potential of the risk of ovarian failure with Avastin (5.11)

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

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing Mothers: Discontinue nursing or discontinue drug. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 08/2014

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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 (5.2)*, *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 (5.3)*, *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)*.]

49 2 DOSAGE AND ADMINISTRATION

50 2.1 Administration

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

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

58 2.2 Recommended Doses and Schedules

59 Patients should continue treatment until disease progression or unacceptable toxicity.

60 *Metastatic Colorectal Cancer (mCRC)*

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

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

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

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

71 *Glioblastoma*

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

73 *Metastatic Renal Cell Carcinoma (mRCC)*

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

75 *Cervical Cancer*

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

79 2.3 Preparation for Administration

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

85 **DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.**

86 2.4 Dose Modifications

87 There are no recommended dose reductions.

88 Discontinue Avastin for:

- 89 • Gastrointestinal perforations (gastrointestinal perforations, fistula formation in the
90 gastrointestinal tract, intra-abdominal abscess), fistula formation involving an internal organ
91 [See *Boxed Warning, Warnings and Precautions (5.1, 5.2).*]
- 92 • Wound dehiscence and wound healing complications requiring medical intervention
93 [See *Warnings and Precautions (5.3).*]
- 94 • Serious hemorrhage (i.e., requiring medical intervention) [See *Boxed Warning, Warnings and*
95 *Precautions (5.4).*]

- 96 • Severe arterial thromboembolic events [*See Warnings and Precautions (5.5).*]
- 97 • Life-threatening (Grade 4) venous thromboembolic events, including pulmonary embolism [*See*
- 98 *Warnings and Precautions (5.6).*]
- 99 • Hypertensive crisis or hypertensive encephalopathy [*See Warnings and Precautions (5.7).*]
- 100 • Posterior Reversible Encephalopathy Syndrome (PRES) [*See Warnings and Precautions*
- 101 *(5.8).*]
- 102 • Nephrotic syndrome [*See Warnings and Precautions (5.9).*]
- 103 Temporarily suspend Avastin for:
- 104 • At least 4 weeks prior to elective surgery [*See Warnings and Precautions (5.3).*]
- 105 • Severe hypertension not controlled with medical management [*See Warnings and Precautions*
- 106 *(5.7).*]
- 107 • Moderate to severe proteinuria [*See Warnings and Precautions (5.9).*]
- 108 • Severe infusion reactions [*See Warnings and Precautions (5.10).*]
- 109

110 **3 DOSAGE FORMS AND STRENGTHS**

- 111 100 mg per 4 mL single-use vial
- 112 400 mg per 16 mL single-use vial
- 113

114 **4 CONTRAINDICATIONS**

115 None.

116

117 **5 WARNINGS AND PRECAUTIONS**

118 **5.1 Gastrointestinal Perforations and Fistulae**

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

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

129 In Avastin clinical trials, gastrointestinal fistulae have been reported with an incidence of up to
130 2% in patients with metastatic colorectal cancer but were also reported less commonly in patients
131 with other types of cancer. In a cervical cancer trial (Study 9), the incidence of
132 gastrointestinal-vaginal fistulae was 8.2% in Avastin-treated patients and 0.9% in control patients,
133 all of whom had a history of prior pelvic radiation. Patients who develop GI vaginal fistulas may
134 also have bowel obstructions and require surgical intervention as well as diverting ostomies. [*See*
135 *Boxed Warning, Dosage and Administration (2.4).*]

136 **5.2 Non-Gastrointestinal Fistulae**

137
138 Serious and sometimes fatal fistula formation involving tracheo-esophageal, bronchopleural,
139 biliary, vaginal, renal and bladder sites occurs at a higher incidence in Avastin-treated patients
140 compared to controls. Uncommon (<1%) reports of fistulae that involve areas of the body other
141 than the gastrointestinal tract were observed in clinical trials across various indications and have also
142 been reported in post-marketing experience. Most events occurred within the first 6 months of
143 Avastin therapy.

144 From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (Study 9),
145 1.8% of Avastin-treated patients and 1.4% of control patients were reported to have had non-
146 gastrointestinal vaginal, vesical, or female genital tract fistulae.

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

150 **5.3 Surgery and Wound Healing Complications**

151 Avastin impairs wound healing in animal models. [See *Nonclinical Toxicology (13.2).*] In clinical
152 trials, administration of Avastin was not allowed until at least 28 days after surgery. In a controlled
153 clinical trial, the incidence of wound healing complications, including serious and fatal
154 complications, in patients with mCRC who underwent surgery during the course of Avastin
155 treatment was 15% and in patients who did not receive Avastin, was 4%. [See *Adverse Reactions*
156 *(6.1).*]

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

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

164 Necrotizing fasciitis including fatal cases, has been reported in patients treated with Avastin;
165 usually secondary to wound healing complications, gastrointestinal perforation or fistula formation.
166 Discontinue Avastin therapy in patients who develop necrotizing fasciitis. [See *Adverse Reactions*
167 *(6.3).*]

168 **5.4 Hemorrhage**

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

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

179 In clinical studies in non-small cell lung cancer where patients with CNS metastases who
180 completed radiation and surgery more than 4 weeks prior to the start of Avastin were evaluated with
181 serial CNS imaging, symptomatic Grade 2 CNS hemorrhage was documented in one of
182 83 Avastin-treated patients (rate 1.2%, 95% CI 0.06%–5.93%).

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

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

188 **5.5 Arterial Thromboembolic Events**

189 Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction,
190 transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a
191 higher incidence in patients receiving Avastin compared to those in the control arm. Across
192 indications, the incidence of Grade ≥ 3 ATE in the Avastin containing arms was 2.6% compared to

193 | 0.8% in the control arms. Among patients receiving Avastin in combination with chemotherapy, the
194 | risk of developing ATE during therapy was increased in patients with a history of arterial
195 | thromboembolism, diabetes, or age greater than 65 years. [See *Use in Specific Populations* (8.5).]

