

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 2.4% 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. (5.2)
- **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. (5.3)

RECENT MAJOR CHANGES

Warnings and Precautions: Ovarian Failure (5.10) 09/2011

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)
- 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)
- Metastatic breast cancer, with paclitaxel for treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer. (1.3)
 - Effectiveness based on improvement in progression-free survival. No data available demonstrating improvement in disease-related symptoms or survival with Avastin.
 - Not indicated for disease progression following anthracycline and taxane chemotherapy administered for metastatic disease.
- Glioblastoma, as a single agent for adult patients with progressive disease following prior therapy. (1.4)
 - 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 (1.5)

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

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

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

Metastatic breast cancer (2.2)

- 10 mg/kg IV every 2 weeks with 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

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

- Non-Gastrointestinal Fistula Formation: Discontinue Avastin if fistula formation occurs. (5.4)
- Arterial Thromboembolic Events (e.g., myocardial infarction, cerebral infarction): Discontinue Avastin for severe ATE. (5.5)
- Hypertension: Monitor blood pressure and treat hypertension. Temporarily suspend Avastin if not medically controlled. Discontinue Avastin for hypertensive crisis or hypertensive encephalopathy. (5.6)
- Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Discontinue Avastin. (5.7)
- Proteinuria: Monitor urine protein. Discontinue for nephrotic syndrome. Temporarily suspend Avastin for moderate proteinuria. (5.8)
- Infusion Reactions: Stop for severe infusion reactions. (5.9)
- Ovarian Failure: Inform females of reproductive potential of the risk of ovarian failure with Avastin (5.10)

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: September 2011

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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 2.4%. Discontinue Avastin in patients with gastrointestinal perforation. [See**
7 ***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. [See**
15 ***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 occurred 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 1.2 Non-Squamous Non-Small Cell Lung Cancer (NSCLC)

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

30 1.3 Metastatic Breast Cancer (MBC)

31 Avastin is indicated for the treatment of patients who have not received chemotherapy for
32 metastatic HER2-negative breast cancer in combination with paclitaxel.

33 The effectiveness of Avastin in MBC is based on an improvement in progression free survival.
34 There are no data demonstrating an improvement in disease-related symptoms or increased survival
35 with Avastin. [See *Clinical Studies (14.3).*]

36 Avastin is not indicated for patients with breast cancer that has progressed following anthracycline
37 and taxane chemotherapy administered for metastatic disease.

38 1.4 Glioblastoma

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

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

44 1.5 Metastatic Renal Cell Carcinoma (mRCC)

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

47 **2 DOSAGE AND ADMINISTRATION**

48 **2.1 Administration**

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

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

56 **2.2 Recommended Doses and Schedules**

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

58 *Metastatic Colorectal Cancer (mCRC)*

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

- 61 • Administer 5 mg/kg when used in combination with bolus-IFL.
- 62 • Administer 10 mg/kg when used in combination with FOLFOX4.

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

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

66 *Metastatic Breast Cancer (MBC)*

67 The recommended dose is 10 mg/kg every 2 weeks in combination with paclitaxel.

68 *Glioblastoma*

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

70 *Metastatic Renal Cell Carcinoma (mRCC)*

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

72 **2.3 Preparation for Administration**

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

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

79 **2.4 Dose Modifications**

80 There are no recommended dose reductions.

81 Discontinue Avastin for:

- 82 • Gastrointestinal perforations (gastrointestinal perforations, fistula formation in the
83 gastrointestinal tract, intra-abdominal abscess), fistula formation involving an internal organ
84 [See *Boxed Warning, Warnings and Precautions (5.1, 5.4).*]
 - 85 • Wound dehiscence and wound healing complications requiring medical intervention [See
86 *Warnings and Precautions (5.2).*]
 - 87 • Serious hemorrhage (i.e., requiring medical intervention) [See *Boxed Warning, Warnings and*
88 *Precautions (5.3).*]
 - 89 • Severe arterial thromboembolic events [See *Warnings and Precautions (5.5).*]
 - 90 • Hypertensive crisis or hypertensive encephalopathy [See *Warnings and Precautions (5.6).*]
 - 91 • Reversible posterior leukoencephalopathy syndrome (RPLS) [See *Warnings and Precautions*
92 *(5.7).*]
 - 93 • Nephrotic syndrome [See *Warnings and Precautions (5.8).*]
- 94

- 95 Temporarily suspend Avastin for:
96 • At least 4 weeks prior to elective surgery [See *Warnings and Precautions* (5.2).]
97 • Severe hypertension not controlled with medical management [See *Warnings and Precautions*
98 (5.6).]
99 • Moderate to severe proteinuria pending further evaluation [See *Warnings and Precautions*
100 (5.8).]
101 • Severe infusion reactions [See *Warnings and Precautions* (5.9).]
102

103 **3 DOSAGE FORMS AND STRENGTHS**

- 104 100 mg per 4 mL single-use vial
105 400 mg per 16 mL single-use vial
106

107 **4 CONTRAINDICATIONS**

108 None.
109

110 **5 WARNINGS AND PRECAUTIONS**

111 **5.1 Gastrointestinal Perforations**

112 Serious and sometimes fatal gastrointestinal perforation occurs at a higher incidence in Avastin
113 treated patients compared to controls. The incidence of gastrointestinal perforation ranged from 0.3
114 to 2.4% across clinical studies. [See *Adverse Reactions* (6.1).]

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

118 Discontinue Avastin in patients with gastrointestinal perforation. [See *Boxed Warning, Dosage*
119 *and Administration* (2.4).]

120 **5.2 Surgery and Wound Healing Complications**

121 Avastin impairs wound healing in animal models. [See *Nonclinical Toxicology* (13.2).] In clinical
122 trials, administration of Avastin was not allowed until at least 28 days after surgery. In a controlled
123 clinical trial, the incidence of wound healing complications, including serious and fatal
124 complications, in patients with mCRC who underwent surgery during the course of Avastin
125 treatment was 15% and in patients who did not receive Avastin, was 4%. [See *Adverse Reactions*
126 (6.1).]

