

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

Indications and Usage (1.1)	1/2013
Dosage and Administration (2.2)	1/2013
Warnings and Precautions, Surgery and Wound Healing Complications (5.2)	3/2013
Warnings and Precautions, Arterial Thromboembolic Events (5.5)	12/2013
Warnings and Precautions, Proteinuria (5.8)	12/2013

INDICATIONS AND USAGE

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

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

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: 12/2013

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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.**

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 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 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.

45 2 DOSAGE AND ADMINISTRATION

46 2.1 Administration

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

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

54 2.2 Recommended Doses and Schedules

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

56 *Metastatic Colorectal Cancer (mCRC)*

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

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

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

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

67 *Glioblastoma*

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

69 *Metastatic Renal Cell Carcinoma (mRCC)*

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

71 2.3 Preparation for Administration

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

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

78 2.4 Dose Modifications

79 There are no recommended dose reductions.

80 Discontinue Avastin for:

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

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

100 **3 DOSAGE FORMS AND STRENGTHS**

- 101 100 mg per 4 mL single-use vial
- 102 400 mg per 16 mL single-use vial

103

104 **4 CONTRAINDICATIONS**

105 None.

106

107 **5 WARNINGS AND PRECAUTIONS**

108 **5.1 Gastrointestinal Perforations**

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

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

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

117 **5.2 Surgery and Wound Healing Complications**

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

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

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

131 Necrotizing fasciitis including fatal cases, has been reported in patients treated with Avastin;
132 usually secondary to wound healing complications, gastrointestinal perforation or fistula formation.
133 Discontinue Avastin therapy in patients who develop necrotizing fasciitis. [See *Adverse Reactions*
134 *(6.3)*.]

135 **5.3 Hemorrhage**

136 Avastin can result in two distinct patterns of bleeding: minor hemorrhage, most commonly
137 Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal
138 hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage,
139 epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin
140 compared to patients receiving only chemotherapy. Across indications, the incidence of Grade ≥ 3

141 hemorrhagic events among patients receiving Avastin ranged from 1.2 to 4.6%. [See *Adverse*
142 *Reactions (6.1).*]

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

146 In clinical studies in non-small cell lung cancer where patients with CNS metastases who
147 completed radiation and surgery more than 4 weeks prior to the start of Avastin were evaluated with
148 serial CNS imaging, symptomatic Grade 2 CNS hemorrhage was documented in one of
149 83 Avastin-treated patients (rate 1.2%, 95% CI 0.06%–5.93%).

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

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

155 **5.4 Non-Gastrointestinal Fistula Formation**

156 Serious and sometimes fatal non-gastrointestinal fistula formation involving tracheo-esophageal,
157 bronchopleural, biliary, vaginal, renal and bladder sites occurs at a higher incidence in
158 Avastin-treated patients compared to controls. The incidence of non-gastrointestinal perforation was
159 $\leq 0.3\%$ in clinical studies. Most events occurred within the first 6 months of Avastin therapy.

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

162 **5.5 Arterial Thromboembolic Events**

163 Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction,
164 transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a
165 higher incidence in patients receiving Avastin compared to those in the control arm. Across
166 indications, the incidence of Grade ≥ 3 ATE in the Avastin containing arms was 2.6% compared to
167 0.8% in the control arms. Among patients receiving Avastin in combination with chemotherapy, the
168 risk of developing ATE during therapy was increased in patients with a history of arterial
169 thromboembolism, diabetes, or age greater than 65 years. [See *Use in Specific Populations (8.5).*]

170 The safety of resumption of Avastin therapy after resolution of an ATE has not been studied.
171 Discontinue Avastin in patients who experience a severe ATE. [See *Dosage and Administration*
172 *(2.4).*]

173 **5.6 Hypertension**

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

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

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

183 **5.7 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**

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

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

193 **5.8 Proteinuria**

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

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

201 Suspend Avastin administration for ≥ 2 grams of proteinuria/24 hours and resume when
202 proteinuria is <2 gm/24 hours. Discontinue Avastin in patients with nephrotic syndrome. [See
203 *Dosage and Administration* (2.4).] Data from a postmarketing safety study showed poor correlation
204 between UPCR (Urine Protein/Creatinine Ratio) and 24 hour urine protein (Pearson Correlation 0.39
205 (95% CI 0.17, 0.57). [See *Use in Specific Populations* (8.5).]