196 | The safety of resumption of Avastin therapy after resolution of an ATE has not been studied.
197 | Discontinue Avastin in patients who experience a severe ATE. [See *Dosage and Administration*
198 | (2.4).]

199 | **5.6 Venous Thromboembolic Events**

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

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

207 | **5.7 Hypertension**

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

210 | Monitor blood pressure every two to three weeks during treatment with Avastin. Treat with
211 | appropriate anti-hypertensive therapy and monitor blood pressure regularly. Continue to monitor
212 | blood pressure at regular intervals in patients with Avastin-induced or -exacerbated hypertension
213 | after discontinuation of Avastin.

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

217 | **5.8 Posterior Reversible Encephalopathy Syndrome (PRES)**

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

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

227 | **5.9 Proteinuria**

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

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

235 | Suspend Avastin administration for ≥ 2 grams of proteinuria/24 hours and resume when
236 | proteinuria is < 2 gm/24 hours. Discontinue Avastin in patients with nephrotic syndrome. [See
237 | *Dosage and Administration* (2.4).] Data from a postmarketing safety study showed poor correlation
238 | between UPCR (Urine Protein/Creatinine Ratio) and 24 hour urine protein (Pearson Correlation 0.39
239 | (95% CI 0.17, 0.57). [See *Use in Specific Populations* (8.5).]

240 **5.10 Infusion Reactions**

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

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

248 **5.11 Ovarian Failure**

249 The incidence of ovarian failure was higher (34% vs. 2%) in premenopausal women receiving
250 Avastin in combination with mFOLFOX chemotherapy as compared to those receiving mFOLFOX
251 chemotherapy alone for adjuvant treatment for colorectal cancer, a use for which Avastin is not
252 approved. Inform females of reproductive potential of the risk of ovarian failure prior to starting
253 treatment with Avastin. [See *Adverse Reactions (6.1), Use in Specific Populations (8.6).*]

254

255 **6 ADVERSE REACTIONS**

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

- 258 • Gastrointestinal Perforations and Fistulae [See *Boxed Warning, Dosage and Administration (2.4),*
259 *Warnings and Precautions (5.1).*]
- 260 • Non-Gastrointestinal Fistulae [See *Dosage and Administration (2.4), Warnings and Precautions*
261 *(5.2).*]
- 262 • Surgery and Wound Healing Complications [See *Boxed Warning, Dosage and Administration*
263 *(2.4), Warnings and Precautions (5.3).*]
- 264 • Hemorrhage [See *Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions*
265 *(5.4).*]
- 266 • Arterial Thromboembolic Events [See *Dosage and Administration (2.4), Warnings and*
267 *Precautions (5.5).*]
- 268 • Venous Thromboembolic Events [See *Dosage and Administration (2.4), Warnings and*
269 *Precautions (5.6).*]
- 270 • Hypertensive Crisis [See *Dosage and Administration (2.4), Warnings and Precautions (5.7).*]
- 271 • Posterior Reversible Encephalopathy Syndrome [See *Dosage and Administration (2.4),*
272 *Warnings and Precautions (5.8).*]
- 273 • Proteinuria [See *Dosage and Administration (2.4), Warnings and Precautions (5.9).*]
- 274 • Infusion Reactions [See *Dosage and Administration (2.4), Warnings and Precautions (5.10)*]
- 275 • Ovarian Failure [See *Warnings and Precautions (5.11), Use in Specific Populations (8.6).*]

276 The most common adverse reactions observed in Avastin patients at a rate > 10% and at least
277 twice the control arm rate, are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration,
278 dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis.

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

281 **6.1 Clinical Trial Experience**

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

285 The data below reflect exposure to Avastin in 4817 patients with CRC, non-squamous NSCLC,
286 glioblastoma, mRCC, or cervical cancer, including controlled (Studies 1, 2, 4, 5, 8 and 9) or
287 uncontrolled, single arm trials (Study 6) treated at the recommended dose and schedule for a median
288 of 6 to 23 doses of Avastin. [See *Clinical Studies (14).*] The population was aged 18-89 years
289 (median 59 years), 44% male and 85% White. The population included 2184 first- and second-line
290 mCRC patients who received a median of 10 doses of Avastin, 480 first-line metastatic NSCLC

291 patients who received a median of 8 doses of Avastin, 163 glioblastoma patients who received a
292 median of 9 doses of Avastin, 337 mRCC patients who received a median of 16 doses of Avastin,
293 and 218 cervical cancer patients who received a median of 6 doses of Avastin. These data also
294 reflect exposure to Avastin in 363 patients with metastatic breast cancer (MBC) who received a
295 median of 9.5 doses of Avastin, 1338 adjuvant CRC patients, including 669 female patients, who
296 received a median of 23 doses of Avastin, and 403 previously untreated patients with diffuse large
297 B-cell lymphoma (DLBCL) who received a median of 8 doses of Avastin. Avastin is not approved
298 for use in MBC, adjuvant CRC, or DLBCL.

299 *Surgery and Wound Healing Complications*

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

305 In Study 6, events of post-operative wound healing complications (craniotomy site wound
306 dehiscence and cerebrospinal fluid leak) occurred in patients with previously treated glioblastoma:
307 3/84 patients in the Avastin alone arm and 1/79 patients in the Avastin plus irinotecan arm.
308 [*See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.3).*]

309 *Hemorrhage*

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

317 *Venous Thromboembolic Events*

318 The overall incidence of Grade 3–4 venous thromboembolic events in Study 1 was 15.1% in
319 patients receiving bolus-IFL plus Avastin and 13.6% in patients receiving bolus-IFL plus placebo.
320 In Study 1, more patients in the Avastin containing arm experienced deep venous thrombosis (34 vs.
321 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

322 The risk of developing a second thromboembolic event while on Avastin and oral anticoagulants
323 was evaluated in two randomized studies. In Study 1, 53 patients (14%) on the bolus-IFL plus
324 Avastin arm and 30 patients (8%) on the bolus-IFL plus placebo arm received full dose warfarin
325 following a venous thromboembolic event (VTE). Among these patients, an additional
326 thromboembolic event occurred in 21% (11/53) of patients receiving bolus-IFL plus Avastin and 3%
327 (1/30) of patients receiving bolus-IFL alone.