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

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

134 **5.3 Hemorrhage**

135 Avastin can result in two distinct patterns of bleeding: minor hemorrhage, most commonly
136 Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal
137 hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage,
138 epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin
139 compared to patients receiving only chemotherapy. Across indications, the incidence of Grade ≥ 3
140 hemorrhagic events among patients receiving Avastin ranged from 1.2 to 4.6%. [See *Adverse*
141 *Reactions* (6.1).]

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

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

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

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

154 **5.4 Non-Gastrointestinal Fistula Formation**

155 Serious and sometimes fatal non-gastrointestinal fistula formation involving tracheo-esophageal,
156 bronchopleural, biliary, vaginal, renal and bladder sites occurs at a higher incidence in
157 Avastin-treated patients compared to controls. The incidence of non-gastrointestinal perforation was
158 $\leq 0.3\%$ in clinical studies. Most events occurred within the first 6 months of Avastin therapy.

159 Discontinue Avastin in patients with fistula formation involving an internal organ. [See *Dosage*
160 *and Administration (2.4).*]

161 **5.5 Arterial Thromboembolic Events**

162 Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction,
163 transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a
164 higher incidence in patients receiving Avastin compared to those in the control arm. Across
165 indications, the incidence of Grade ≥ 3 ATE in the Avastin containing arms was 2.4% compared to
166 0.7% in the control arms. Among patients receiving Avastin in combination with chemotherapy, the
167 risk of developing ATE during therapy was increased in patients with a history of arterial
168 thromboembolism, or age greater than 65 years. [See *Use in Specific Populations (8.5).*]

169 The safety of resumption of Avastin therapy after resolution of an ATE has not been studied.
170 Discontinue Avastin in patients who experience a severe ATE. [See *Dosage and Administration*
171 *(2.4).*]

172 **5.6 Hypertension**

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

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

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

182 **5.7 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**

183 RPLS has been reported with an incidence of $<0.1\%$ in clinical studies. The onset of symptoms
184 occurred from 16 hours to 1 year after initiation of Avastin. RPLS is a neurological disorder which
185 can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic
186 disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging (MRI) is
187 necessary to confirm the diagnosis of RPLS.

188 Discontinue Avastin in patients developing RPLS. Symptoms usually resolve or improve within
189 days, although some patients have experienced ongoing neurologic sequelae. The safety of

190 reinitiating Avastin therapy in patients previously experiencing RPLS is not known. [See *Dosage*
191 *and Administration (2.4).*]

192 **5.8 Proteinuria**

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

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

200 Suspend Avastin administration for ≥ 2 grams of proteinuria/24 hours and resume when
201 proteinuria is < 2 gm/24 hours. Discontinue Avastin in patients with nephrotic syndrome. Data from
202 a postmarketing safety study showed poor correlation between UPCR (Urine Protein/Creatinine
203 Ratio) and 24 hour urine protein (Pearson Correlation 0.39 (95% CI 0.17, 0.57)). [See *Use in Specific*
204 *Populations (8.5).*] The safety of continued Avastin treatment in patients with moderate to severe
205 proteinuria has not been evaluated. [See *Dosage and Administration (2.4).*]

206 **5.9 Infusion Reactions**

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

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

214 **5.10 Ovarian Failure**

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

220 **6 ADVERSE REACTIONS**

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

- 223 • Gastrointestinal Perforations [See *Boxed Warning, Dosage and Administration (2.4), Warnings*
224 *and Precautions (5.1).*]
- 225 • Surgery and Wound Healing Complications [See *Boxed Warning, Dosage and Administration*
226 *(2.4), Warnings and Precautions (5.2).*]
- 227 • Hemorrhage [See *Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions*
228 *(5.3).*]
- 229 • Non-Gastrointestinal Fistula Formation [See *Dosage and Administration (2.4), Warnings and*
230 *Precautions (5.4).*]
- 231 • Arterial Thromboembolic Events [See *Dosage and Administration (2.4), Warnings and*
232 *Precautions (5.5).*]
- 233 • Hypertensive Crisis [See *Dosage and Administration (2.4), Warnings and Precautions (5.6).*]
- 234 • Reversible Posterior Leukoencephalopathy Syndrome [See *Dosage and Administration (2.4),*
235 *Warnings and Precautions (5.7).*]
- 236 • Proteinuria [See *Dosage and Administration (2.4), Warnings and Precautions (5.8).*]
- 237 • Ovarian Failure [See *Warnings and Precautions (5.10), Use in Specific Populations (8.6).*]

238

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

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

244 **6.1 Clinical Trial Experience**

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

248 The data below reflect exposure to Avastin in 4024 patients with CRC, non-squamous NSCLC,
249 MBC, glioblastoma, or mRCC trials including controlled (Studies 1, 2, 4, 5, 6 and 9) or
250 uncontrolled, single arm (Study 7) treated at the recommended dose and schedule for a median of 8
251 to 23 doses of Avastin. [See *Clinical Studies (14)*.] The population was aged 18-88 years (median
252 59), 41% male and 85.1% white. The population included 1783 first- and second-line mCRC
253 patients who received a median of 10 doses of Avastin, 669 female adjuvant CRC patients who
254 received a median of 23 doses of Avastin, 480 first-line metastatic NSCLC patients who received a
255 median of 8 doses of Avastin, 592 MBC patients who had not received chemotherapy for metastatic
256 disease received a median of 8 doses of Avastin, 163 glioblastoma patients who received a median
257 of 9 doses of Avastin, and 337 mRCC patients who received a median of 16 doses of Avastin.

258 *Surgery and Wound Healing Complications*

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

264 In Study 7, events of post-operative wound healing complications (craniotomy site wound
265 dehiscence and cerebrospinal fluid leak) occurred in patients with previously treated glioblastoma:
266 3/84 patients in the Avastin alone arm and 1/79 patients in the Avastin plus irinotecan arm. [See
267 *Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.2)*.]