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

221 **6 ADVERSE REACTIONS**

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

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

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 4599 patients with CRC, non-squamous NSCLC,
249 glioblastoma, or mCRC trials including controlled (Studies 1, 2, 4, 5 and 8) or uncontrolled, single
250 arm (Study 6) treated at the recommended dose and schedule for a median of 8 to 23 doses of
251 Avastin. [See *Clinical Studies (14)*.] The population was aged 18-89 years (median 60 years),
252 45.4% male and 85.8% (3729/4345) White. The population included 2184 first- and second-line
253 mCRC patients who received a median of 10 doses of Avastin, 480 first-line metastatic NSCLC
254 patients who received a median of 8 doses of Avastin, 163 glioblastoma patients who received a
255 median of 9 doses of Avastin, and 337 mCRC patients who received a median of 16 doses of
256 Avastin. These data also reflect exposure to Avastin in 363 patients with metastatic breast cancer
257 (MBC) who received a median of 9.5 doses of Avastin, 669 female adjuvant CRC patients who
258 received a median of 23 doses of Avastin and exposure to Avastin in 403 previously untreated
259 patients with diffuse large B-cell lymphoma (DLBCL) who received a median of 8 doses of Avastin.
260 Avastin is not approved for use in MBC, adjuvant CRC, or DLBCL.

261 *Surgery and Wound Healing Complications*

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

267 In Study 6, events of post-operative wound healing complications (craniotomy site wound
268 dehiscence and cerebrospinal fluid leak) occurred in patients with previously treated glioblastoma:
269 3/84 patients in the Avastin alone arm and 1/79 patients in the Avastin plus irinotecan arm.
270 [See *Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.2)*.]

271 *Hemorrhage*

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

279 *Venous Thromboembolic Events*

280 The overall incidence of Grade 3–4 venous thromboembolic events in Study 1 was 15.1% in
281 patients receiving bolus-IFL plus Avastin and 13.6% in patients receiving bolus-IFL plus placebo.
282 In Study 1, more patients in the Avastin containing arm experienced deep venous thrombosis (34 vs.
283 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

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

288 thromboembolic event occurred in 21% (11/53) of patients receiving bolus-IFL plus Avastin and 3%
289 (1/30) of patients receiving bolus-IFL alone.

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

299 *Neutropenia and Infection*

300 The incidences of neutropenia and febrile neutropenia are increased in patients receiving Avastin
301 plus chemotherapy compared to chemotherapy alone. In Study 1, the incidence of Grade 3 or 4
302 neutropenia was increased in mCRC patients receiving IFL plus Avastin (21%) compared to patients
303 receiving IFL alone (14%). In Study 5, the incidence of Grade 4 neutropenia was increased in
304 NSCLC patients receiving paclitaxel/carboplatin (PC) plus Avastin (26.2%) compared with patients
305 receiving PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC plus Avastin vs.
306 1.8% for PC alone). There were 19 (4.5%) infections with Grade 3 or 4 neutropenia in the PC plus
307 Avastin arm of which 3 were fatal compared to 9 (2%) neutropenic infections in patients receiving
308 PC alone, of which none were fatal. During the first 6 cycles of treatment, the incidence of serious
309 infections including pneumonia, febrile neutropenia, catheter infections and wound infections was
310 increased in the PC plus Avastin arm [58 patients (13.6%)] compared to the PC alone arm
311 [29 patients (6.6%)].

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

315 *Proteinuria*

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

322 In an exploratory, pooled analysis of 8,273 patients treated in 7 randomized clinical trials, 5.4%
323 (271 of 5037) of patients receiving Avastin in combination with chemotherapy experienced
324 Grade ≥ 2 proteinuria. The Grade ≥ 2 proteinuria resolved in 74.2% (201 of 271) of patients.
325 Avastin was re-initiated in 41.7% (113 of 271) of patients. Of the 113 patients who re-initiated
326 Avastin, 47.8% (54 of 113) experienced a second episode of Grade ≥ 2 proteinuria. [See *Warnings*
327 *and Precautions (5.8).*]

328 *Congestive Heart Failure (CHF)*

329 The incidence of Grade ≥ 3 left ventricular dysfunction was 1.0% in patients receiving Avastin
330 compared to 0.6% in the control arm across indications. In patients with metastatic breast cancer
331 (MBC), an indication for which Avastin is not approved, the incidence of Grade 3–4 CHF was
332 increased in patients in the Avastin plus paclitaxel arm (2.2%) as compared to the control arm
333 (0.3%). Among patients receiving prior anthracyclines for MBC, the rate of CHF was 3.8% for
334 patients receiving Avastin as compared to 0.6% for patients receiving paclitaxel alone. The safety of
335 continuation or resumption of Avastin in patients with cardiac dysfunction has not been studied.