328 In a second, randomized, 4-arm study in 1401 patients with mCRC, prospectively evaluating the
329 incidence of VTE (all grades), the overall incidence of first VTE was higher in the Avastin
330 containing arms (13.5%) than the chemotherapy alone arms (9.6%). Among the 116 patients treated
331 with anticoagulants following an initial VTE event (73 in the Avastin plus chemotherapy arms and
332 43 in the chemotherapy alone arms), the overall incidence of subsequent VTEs was also higher
333 among the Avastin treated patients (31.5% vs. 25.6%). In this subgroup of patients treated with
334 anticoagulants, the overall incidence of bleeding, the majority of which were Grade 1, was higher in
335 the Avastin treated arms than the chemotherapy arms (27.4% vs. 20.9%).

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

340 *Neutropenia and Infection*

341 The incidences of neutropenia and febrile neutropenia are increased in patients receiving Avastin
342 plus chemotherapy compared to chemotherapy alone. In Study 1, the incidence of Grade 3 or 4
343 neutropenia was increased in mCRC patients receiving IFL plus Avastin (21%) compared to patients
344 receiving IFL alone (14%). In Study 5, the incidence of Grade 4 neutropenia was increased in
345 NSCLC patients receiving paclitaxel/carboplatin (PC) plus Avastin (26.2%) compared with patients
346 receiving PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC plus Avastin vs.
347 1.8% for PC alone). There were 19 (4.5%) infections with Grade 3 or 4 neutropenia in the PC plus
348 Avastin arm of which 3 were fatal compared to 9 (2%) neutropenic infections in patients receiving
349 PC alone, of which none were fatal. During the first 6 cycles of treatment, the incidence of serious
350 infections including pneumonia, febrile neutropenia, catheter infections and wound infections was
351 increased in the PC plus Avastin arm [58 patients (13.6%)] compared to the PC alone arm
352 [29 patients (6.6%)].

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

356 *Proteinuria*

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

363 In an exploratory, pooled analysis of 8,273 patients treated in 7 randomized clinical trials, 5.4%
364 (271 of 5037) of patients receiving Avastin in combination with chemotherapy experienced
365 Grade ≥ 2 proteinuria. The Grade ≥ 2 proteinuria resolved in 74.2% (201 of 271) of patients.
366 Avastin was re-initiated in 41.7% (113 of 271) of patients. Of the 113 patients who re-initiated
367 Avastin, 47.8% (54 of 113) experienced a second episode of Grade ≥ 2 proteinuria. [*See Warnings*
368 *and Precautions* (5.9).]

369 *Congestive Heart Failure (CHF)*

370 The incidence of Grade ≥ 3 left ventricular dysfunction was 1.0% in patients receiving Avastin
371 compared to 0.6% in the control arm across indications. In patients with metastatic breast cancer
372 (MBC), an indication for which Avastin is not approved, the incidence of Grade 3–4 CHF was
373 increased in patients in the Avastin plus paclitaxel arm (2.2%) as compared to the control arm
374 (0.3%). Among patients receiving prior anthracyclines for MBC, the rate of CHF was 3.8% for
375 patients receiving Avastin as compared to 0.6% for patients receiving paclitaxel alone. The safety of
376 continuation or resumption of Avastin in patients with cardiac dysfunction has not been studied.

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

389 *Ovarian Failure*

390 The incidence of new cases of ovarian failure (defined as amenorrhoea lasting 3 or more months,
391 FSH level ≥ 30 mIU/mL and a negative serum β -HCG pregnancy test) was prospectively evaluated
392 in a subset of 179 women receiving mFOLFOX chemotherapy alone (n=84) or with Avastin
393 (n=95). New cases of ovarian failure were identified in 34% (32/95) of women receiving Avastin in
394 combination with chemotherapy compared with 2% (2/84) of women receiving chemotherapy alone
395 [relative risk of 14 (95% CI 4, 53)]. After discontinuation of Avastin treatment, recovery of ovarian
396 function at all time points during the post-treatment period was demonstrated in 22% (7/32) of the
397 Avastin-treated women. Recovery of ovarian function is defined as resumption of menses, a positive
398 serum β -HCG pregnancy test, or a FSH level < 30 mIU/mL during the post-treatment period. Long
399 term effects of Avastin exposure on fertility are unknown. [See *Warnings and Precautions (5.11)*,
400 *Use in Specific Populations (8.6)*.]

401 *Post-Treatment Vascular Events*

402 In an open-label, randomized, controlled trial of Avastin in adjuvant colorectal cancer, an indication
403 for which Avastin is not approved, the overall incidence rate of post-treatment Grade ≥ 3 vascular
404 events was 3.1% (41 of 1338) among patients receiving mFOLFOX6 plus Avastin, compared to
405 1.6% (21 of 1349) among patients receiving mFOLFOX6 alone. Post-treatment vascular events
406 included arterial and venous thromboembolic events, ischemic events, and vascular aneurysms.

407 *Metastatic Colorectal Cancer (mCRC)*

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

411 All Grade 3–4 adverse events and selected Grade 1–2 adverse events (hypertension, proteinuria,
412 thromboembolic events) were collected in the entire study population. Severe and life-threatening
413 (Grade 3–4) adverse events, which occurred at a higher incidence ($\geq 2\%$) in patients receiving
414 bolus-IFL plus Avastin as compared to bolus-IFL plus placebo, are presented in Table 1.
415

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.