268 *Hemorrhage*

269 The incidence of epistaxis was higher (35% vs. 10%) in patients with mCRC receiving bolus-IFL
270 plus Avastin compared with patients receiving bolus-IFL plus placebo. All but one of these events
271 were Grade 1 in severity and resolved without medical intervention. Grade 1 or 2 hemorrhagic
272 events were more frequent in patients receiving bolus-IFL plus Avastin when compared to those
273 receiving bolus-IFL plus placebo and included gastrointestinal hemorrhage (24% vs. 6%), minor
274 gum bleeding (2% vs. 0), and vaginal hemorrhage (4% vs. 2%). [See *Boxed Warning, Dosage and*
275 *Administration (2.4), Warnings and Precautions (5.3)*.]

276 *Venous Thromboembolic Events*

277 The overall incidence of Grade 3–4 venous thromboembolic events in Study 1 was 15.1% in
278 patients receiving bolus-IFL plus Avastin and 13.6% in patients receiving bolus-IFL plus placebo.
279 In Study 1, more patients in the Avastin containing arm experienced deep venous thrombosis (34 vs.
280 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

281 The risk of developing a second thromboembolic event while on Avastin and oral anticoagulants
282 was evaluated in two randomized studies. In Study 1, 53 patients (14%) on the bolus-IFL plus
283 Avastin arm and 30 patients (8%) on the bolus-IFL plus placebo arm received full dose warfarin
284 following a venous thromboembolic event (VTE). Among these patients, an additional
285 thromboembolic event occurred in 21% (11/53) of patients receiving bolus-IFL plus Avastin and 3%
286 (1/30) of patients receiving bolus-IFL alone.

287 In a second, randomized, 4-arm study in 1401 patients with mCRC, prospectively evaluating the
288 incidence of VTE (all grades), the overall incidence of first VTE was higher in the Avastin
289 containing arms (13.5%) than the chemotherapy alone arms (9.6%). Among the 116 patients treated
290 with anticoagulants following an initial VTE event (73 in the Avastin plus chemotherapy arms and
291 43 in the chemotherapy alone arms), the overall incidence of subsequent VTEs was also higher
292 among the Avastin treated patients (31.5% vs. 25.6%). In this subgroup of patients treated with
293 anticoagulants, the overall incidence of bleeding, the majority of which were Grade 1, was higher in
294 the Avastin treated arms than the chemotherapy arms (27.4% vs. 20.9%). [See *Dosage and*
295 *Administration (2.4), Warnings and Precautions (5.6).*]

296 *Neutropenia and Infection*

297 The incidences of neutropenia and febrile neutropenia are increased in patients receiving Avastin
298 plus chemotherapy compared to chemotherapy alone. In Study 1, the incidence of Grade 3 or 4
299 neutropenia was increased in mCRC patients receiving IFL plus Avastin (21%) compared to patients
300 receiving IFL alone (14%). In Study 4, the incidence of Grade 4 neutropenia was increased in
301 NSCLC patients receiving paclitaxel/carboplatin (PC) plus Avastin (26.2%) compared with patients
302 receiving PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC plus Avastin vs.
303 1.8% for PC alone). There were 19 (4.5%) infections with Grade 3 or 4 neutropenia in the PC plus
304 Avastin arm of which 3 were fatal compared to 9 (2%) neutropenic infections in patients receiving
305 PC alone, of which none were fatal. During the first 6 cycles of treatment, the incidence of serious
306 infections including pneumonia, febrile neutropenia, catheter infections and wound infections was
307 increased in the PC plus Avastin arm [58 patients (13.6%)] compared to the PC alone arm
308 [29 patients (6.6%)].

309 In Study 7, one fatal event of neutropenic infection occurred in a patient with previously treated
310 glioblastoma receiving Avastin alone. The incidence of any grade of infection in patients receiving
311 Avastin alone was 55% and the incidence of Grade 3-5 infection was 10%.

312 *Proteinuria*

313 Grade 3-4 proteinuria ranged from 0.7 to 7.4% in Studies 1, 2, 4 and 9. The overall incidence of
314 proteinuria (all grades) was only adequately assessed in Study 9, in which the incidence was 20%.
315 Median onset of proteinuria was 5.6 months (range 15 days to 37 months) after initiation of Avastin.
316 Median time to resolution was 6.1 months (95% CI 2.8 months, 11.3 months). Proteinuria did not
317 resolve in 40% of patients after median follow up of 11.2 months and required permanent
318 discontinuation of Avastin in 30% of the patients who developed proteinuria (Study 9). [See
319 *Warnings and Precautions (5.8).*]

320 *Congestive Heart Failure*

321 The incidence of Grade ≥ 3 left ventricular dysfunction was 1.0% in patients receiving Avastin
322 compared to 0.6% in the control arm across indications. In patients with MBC, the incidence of
323 Grade 3-4 congestive heart failure (CHF) was increased in patients in the Avastin plus paclitaxel arm
324 (2.2%) as compared to the control arm (0.3%). Among patients receiving prior anthracyclines for
325 MBC, the rate of CHF was 3.8% for patients receiving Avastin as compared to 0.6% for patients
326 receiving paclitaxel alone. The safety of continuation or resumption of Avastin in patients with
327 cardiac dysfunction has not been studied.

328 *Ovarian Failure*

329 The incidence of new cases of ovarian failure (defined as amenorrhoea lasting 3 or more months,
330 FSH level ≥ 30 mIU/mL and a negative serum β -HCG pregnancy test) was prospectively evaluated in
331 a subset of 179 women receiving mFOLFOX chemotherapy alone (n= 84 or with Avastin (n=95).
332 New cases of ovarian failure were identified in 34% (32/95) of women receiving Avastin in
333 combination with chemotherapy compared with 2% (2/84) of women receiving chemotherapy alone
334 [relative risk of 14 (95% CI 4, 53)]. After discontinuation of Avastin treatment, recovery of ovarian

335 function at all time points during the post-treatment period was demonstrated in 22% (7/32) of the
 336 Avastin-treated women. Recovery of ovarian function is defined as resumption of menses, a positive
 337 serum β -HCG pregnancy test, or a FSH level < 30 mIU/mL during the post-treatment period. Long
 338 term effects of Avastin exposure on fertility are unknown. [See *Warnings and Precautions (5.10)*,
 339 *Use in Specific Populations (8.6)*.]

340 *Metastatic Colorectal Cancer (mCRC)*

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

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

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

348
 349 Grade 1–4 adverse events which occurred at a higher incidence ($\geq 5\%$) in patients receiving
 350 bolus-IFL plus Avastin as compared to the bolus-IFL plus placebo arm are presented in Table 2.
 351 Grade 1–4 adverse events were collected for the first approximately 100 patients in each of the three
 352 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/LY+Avastin (n=109)
<u>Special Senses</u>			
Taste Disorder	9%	14%	21%
<u>Urogenital</u>			
Proteinuria	24%	36%	36%

354

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

356 Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events related to treatment
 357 were collected in Study 2. The most frequent adverse events (selected Grade 3-5 non-hematologic
 358 and Grade 4-5 hematologic adverse events) occurring at a higher incidence ($\geq 2\%$) in 287 patients
 359 receiving FOLFOX4 plus Avastin compared to 285 patients receiving FOLFOX4 alone were fatigue
 360 (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%),
 361 vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8%
 362 vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache
 363 (3% vs. 0%). These data are likely to under-estimate the true adverse event rates due to the reporting
 364 mechanisms used in Study 2.

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

366 Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected in
 367 Study 4. Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events (occurring at a
 368 higher incidence ($\geq 2\%$) in 427 patients receiving PC plus Avastin compared with 441 patients
 369 receiving PC alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs.
 370 0.7%), infection without neutropenia (7% vs. 3%), venous thrombus/embolism (5% vs. 3%), febrile
 371 neutropenia (5% vs. 2%), pneumonitis/pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or
 372 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3%
 373 vs. 0%).

374 *Metastatic Breast Cancer (MBC)*

375 Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected in
 376 Study 5. Grade 3-4 adverse events occurring at a higher incidence ($\geq 2\%$) in 363 patients receiving
 377 paclitaxel plus Avastin compared with 348 patients receiving paclitaxel alone were sensory
 378 neuropathy (24% vs. 18%), hypertension (16% vs. 1%), fatigue (11% vs. 5%), infection without
 379 neutropenia (9% vs. 5%), neutrophils (6% vs. 3%), vomiting (6% vs. 2%), diarrhea (5% vs. 1%),
 380 bone pain (4% vs. 2%), headache (4% vs. 1%), nausea (4% vs. 1%), cerebrovascular ischemia (3%
 381 vs. 0%), dehydration (3% vs. 1%), infection with unknown ANC (3% vs. 0.3%), rash/desquamation
 382 (3% vs. 0.3%) and proteinuria (3% vs. 0%).

383 Sensory neuropathy, hypertension, and fatigue were reported at a $\geq 5\%$ higher absolute incidence
 384 in the paclitaxel plus Avastin arm compared with the paclitaxel alone arm.

385 Fatal adverse reactions occurred in 6/363 (1.7%) of patients who received paclitaxel plus Avastin.
 386 Causes of death were gastrointestinal perforation (2), myocardial infarction (2), diarrhea/abdominal,
 387 and pain/weakness/hypotension (2).

388 Avastin is not approved for use in combination with capecitabine or for use in second or third line
 389 treatment of MBC. The data below are presented to provide information on the overall safety profile
 390 of Avastin in women with breast cancer since Study 6 is the only randomized, controlled study in
 391 which all adverse events were collected for all patients. All patients in Study 6 received prior
 392 anthracycline and taxane therapy in the adjuvant setting or for metastatic disease. Grade 1–4 events
 393 which occurred at a higher incidence ($\geq 5\%$) in patients receiving capecitabine plus Avastin
 394 compared to the capecitabine alone arm are presented in Table 3.
 395

Table 3
 NCI-CTC Grade 1–4 Adverse Events in Study 6 (Occurring at Higher
 Incidence [$\geq 5\%$] in Capecitabine + Avastin vs. Capecitabine Alone)

	Capecitabine (n=215)	Capecitabine+Avastin (n=229)
<u>Body as a Whole</u>		
Asthenia	47%	57%
Headache	13%	33%
Pain	25%	31%
<u>Cardiovascular</u>		
Hypertension	2%	24%
<u>Digestive</u>		
Stomatitis	19%	25%
<u>Metabolic/Nutrition</u>		
Weight loss	4%	9%
<u>Musculoskeletal</u>		
Myalgia	8%	14%
<u>Respiratory</u>		
Dyspnea	18%	27%
Epistaxis	1%	16%
<u>Skin/Appendages</u>		
Exfoliative dermatitis	75%	84%
<u>Urogenital</u>		
Albuminuria	7%	22%

396

397 *Glioblastoma*

398 All adverse events were collected in 163 patients enrolled in Study 7 who either received Avastin
 399 alone or Avastin plus irinotecan. All patients received prior radiotherapy and temozolomide.
 400 Avastin was administered at 10 mg/kg every 2 weeks alone or in combination with irinotecan.
 401 Avastin was discontinued due to adverse events in 4.8% of patients treated with Avastin alone.

402 In patients receiving Avastin alone (N=84), the most frequently reported adverse events of any
 403 grade were infection (55%), fatigue (45%), headache (37%), hypertension (30%), epistaxis (19%)
 404 and diarrhea (21%). Of these, the incidence of Grade ≥ 3 adverse events was infection (10%), fatigue
 405 (4%), headache (4%), hypertension (8%) and diarrhea (1%). Two deaths on study were possibly
 406 related to Avastin: one retroperitoneal hemorrhage and one neutropenic infection.