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

Table 2
 NCI-CTC Grade 1-4 Adverse Events in Study 1
 (Occurring at Higher Incidence [$\geq 5\%$] 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%

423

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

425 Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events related to treatment
 426 were collected in Study 2. The most frequent adverse events (selected Grade 3-5 non-hematologic
 427 and Grade 4-5 hematologic adverse events) occurring at a higher incidence ($\geq 2\%$) in 287 patients
 428 receiving FOLFOX4 plus Avastin compared to 285 patients receiving FOLFOX4 alone were fatigue
 429 (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%),
 430 vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8%
 431 vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache
 432 (3% vs. 0%). These data are likely to under-estimate the true adverse event rates due to the reporting
 433 mechanisms used in Study 2.

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

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

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

441 Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected in
 442 Study 5. Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events (occurring at a
 443 higher incidence ($\geq 2\%$) in 427 patients receiving PC plus Avastin compared with 441 patients
 444 receiving PC alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs.
 445 0.7%), infection without neutropenia (7% vs. 3%), venous thrombus/embolism (5% vs. 3%), febrile
 446 neutropenia (5% vs. 2%), pneumonitis/pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or
 447 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3%
 448 vs. 0%).

449 *Glioblastoma*

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

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

459 In patients receiving Avastin alone or Avastin plus irinotecan (N= 163), the incidence of
460 Avastin-related adverse events (Grade 1–4) were bleeding/hemorrhage (40%), epistaxis (26%), CNS
461 hemorrhage (5%), hypertension (32%), venous thromboembolic event (8%), arterial thromboembolic
462 event (6%), wound-healing complications (6%), proteinuria (4%), gastrointestinal perforation (2%),
463 and PRES (1%). The incidence of Grade 3–5 events in these 163 patients were bleeding/hemorrhage
464 (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic event (7%), arterial
465 thromboembolic event (3%), wound-healing complications (3%), proteinuria (1%), and
466 gastrointestinal perforation (2%).

467 *Metastatic Renal Cell Carcinoma (mRCC)*

468 All grade adverse events were collected in Study 8. Grade 3–5 adverse events occurring at a
469 higher incidence ($\geq 2\%$) in 337 patients receiving interferon alfa (IFN- α) plus Avastin compared to
470 304 patients receiving IFN- α plus placebo arm were fatigue (13% vs. 8%), asthenia (10% vs. 7%),
471 proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis),
472 and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured,
473 gastric ulcer hemorrhage, gingival bleeding, haemoptysis, hemorrhage intracranial, large intestinal
474 hemorrhage, respiratory tract hemorrhage, and traumatic hematoma).

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

477

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%		

489

490 Grade 3 or 4 adverse reactions occurring at a higher incidence ($\geq 2\%$) in 218 patients receiving
491 chemotherapy plus Avastin compared to 222 patients receiving chemotherapy alone were abdominal
492 pain (11.9% vs. 9.9%), diarrhea (5.5% vs. 2.7%), anal fistula (3.7% vs. 0%), proctalgia (2.8% vs.
493 0%), urinary tract infection 8.3% vs. 6.3%), cellulitis (3.2% vs. 0.5%), fatigue (14.2% vs. 9.9%),
494 hypokalemia (7.3% vs. 4.5%), hyponatremia (3.7% vs. 1.4%), dehydration (4.1% vs. 0.5%),
495 neutropenia (7.8% vs. 4.1%), lymphopenia (6.0% vs. 3.2%), back pain (5.5% vs. 3.2%), and pelvic
496 pain (5.5% vs. 1.4%).

497

498 There were no Grade 5 adverse reactions occurring at a higher incidence ($\geq 2\%$) in patients
499 receiving chemotherapy plus Avastin compared to patients receiving chemotherapy alone.
500

501 **6.2 Immunogenicity**

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

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

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

513 **6.3 Postmarketing Experience**

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

517 *Body as a Whole:* Polyserositis

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

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

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

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

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

524 *Hemic and lymphatic:* Pancytopenia

525 *Hepatobiliary disorders:* Gallbladder perforation

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

528 *Musculoskeletal:* Osteonecrosis of the jaw

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

530 *Respiratory:* Nasal septum perforation, dysphonia

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

532 Arterial thromboembolic events, Hypertension, Gastrointestinal perforation, Hemorrhage

533

534 **7 DRUG INTERACTIONS**

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

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

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

546

547 **8 USE IN SPECIFIC POPULATIONS**

548 **8.1 Pregnancy**

549 *Pregnancy Category C*

550 There are no adequate or well controlled studies of bevacizumab in pregnant women. While it is
551 not known if bevacizumab crosses the placenta, human IgG is known to cross the placenta
552 Reproduction studies in rabbits treated with approximately 1 to 12 times the recommended human
553 dose of bevacizumab demonstrated teratogenicity, including an increased incidence of specific gross
554 and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested. Other
555 observed effects included decreases in maternal and fetal body weights and an increased number of
556 fetal resorptions. [*See Nonclinical Toxicology (13.3).*]

557 Because of the observed teratogenic effects of bevacizumab in animals and of other inhibitors of
558 angiogenesis in humans, bevacizumab should be used during pregnancy only if the potential benefit
559 to the pregnant woman justifies the potential risk to the fetus.

560 **8.3 Nursing Mothers**

561 It is not known whether Avastin is secreted in human milk. Human IgG is excreted in human
562 milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant
563 circulation in substantial amounts. Because many drugs are secreted in human milk and because of
564 the potential for serious adverse reactions in nursing infants from bevacizumab, a decision should be
565 made whether to discontinue nursing or discontinue drug, taking into account the half-life of the
566 bevacizumab (approximately 20 days [range 11–50 days]) and the importance of the drug to the
567 mother. [*See Clinical Pharmacology (12.3).*]

568 **8.4 Pediatric Use**

569 The safety, effectiveness and pharmacokinetic profile of Avastin in pediatric patients have not
570 been established.