407 In patients receiving Avastin alone or Avastin plus irinotecan (N=163), the incidence of
408 Avastin-related adverse events (Grade 1–4) were bleeding/hemorrhage (40%), epistaxis (26%), CNS
409 hemorrhage (5%), hypertension (32%), venous thromboembolic event (8%), arterial thromboembolic
410 event (6%), wound-healing complications (6%), proteinuria (4%), gastrointestinal perforation (2%),
411 and RPLS (1%). The incidence of Grade 3–5 events in these 163 patients were bleeding/hemorrhage
412 (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic event (7%), arterial
413 thromboembolic event (3%), wound-healing complications (3%), proteinuria (1%), and
414 gastrointestinal perforation (2%).

415 *Metastatic Renal Cell Carcinoma (mRCC)*

416 All grade adverse events were collected in Study 9. Grade 3–5 adverse events occurring at a
417 higher incidence ($\geq 2\%$) in 337 patients receiving interferon alfa (IFN- α) plus Avastin compared to
418 304 patients receiving IFN- α plus placebo arm were fatigue (13% vs. 8%), asthenia (10% vs. 7%),
419 proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis),
420 and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured,
421 gastric ulcer hemorrhage, gingival bleeding, haemoptysis, hemorrhage intracranial, large intestinal
422 hemorrhage, respiratory tract hemorrhage, and traumatic hematoma).

423 Grade 1–5 adverse events occurring at a higher incidence ($\geq 5\%$) in patients receiving IFN- α plus
424 Avastin compared to the IFN- α plus placebo arm are presented in Table 4.

Table 4
 NCI-CTC Grades 1–5 Adverse Events in Study 9 (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 4: 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).

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Avastin has not been adequately determined because the assay sensitivity was inadequate to reliably detect lower titers. Enzyme-linked immunosorbent assays (ELISAs) were performed on sera from approximately 500 patients treated with Avastin, primarily in combination with chemotherapy. High titer human anti-Avastin antibodies were not detected.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and

441 underlying disease. For these reasons, comparison of the incidence of antibodies to Avastin with the
442 incidence of antibodies to other products may be misleading.

443 **6.3 Postmarketing Experience**

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

447 *Body as a Whole:* Polyserositis

448 *Cardiovascular:* Pulmonary hypertension, RPLS, Mesenteric venous occlusion

449 *Eye disorders (reported from unapproved use for treatment of various ocular disorders):*

450 Endophthalmitis; Intraocular inflammation such as iritis and vitritis; Retinal detachment; Other
451 retinal disorders; Increased intraocular pressure; Hemorrhage following intraocular injection
452 including conjunctival, vitreous hemorrhage or retinal hemorrhage; Vitreous floaters; Visual
453 disturbances; Ocular hyperemia; Ocular pain and/or discomfort

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

455 *Hemic and lymphatic:* Pancytopenia

456 *Musculoskeletal:* Osteonecrosis of the jaw

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

458 *Respiratory:* Nasal septum perforation, dysphonia

459 **7 DRUG INTERACTIONS**

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

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

469 In Study 9, there was no difference in the mean exposure of interferon alfa administered in
470 combination with Avastin when compared to interferon alfa alone.

471 **8 USE IN SPECIFIC POPULATIONS**

472 **8.1 Pregnancy**

473 *Pregnancy Category C*

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

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

484 **8.3 Nursing Mothers**

485 It is not known whether Avastin is secreted in human milk. Human IgG is excreted in human
486 milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant
487 circulation in substantial amounts. Because many drugs are secreted in human milk and because of

488 the potential for serious adverse reactions in nursing infants from bevacizumab, a decision should be
489 made whether to discontinue nursing or discontinue drug, taking into account the half-life of the
490 bevacizumab (approximately 20 days [range 11–50 days]) and the importance of the drug to the
491 mother. [See *Clinical Pharmacology* (12.3).]

492 **8.4 Pediatric Use**

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

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

498 Juvenile cynomolgus monkeys with open growth plates exhibited physeal dysplasia following 4 to
499 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure).
500 The incidence and severity of physeal dysplasia were dose-related and were partially reversible upon
501 cessation of treatment.

502 **8.5 Geriatric Use**

503 In Study 1, severe adverse events that occurred at a higher incidence ($\geq 2\%$) in patients aged
504 ≥ 65 years as compared to younger patients were asthenia, sepsis, deep thrombophlebitis,
505 hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhea, constipation,
506 anorexia, leukopenia, anemia, dehydration, hypokalemia, and hyponatremia. The effect of Avastin
507 on overall survival was similar in elderly patients as compared to younger patients.

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

510 In Study 4, patients aged ≥ 65 years receiving carboplatin, paclitaxel, and Avastin had a greater
511 relative risk for proteinuria as compared to younger patients. [See *Warnings and Precautions* (5.8).]

512 In Study 5, there were insufficient numbers of patients ≥ 65 years old to determine whether the
513 overall adverse events profile was different in the elderly as compared with younger patients.

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

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

526 **8.6 Females of Reproductive Potential**

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

530 In a prospectively designed substudy of 179 premenopausal women randomized to receive
531 chemotherapy with or without Avastin, the incidence of ovarian failure was higher in the Avastin
532 arm (34%) compared to the control arm (2%). After discontinuation of Avastin and chemotherapy,
533 recovery of ovarian function occurred in 22% (7/32) of these Avastin-treated patients. [See
534 *Warnings and Precautions* (5.10), *Adverse Reactions* (6.1).]

535

536 **10 OVERDOSAGE**

537 The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of
538 16 patients and with severe headache in three of 16 patients.

539

540 **11 DESCRIPTION**

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

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

556

557 **12 CLINICAL PHARMACOLOGY**

558 **12.1 Mechanism of Action**

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

564 **12.3 Pharmacokinetics**

565 The pharmacokinetic profile of bevacizumab was assessed using an assay that measures total
566 serum bevacizumab concentrations (i.e., the assay did not distinguish between free bevacizumab and
567 bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of
568 491 patients who received 1 to 20 mg/kg of Avastin weekly, every 2 weeks, or every 3 weeks, the
569 estimated half-life of bevacizumab was approximately 20 days (range 11–50 days). The predicted
570 time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg of
571 bevacizumab every 2 weeks was 2.8.

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

580

581 **13 NONCLINICAL TOXICOLOGY**

582 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

593 **13.2 Animal Toxicology and/or Pharmacology**

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

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

605 **13.3 Reproductive and Developmental Toxicology**

606 Pregnant rabbits dosed with 1 to 12 times the human dose of bevacizumab every three days during
607 the period of organogenesis (gestation day 6-18) exhibited teratogenic effects, decreases in maternal
608 and fetal body weights, and increased number of fetal resorptions. Teratogenic effects included:
609 reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws;
610 meningocele; fontanel, rib and hindlimb deformities; corneal opacity; and absent hindlimb
611 phalanges. There are no data available regarding the level of bevacizumab exposure in the offspring.
612

613 **14 CLINICAL STUDIES**

614 **14.1 Metastatic Colorectal Cancer (mCRC)**

615 *Study 1*

616 In this double-blind, active-controlled study, patients were randomized (1:1:1) to IV bolus-IFL
617 (irinotecan 125 mg/m², 5-FU 500 mg/m², and leucovorin (LV) 20 mg/m² given once weekly for
618 4 weeks every 6 weeks) plus placebo (Arm 1), bolus-IFL plus Avastin (5 mg/kg every 2 weeks)
619 (Arm 2), or 5-FU/LV plus Avastin (5 mg/kg every 2 weeks) (Arm 3). Enrollment in Arm 3 was
620 discontinued, as pre-specified, when the toxicity of Avastin in combination with the bolus-IFL
621 regimen was deemed acceptable. The main outcome measure was overall survival (OS).

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

626 The addition of Avastin resulted in an improvement in survival across subgroups defined by age
627 (< 65 yrs, ≥ 65 yrs) and gender. Results are presented in Table 5 and Figure 1.

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.

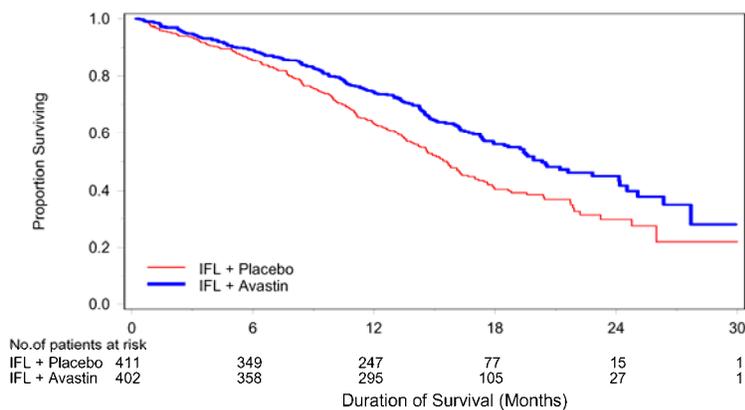
^b p<0.01 by χ^2 test.

628

629

630

Figure 1
Duration of Survival in Study 1



631

632

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

636 *Study 2*

637 Study 2 was a randomized, open-label, active-controlled trial in patients who were previously
638 treated with irinotecan ± 5-FU for initial therapy for metastatic disease or as adjuvant therapy.
639 Patients were randomized (1:1:1) to IV FOLFOX4 (Day 1: oxaliplatin 85 mg/m² and LV 200 mg/m²
640 concurrently, then 5-FU 400 mg/m² bolus followed by 600 mg/m² continuously; Day 2: LV
641 200 mg/m², then 5-FU 400 mg/m² bolus followed by 600 mg/m² continuously; repeated every

642 2 weeks), FOLFOX4 plus Avastin (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1), or
643 Avastin monotherapy(10 mg/kg every 2 weeks). The main outcome measure was OS.

644 The Avastin monotherapy arm was closed to accrual after enrollment of 244 of the planned
645 290 patients following a planned interim analysis by the data monitoring committee based on
646 evidence of decreased survival compared to FOLFOX4 alone.

647 Of the 829 patients randomized to the three arms, the median age was 61 years, 40% were female,
648 87% were Caucasian, 49% had an ECOG performance status of 0, 26% received prior radiation
649 therapy, and 80% received prior adjuvant chemotherapy, 99% received prior irinotecan, with or
650 without 5-FU as therapy for metastatic disease, and 1% received prior irinotecan and 5-FU as
651 adjuvant therapy.

652 The addition of Avastin to FOLFOX4 resulted in significantly longer survival as compared to
653 FOLFOX4 alone (median OS 13.0 months vs. 10.8 months; hazard ratio 0.75 [95% CI 0.63, 0.89],
654 $p=0.001$ stratified log rank test) with clinical benefit seen in subgroups defined by age (<65 yrs,
655 ≥ 65 yrs) and gender. PFS and ORR based on investigator assessment were higher in the Avastin
656 plus FOLFOX4 arm.

657 *Study 3*

658 The activity of Avastin in combination with bolus or infusional 5-FU/LV was evaluated in a
659 single arm study enrolling 339 patients with mCRC with disease progression following both
660 irinotecan- and oxaliplatin-containing chemotherapy regimens. Seventy-three percent of patients
661 received concurrent bolus 5-FU/LV. One objective partial response was verified in the first
662 100 evaluable patients for an overall response rate of 1% (95% CI 0–5.5%).