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

574 Juvenile cynomolgus monkeys with open growth plates exhibited physeal dysplasia following 4 to
575 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure).
576 The incidence and severity of physeal dysplasia were dose-related and were partially reversible upon
577 cessation of treatment.

578 **8.5 Geriatric Use**

579 In Study 1, severe adverse events that occurred at a higher incidence ($\geq 2\%$) in patients aged
580 ≥ 65 years as compared to younger patients were asthenia, sepsis, deep thrombophlebitis,
581 hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhea, constipation,
582 anorexia, leukopenia, anemia, dehydration, hypokalemia, and hyponatremia. The effect of Avastin
583 on overall survival was similar in elderly patients as compared to younger patients.

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

586 In Study 5, patients aged ≥ 65 years receiving carboplatin, paclitaxel, and Avastin had a greater
587 relative risk for proteinuria as compared to younger patients. [*See Warnings and Precautions (5.8).*]

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

593 In an exploratory, pooled analysis of 1745 patients treated in five randomized, controlled studies,
594 there were 618 (35%) patients aged ≥ 65 years and 1127 patients < 65 years of age. The overall

595 incidence of arterial thromboembolic events was increased in all patients receiving Avastin with
596 chemotherapy as compared to those receiving chemotherapy alone, regardless of age. However, the
597 increase in arterial thromboembolic events incidence was greater in patients aged ≥ 65 years (8.5%
598 vs. 2.9%) as compared to those < 65 years (2.1% vs. 1.4%). [See *Warnings and Precautions* (5.5).]

599 **8.6 Females of Reproductive Potential**

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

603 In a prospectively designed substudy of 179 premenopausal women randomized to receive
604 chemotherapy with or without Avastin, the incidence of ovarian failure was higher in the Avastin
605 arm (34%) compared to the control arm (2%). After discontinuation of Avastin and chemotherapy,
606 recovery of ovarian function occurred in 22% (7/32) of these Avastin-treated patients.
607 [See *Warnings and Precautions* (5.11), *Adverse Reactions* (6.1).]

608

609 **10 OVERDOSAGE**

610 The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of
611 16 patients and with severe headache in three of 16 patients.

612

613 **11 DESCRIPTION**

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

621 Avastin is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for
622 intravenous infusion. Avastin is supplied in 100 mg and 400 mg preservative-free, single-use vials
623 to deliver 4 mL or 16 mL of Avastin (25 mg/mL). The 100 mg product is formulated in 240 mg
624 α, α -trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium
625 phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The 400 mg
626 product is formulated in 960 mg α, α -trehalose dihydrate, 92.8 mg sodium phosphate (monobasic,
627 monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water
628 for Injection, USP.

629

630 **12 CLINICAL PHARMACOLOGY**

631 **12.1 Mechanism of Action**

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

637 **12.3 Pharmacokinetics**

638 The pharmacokinetic profile of bevacizumab was assessed using an assay that measures total
639 serum bevacizumab concentrations (i.e., the assay did not distinguish between free bevacizumab and
640 bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of
641 491 patients who received 1 to 20 mg/kg of Avastin weekly, every 2 weeks, or every 3 weeks, the
642 estimated half-life of bevacizumab was approximately 20 days (range 11–50 days). The predicted

643 time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg of
644 bevacizumab every 2 weeks was 2.8.

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

653

654 **13 NONCLINICAL TOXICOLOGY**

655 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

666 **13.2 Animal Toxicology and/or Pharmacology**

667 In cynomolgus monkeys, when bevacizumab was administered at doses of 0.4 to 20 times the
668 weekly human exposure, anatomical pathology revealed several adverse effects on general growth
669 and skeletal development, fertility and wound healing capacity. Severe physal dysplasia was
670 consistently reported in juvenile monkeys with open growth plates receiving 0.4 to 20 times the
671 human dose. The physal dysplasia was characterized by a linear cessation of growth line and
672 chondrocyte hyperplasia which did not completely resolve after the 4 to 12 weeks recovery period
673 without drug exposure.

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

678 **13.3 Reproductive and Developmental Toxicology**

679 Pregnant rabbits dosed with 1 to 12 times the human dose of bevacizumab every three days during
680 the period of organogenesis (gestation day 6–18) exhibited teratogenic effects, decreases in maternal
681 and fetal body weights, and increased number of fetal resorptions. Teratogenic effects included:
682 reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws;
683 meningocele; fontanel, rib and hindlimb deformities; corneal opacity; and absent hindlimb
684 phalanges. There are no data available regarding the level of bevacizumab exposure in the offspring.

685

686 **14 CLINICAL STUDIES**

687 **14.1 Metastatic Colorectal Cancer (mCRC)**

688 *Study 1*

689 In this double-blind, active-controlled study, patients were randomized (1:1:1) to IV bolus-IFL
690 (irinotecan 125 mg/m², 5-FU 500 mg/m², and leucovorin (LV) 20 mg/m² given once weekly for

691 4 weeks every 6 weeks) plus placebo (Arm 1), bolus-IFL plus Avastin (5 mg/kg every 2 weeks)
 692 (Arm 2), or 5-FU/LV plus Avastin (5 mg/kg every 2 weeks) (Arm 3). Enrollment in Arm 3 was
 693 discontinued, as pre-specified, when the toxicity of Avastin in combination with the bolus-IFL
 694 regimen was deemed acceptable. The main outcome measure was overall survival (OS).

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

699 The addition of Avastin resulted in an improvement in survival across subgroups defined by age
 700 (<65 yrs, ≥65 yrs) and gender. Results are presented in Table 5 and Figure 1.
 701

Table 5
 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.