663 **14.2 Unresectable Non–Squamous Non–Small Cell Lung Cancer (NSCLC)**

664 *Study 4*

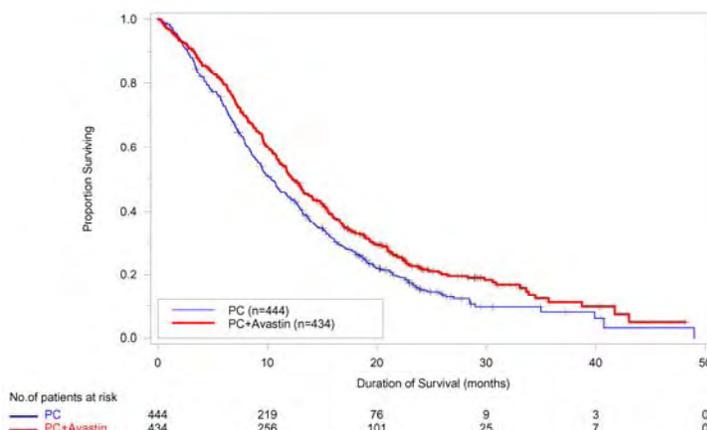
665 The safety and efficacy of Avastin as first-line treatment of patients with locally advanced,
666 metastatic, or recurrent non–squamous NSCLC was studied in a single, large, randomized,
667 active-controlled, open-label, multicenter study.

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

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

681 The results are presented in Figure 2. OS was statistically significantly higher among patients
682 receiving PC plus Avastin compared with those receiving PC alone; median OS was 12.3 months vs.
683 10.3 months [hazard ratio 0.80 (repeated 95% CI 0.68, 0.94), final p- value 0.013, stratified log-rank
684 test]. Based on investigator assessment which was not independently verified, patients were
685 reported to have longer PFS with Avastin in combination with PC compared to PC alone.

Figure 2
Duration of Survival in Study 4



688

689 In an exploratory analyses across patient subgroups, the impact of Avastin on OS was less robust
690 in the following: women [HR = 0.99 (95% CI: 0.79, 1.25)], age \geq 65 years [HR = 0.91 (95% CI:
691 0.72, 1.14)] and patients with \geq 5% weight loss at study entry [HR = 0.96 (95% CI: 0.73, 1.26)].

692 The safety and efficacy of Avastin in patients with locally advanced, metastatic or recurrent
693 non-squamous NSCLC, who had not received prior chemotherapy was studied in another
694 randomized, double-blind, placebo controlled, three-arm study of Avastin in combination with
695 cisplatin and gemcitabine (CG) versus placebo and CG. A total of 1043 patients were randomized
696 1:1:1 to receive placebo plus CG, Avastin 7.5 mg/kg plus CG or Avastin 15.0 mg/kg plus CG. The
697 median age was 58 years, 36% were female, and 29% were \geq age 65. Eight percent had recurrent
698 disease and 77% had Stage IV disease. Progression-free survival, the main efficacy outcome
699 measure, was significantly higher in both Avastin containing arms compared to the placebo arm [HR
700 0.75 (95% CI 0.62, 0.91), $p=0.0026$ for the Avastin 7.5 mg/kg plus CG arm and HR 0.82 (95% CI
701 0.68; 0.98), $p=0.0301$ for the Avastin 15.0 mg/kg plus CG arm]. The addition of Avastin to CG
702 chemotherapy failed to demonstrate an improvement in the duration of overall survival, an additional
703 efficacy outcome measure, [HR 0.93 (95% CI 0.78; 1.11), $p=0.4203$ for the Avastin 7.5 mg/kg plus
704 CG arm and HR 1.03 (95% CI 0.86; 1.23), $p=0.7613$ for the Avastin 15.0 mg/kg plus CG arm].

705

706 14.3 Metastatic Breast Cancer (MBC)

707 Study 5

708 The efficacy and safety of Avastin as first-line treatment of patients with MBC was studied in a
709 single, open-label, randomized, multicenter study. Patients who had not received chemotherapy for
710 locally recurrent or MBC were randomized (1:1) to receive paclitaxel (90 mg/m² IV once weekly for
711 3 out of 4 weeks) alone or in combination with Avastin (10 mg/kg IV infusion every 2 weeks).
712 Patients were treated until disease progression or unacceptable toxicity. In situations where
713 paclitaxel was discontinued or held, treatment with Avastin alone could be continued until disease
714 progression. Patients with breast cancer overexpressing HER2 were not eligible unless they had
715 received prior therapy with trastuzumab.

716 Prior hormonal therapy for the treatment of metastatic disease was allowed, as was prior adjuvant
717 chemotherapy or hormonal therapy. Adjuvant taxane therapy, if received, must have been
718 completed 12 or more months prior to study entry. Patients with central nervous system metastasis
719 were excluded. The main outcome measure of the study was PFS as assessed by independent
720 radiographic review. Secondary outcome measures were OS and ORR.

721 Of the 722 patients randomized, the median age was 55 years, 76% were white, 55% were
 722 postmenopausal, and 64% were ER and/or PR positive. Patient characteristics were similar across
 723 treatment arms. Thirty-six percent had received prior hormonal therapy for advanced disease, and
 724 66% had received adjuvant chemotherapy, including 20% with prior taxane use and 50% with prior
 725 anthracycline use. Efficacy results are summarized in Table 6.

Table 6
 Avastin Efficacy Results from Study 5

Efficacy Parameter	Avastin + Paclitaxel (n=368)	Paclitaxel Alone (n=354)	p-value	HR (95% CI)
<u>Progression-free Survival</u>	11.3	5.8		0.48
[median, months (95% CI)]	(10.5, 13.3)	(5.4, 8.2)	<0.0001	(0.39, 0.61)
<u>Overall Survival</u>	26.5	24.8		0.87
[median, months (95% CI)]	(23.7, 29.2)	(21.4, 27.4)	0.14	(0.72, 1.05)
Partial Response Rate ^a (PR)	48.9% ^b	22.2%	<0.001	—

^a Includes only patients with measurable disease.