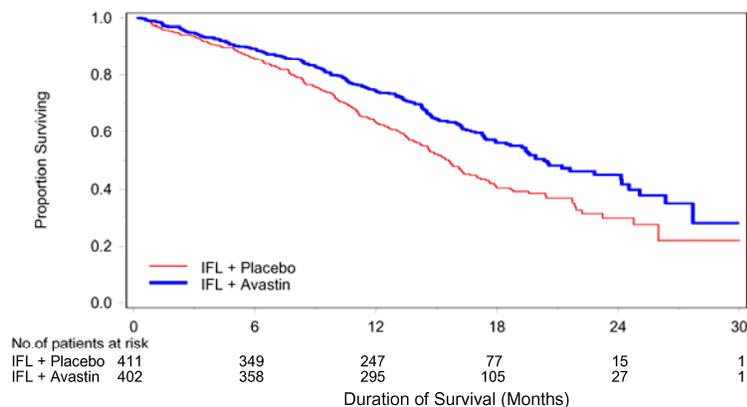
^b p<0.01 by χ^2 test.

702

703

704

Figure 1
 Duration of Survival in Study 1



705

706

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

710 *Study 2*

711 Study 2 was a randomized, open-label, active-controlled trial in patients who were previously
712 treated with irinotecan ± 5-FU for initial therapy for metastatic disease or as adjuvant therapy.
713 Patients were randomized (1:1:1) to IV FOLFOX4 (Day 1: oxaliplatin 85 mg/m² and LV 200 mg/m²
714 concurrently, then 5-FU 400 mg/m² bolus followed by 600 mg/m² continuously; Day 2: LV
715 200 mg/m², then 5-FU 400 mg/m² bolus followed by 600 mg/m² continuously; repeated every
716 2 weeks), FOLFOX4 plus Avastin (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1), or
717 Avastin monotherapy (10 mg/kg every 2 weeks). The main outcome measure was OS.

718 The Avastin monotherapy arm was closed to accrual after enrollment of 244 of the planned
719 290 patients following a planned interim analysis by the data monitoring committee based on
720 evidence of decreased survival compared to FOLFOX4 alone.

721 Of the 829 patients randomized to the three arms, the median age was 61 years, 40% were female,
722 87% were Caucasian, 49% had an ECOG performance status of 0, 26% received prior radiation
723 therapy, and 80% received prior adjuvant chemotherapy, 99% received prior irinotecan, with or
724 without 5-FU as therapy for metastatic disease, and 1% received prior irinotecan and 5-FU as
725 adjuvant therapy.

726 The addition of Avastin to FOLFOX4 resulted in significantly longer survival as compared to
727 FOLFOX4 alone (median OS 13.0 months vs. 10.8 months; hazard ratio 0.75 [95% CI 0.63, 0.89],
728 p=0.001 stratified log rank test) with clinical benefit seen in subgroups defined by age (<65 yrs,
729 ≥65 yrs) and gender. PFS and ORR based on investigator assessment were higher in the Avastin
730 plus FOLFOX4 arm.

731 *Study 3*

732 The activity of Avastin in combination with bolus or infusional 5-FU/LV was evaluated in a
733 single arm study enrolling 339 patients with mCRC with disease progression following both
734 irinotecan- and oxaliplatin-containing chemotherapy regimens. Seventy-three percent of patients
735 received concurrent bolus 5-FU/LV. One objective partial response was verified in the first
736 100 evaluable patients for an overall response rate of 1% (95% CI 0–5.5%).

737 *Study 4*

738 Study 4 was a prospective, randomized, open-label, multinational, controlled trial in patients with
739 histologically confirmed metastatic colorectal cancer who had progressed on a first-line Avastin
740 containing regimen. Patients were excluded if they progressed within 3 months of initiating first-
741 line chemotherapy and if they received Avastin for less than 3 consecutive months in the first-line
742 setting.

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

749 Of the 820 patients randomized, the majority of patients were male (64%) and the median age was
750 63.0 years (range 21 to 84 years). At baseline, 52% of patients were ECOG performance status (PS)
751 1, 44% were ECOG PS 0, 58% received irinotecan-based therapy as first-line treatment, 55%
752 progressed on first-line treatment within 9 months, and 77% received their last dose of Avastin as
753 first-line treatment within 42 days of being randomized. Second-line chemotherapy regimens were
754 generally balanced between each treatment arm.

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

758
 759 **Table 6**
 760 Study 4 Efficacy Results
 761

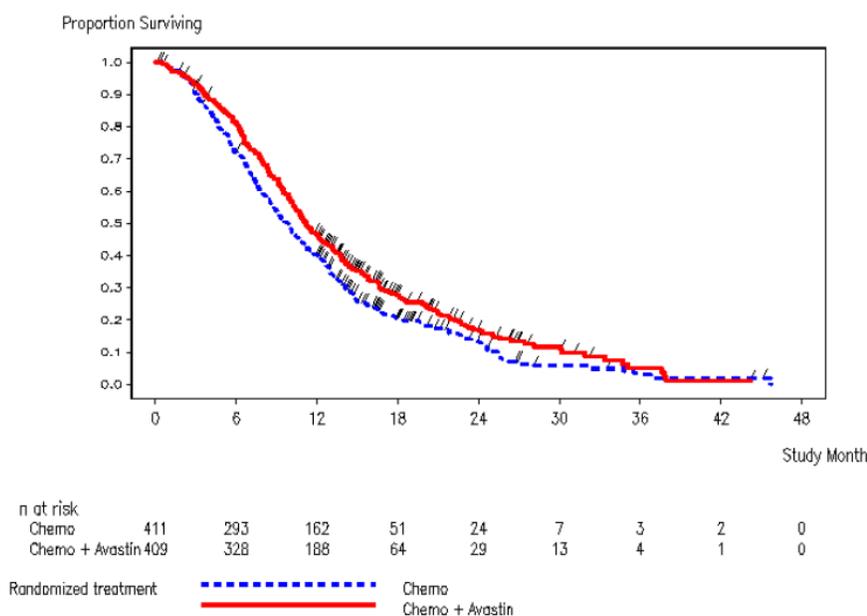
	Chemotherapy	Avastin + Chemotherapy
Number of Patients	411	409
Overall Survival^a		
Median (months)	9.8	11.2
Hazard ratio (95% CI)	0.81 (0.69, 0.94)	
Progression-Free Survival^b		
Median (months)	4.0	5.7
Hazard ratio (95% CI)	0.68 (0.59, 0.78)	

^a p = 0.0057 by unstratified log rank test.