^b The difference in partial response rates is 26.7% with a 95% CI (18.4%, 35.0%).

726

727 The addition of Avastin to paclitaxel resulted in an improvement in PFS with no significant
 728 improvement in OS. Partial response rates in patients with measurable disease were higher with
 729 Avastin plus paclitaxel. No complete responses were observed.

730 Thirty-four percent of the patients had incomplete follow-up for disease progression; therefore an
 731 exploratory analysis using similar imputation between arms was performed, which yielded a hazard
 732 ratio of 0.57.

733 *Study 6*

734 The efficacy and safety of Avastin as second- and third-line treatment of patients with MBC was
 735 studied in a single open-label randomized study. Patients who had received prior anthracycline and
 736 taxane therapy in the adjuvant setting or for their MBC were randomized (1:1) to receive
 737 capecitabine alone or in combination with Avastin. Of the 462 enrolled patients, the median age was
 738 51 years, 81% were white, and 50% were ER positive. Patient characteristics were similar across the
 739 treatment arms.

740 The study failed to demonstrate a statistically significant effect on PFS or OS. The median PFS
 741 was 4.2 months in the capecitabine arm and 4.9 months in the capecitabine plus Avastin arm
 742 (log-rank p-value = 0.86, hazard ratio 0.98). The median OS was 14.5 months in the capecitabine
 743 arm and 15.1 months in the capecitabine plus Avastin arm (hazard ratio of 1.08).

744 **14.4 Glioblastoma**

745 *Study 7*

746 The efficacy and safety of Avastin was evaluated in Study 7, an open-label, multicenter,
 747 randomized, non-comparative study of patients with previously treated glioblastoma. Patients
 748 received Avastin (10 mg/kg IV) alone or Avastin plus irinotecan every 2 weeks until disease
 749 progression or until unacceptable toxicity. All patients received prior radiotherapy (completed at
 750 least 8 weeks prior to receiving Avastin) and temozolomide. Patients with active brain hemorrhage
 751 were excluded.

752 Of the 85 patients randomized to the Avastin arm, the median age was 54 years, 32% were
 753 female, 81% were in first relapse, Karnofsky performance status was 90–100 for 45% and 70–80 for
 754 55%.

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

760 *Study 8*

761 Study 8, was a single-arm, single institution trial with 56 patients with glioblastoma. All patients
762 had documented disease progression after receiving temozolomide and radiation therapy. Patients
763 received Avastin 10 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity.

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

766 The efficacy of Avastin was supported by an objective response rate of 19.6% (95% CI 10.9%,
767 31.3%) using the same response criteria as in Study 7. Median duration of response was 3.9 months
768 (95% CI 2.4, 17.4).

769 **14.5 Metastatic Renal Cell Carcinoma (mRCC)**

770 *Study 9*

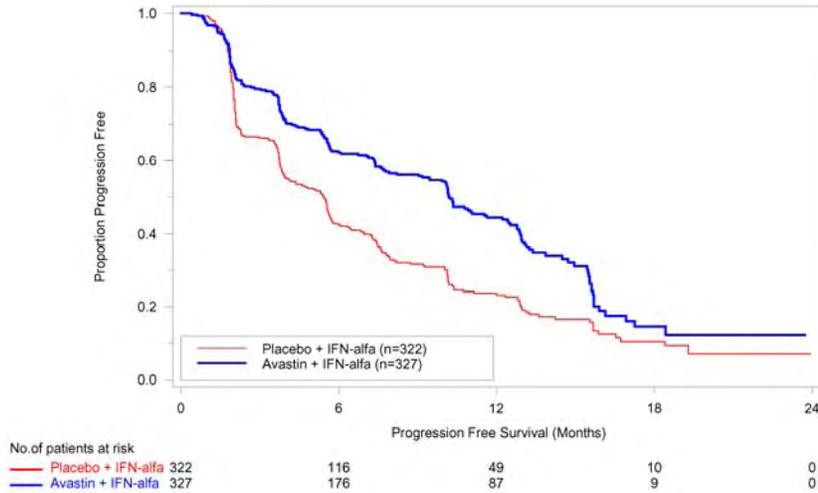
771 Patients with treatment-naïve mRCC were evaluated in a multicenter, randomized, double-blind,
772 international study comparing Avastin plus interferon alfa 2a (IFN- α 2a) versus placebo plus
773 IFN- α 2a. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to
774 receive either Avastin (10 mg/kg IV infusion every 2 weeks; n=327) or placebo (IV every 2 weeks;
775 n=322) in combination with IFN- α 2a (9 MIU subcutaneously three times weekly, for a maximum of
776 52 weeks). Patients were treated until disease progression or unacceptable toxicity. The main
777 outcome measure of the study was investigator-assessed PFS. Secondary outcome measures were
778 ORR and OS.

779 The median age was 60 years (range 18–82), 96% were white, and 70% were male. The study
780 population was characterized by Motzer scores as follows: 28% favorable (0), 56% intermediate
781 (1-2), 8% poor (3-5), and 7% missing.

782 The results are presented in Figure 3. PFS was statistically significantly prolonged among
783 patients receiving Avastin plus IFN- α 2a compared to those receiving IFN- α 2a alone; median PFS
784 was 10.2 months vs. 5.4 months [HR 0.60 (95% CI 0.49, 0.72), p-value < 0.0001, stratified log-rank
785 test]. Among the 595 patients with measureable disease, ORR was also significantly higher (30%
786 vs. 12%, p < 0.0001, stratified CMH test). There was no improvement in OS based on the final
787 analysis conducted after 444 deaths, with a median OS of 23 months in the Avastin plus IFN- α 2a
788 arm and 21 months in the IFN- α 2a plus placebo arm [HR 0.86, (95% CI 0.72, 1.04)].

789
790

Figure 3
Progression-Free Survival in Study 9



791
792

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.

799

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.

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Avastin® (bevacizumab)

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

10133652
Initial U.S. Approval: February 2004
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