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

762
 763
 764

Figure 2
 Duration of Survival in Study 4



765
 766

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,

775 and 1145 to XELOX plus Avastin arm. The median age was 58 years, 54% were male, 84% were
776 Caucasian and 29% were \geq age 65. Eighty-three percent had stage III disease.

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

787 In a second study, 2710 patients with stage II and III colon cancer who had undergone surgery with
788 curative intent, were randomized to receive either Avastin administered at a dose equivalent to
789 2.5 mg/kg/week in combination with mFOLFOX6 (N=1354) or mFOLFOX6 alone (N=1356). The
790 median age was 57 years, 50% were male and 87% Caucasian. Seventy-five percent had stage III
791 disease. The main efficacy outcome was DFS among stage III patients. The hazard ratio for DFS
792 was 0.92 (95% CI: 0.77, 1.10). Overall survival, an additional efficacy outcome, was not
793 significantly improved with the addition of Avastin to mFOLFOX6 (HR=0.96, 95% CI=[0.75,1.22]).

794 **14.3 Unresectable Non–Squamous Non–Small Cell Lung Cancer (NSCLC)**

795 *Study 5*

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

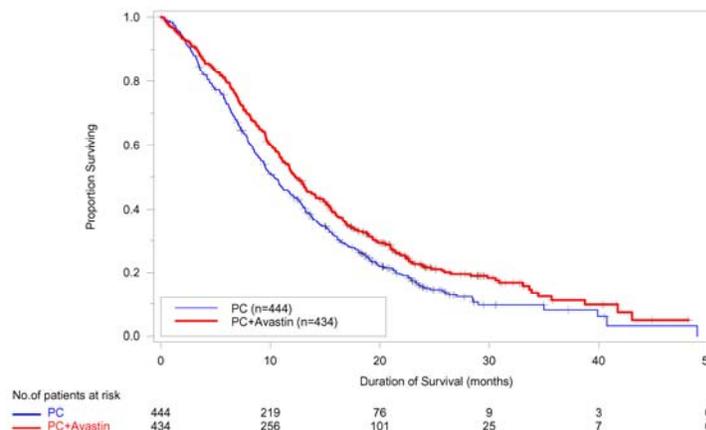
799 Chemotherapy-naïve patients with locally advanced, metastatic or recurrent non–squamous
800 NSCLC were randomized (1:1) to receive six 21-day cycles of paclitaxel 200 mg/m² and carboplatin
801 AUC=6.0, by IV on day 1 (PC) or PC in combination with Avastin 15 mg/kg by IV on day 1 (PC
802 plus Avastin).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

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

812 The results are presented in Figure 3. OS was statistically significantly higher among patients
813 receiving PC plus Avastin compared with those receiving PC alone; median OS was 12.3 months vs.
814 10.3 months [hazard ratio 0.80 (repeated 95% CI 0.68, 0.94), final p- value 0.013, stratified log-rank
815 test]. Based on investigator assessment which was not independently verified, patients were
816 reported to have longer PFS with Avastin in combination with PC compared to PC alone.

817

Figure 3
Duration of Survival in Study 5

820
821

822 In an exploratory analyses across patient subgroups, the impact of Avastin on OS was less robust
823 in the following: women [HR=0.99 (95% CI: 0.79, 1.25)], age \geq 65 years [HR=0.91 (95% CI:
824 0.72, 1.14)] and patients with \geq 5% weight loss at study entry [HR=0.96 (95% CI: 0.73, 1.26)].

825 The safety and efficacy of Avastin in patients with locally advanced, metastatic or recurrent
826 non-squamous NSCLC, who had not received prior chemotherapy was studied in another
827 randomized, double-blind, placebo controlled, three-arm study of Avastin in combination with
828 cisplatin and gemcitabine (CG) versus placebo and CG. A total of 1043 patients were randomized
829 1:1:1 to receive placebo plus CG, Avastin 7.5 mg/kg plus CG or Avastin 15.0 mg/kg plus CG.
830 The median age was 58 years, 36% were female, and 29% were \geq age 65. Eight percent had
831 recurrent disease and 77% had Stage IV disease. Progression-free survival, the main efficacy
832 outcome measure, was significantly higher in both Avastin containing arms compared to the placebo
833 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
834 (95% CI 0.68; 0.98), $p=0.0301$ for the Avastin 15.0 mg/kg plus CG arm]. The addition of Avastin
835 to CG chemotherapy failed to demonstrate an improvement in the duration of overall survival, an
836 additional efficacy outcome measure, [HR 0.93 (95% CI 0.78; 1.11), $p=0.4203$ for the Avastin
837 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
838 plus CG arm].

839 14.4 Glioblastoma

840 Study 6

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

847 Of the 85 patients randomized to the Avastin arm, the median age was 54 years, 32% were
848 female, 81% were in first relapse, Karnofsky performance status was 90–100 for 45% and 70–80 for
849 55%.

850 The efficacy of Avastin was demonstrated using response assessment based on both WHO
851 radiographic criteria and by stable or decreasing corticosteroid use, which occurred in 25.9% (95%
852 CI 17.0%, 36.1%) of the patients. Median duration of response was 4.2 months (95% CI 3.0, 5.7).

853 Radiologic assessment was based on MRI imaging (using T1 and T2/FLAIR). MRI does not
854 necessarily distinguish between tumor, edema, and radiation necrosis.

855 *Study 7*

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

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

861 The efficacy of Avastin was supported by an objective response rate of 19.6% (95% CI 10.9%,
862 31.3%) using the same response criteria as in Study 6. Median duration of response was 3.9 months
863 (95% CI 2.4, 17.4).

864 **14.5 Metastatic Renal Cell Carcinoma (mRCC)**

865 *Study 8*

866 Patients with treatment-naïve mRCC were evaluated in a multicenter, randomized, double-blind,
867 international study comparing Avastin plus interferon alfa 2a (IFN- α 2a) versus placebo plus
868 IFN- α 2a. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to
869 receive either Avastin (10 mg/kg IV infusion every 2 weeks; n=327) or placebo (IV every 2 weeks;
870 n=322) in combination with IFN- α 2a (9 MIU subcutaneously three times weekly, for a maximum of
871 52 weeks). Patients were treated until disease progression or unacceptable toxicity. The main
872 outcome measure of the study was investigator-assessed PFS. Secondary outcome measures were
873 ORR and OS.

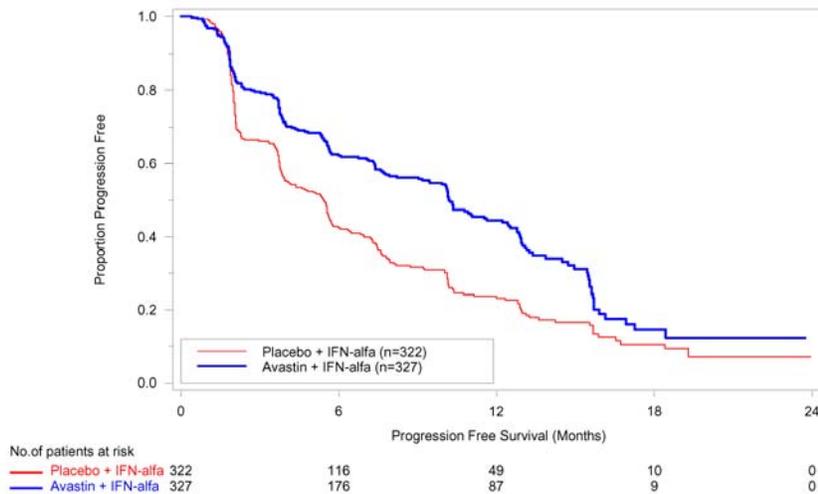
874 The median age was 60 years (range 18–82), 96% were white, and 70% were male. The study
875 population was characterized by Motzer scores as follows: 28% favorable (0), 56% intermediate
876 (1-2), 8% poor (3–5), and 7% missing.

877 The results are presented in Figure 4. PFS was statistically significantly prolonged among
878 patients receiving Avastin plus IFN- α 2a compared to those receiving IFN- α 2a alone; median PFS
879 was 10.2 months vs. 5.4 months [HR 0.60 (95% CI 0.49, 0.72), p-value <0.0001, stratified log-rank
880 test]. Among the 595 patients with measurable disease, ORR was also significantly higher (30% vs.
881 12%, p <0.0001, stratified CMH test). There was no improvement in OS based on the final analysis
882 conducted after 444 deaths, with a median OS of 23 months in the Avastin plus IFN- α 2a arm and
883 21 months in the IFN- α 2a plus placebo arm [HR 0.86, (95% CI 0.72, 1.04)].

884

885
886

Figure 4
Progression-Free Survival in Study 8



887

888 14.6 Persistent, Recurrent, or Metastatic Carcinoma of the Cervix

889 Study 9

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

894

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

896

- 897 • Day 1: Paclitaxel 135 mg/m² IV over 24 hours, Day 2: cisplatin 50 mg/m² IV plus Avastin;
898 or Day 1: paclitaxel 175 mg/m² IV over 3 hours, Day 2: cisplatin 50 mg/m² IV plus Avastin ;
899 or Day 1: paclitaxel 175 mg/m² IV over 3 hours plus cisplatin 50 mg/m² IV plus Avastin
- 900 • Day 1: Paclitaxel 175 mg/m² over 3 hours plus Avastin, Days 1-3: topotecan 0.75 mg/m²
901 over 30 minutes

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

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

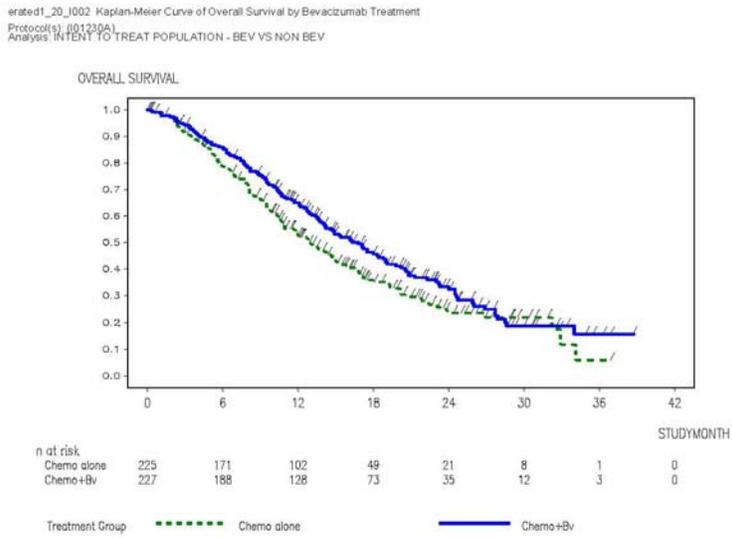
910

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

913

914
915

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



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Table 7
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).

917 The overall response rate was also higher in patients who received chemotherapy plus Avastin [45%
918 (95% CI: 39, 52)] than in patients who received chemotherapy alone [34% (95% CI: 28,40)].
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Table 8

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).

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 potential risk to the fetus during and following Avastin and the need to continue adequate contraception for at least 6 months following last dose of Avastin.
- Of the increased risk for ovarian failure following Avastin treatment.

Avastin® (bevacizumab)

Manufactured by:

Genentech, Inc.

A Member of the Roche Group

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