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

348 *Ovarian Failure*

349 The incidence of new cases of ovarian failure (defined as amenorrhoea lasting 3 or more months,
350 FSH level ≥ 30 mIU/mL and a negative serum β -HCG pregnancy test) was prospectively evaluated
351 in a subset of 179 women receiving mFOLFOX chemotherapy alone (n=84) or with Avastin
352 (n=95). New cases of ovarian failure were identified in 34% (32/95) of women receiving Avastin in
353 combination with chemotherapy compared with 2% (2/84) of women receiving chemotherapy alone
354 [relative risk of 14 (95% CI 4, 53)]. After discontinuation of Avastin treatment, recovery of ovarian
355 function at all time points during the post-treatment period was demonstrated in 22% (7/32) of the
356 Avastin-treated women. Recovery of ovarian function is defined as resumption of menses, a positive
357 serum β -HCG pregnancy test, or a FSH level < 30 mIU/mL during the post-treatment period. Long
358 term effects of Avastin exposure on fertility are unknown. [See *Warnings and Precautions (5.10)*,
359 *Use in Specific Populations (8.6)*.]

360 *Metastatic Colorectal Cancer (mCRC)*

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

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

368

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.

369

370 Grade 1–4 adverse events which occurred at a higher incidence ($\geq 5\%$) in patients receiving
 371 bolus-IFL plus Avastin as compared to the bolus-IFL plus placebo arm are presented in Table 2.
 372 Grade 1–4 adverse events were collected for the first approximately 100 patients in each of the three
 373 treatment arms who were enrolled until enrollment in Arm 3 (5-FU/LV + Avastin) was discontinued.
 374

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%

376

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

378 Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events related to treatment
 379 were collected in Study 2. The most frequent adverse events (selected Grade 3-5 non-hematologic
 380 and Grade 4-5 hematologic adverse events) occurring at a higher incidence ($\geq 2\%$) in 287 patients
 381 receiving FOLFOX4 plus Avastin compared to 285 patients receiving FOLFOX4 alone were fatigue
 382 (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%),
 383 vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8%
 384 vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache
 385 (3% vs. 0%). These data are likely to under-estimate the true adverse event rates due to the reporting
 386 mechanisms used in Study 2.

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

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

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

394 Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected in
 395 Study 5. Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events (occurring at a
 396 higher incidence ($\geq 2\%$) in 427 patients receiving PC plus Avastin compared with 441 patients
 397 receiving PC alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs.
 398 0.7%), infection without neutropenia (7% vs. 3%), venous thrombus/embolism (5% vs. 3%), febrile
 399 neutropenia (5% vs. 2%), pneumonitis/pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or
 400 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3%
 401 vs. 0%).

402 *Glioblastoma*

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

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

412 In patients receiving Avastin alone or Avastin plus irinotecan (N= 163), the incidence of
413 Avastin-related adverse events (Grade 1–4) were bleeding/hemorrhage (40%), epistaxis (26%), CNS
414 hemorrhage (5%), hypertension (32%), venous thromboembolic event (8%), arterial thromboembolic
415 event (6%), wound-healing complications (6%), proteinuria (4%), gastrointestinal perforation (2%),
416 and RPLS (1%). The incidence of Grade 3–5 events in these 163 patients were bleeding/hemorrhage
417 (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic event (7%), arterial
418 thromboembolic event (3%), wound-healing complications (3%), proteinuria (1%), and
419 gastrointestinal perforation (2%).

420 *Metastatic Renal Cell Carcinoma (mRCC)*

421 All grade adverse events were collected in Study 8. Grade 3–5 adverse events occurring at a
422 higher incidence ($\geq 2\%$) in 337 patients receiving interferon alfa (IFN- α) plus Avastin compared to
423 304 patients receiving IFN- α plus placebo arm were fatigue (13% vs. 8%), asthenia (10% vs. 7%),
424 proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis),
425 and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured,
426 gastric ulcer hemorrhage, gingival bleeding, haemoptysis, hemorrhage intracranial, large intestinal
427 hemorrhage, respiratory tract hemorrhage, and traumatic hematoma).

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

430

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).

6.2 Immunogenicity

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

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

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

447 incidence of antibodies to Avastin with the incidence of antibodies to other products may be
448 misleading.

449 **6.3 Postmarketing Experience**

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

453 *Body as a Whole:* Polyserositis

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

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

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

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

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

460 *Hemic and lymphatic:* Pancytopenia

461 *Hepatobiliary disorders:* Gallbladder perforation

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

464 *Musculoskeletal:* Osteonecrosis of the jaw

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

466 *Respiratory:* Nasal septum perforation, dysphonia

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

468 Arterial thromboembolic events, Hypertension, Gastrointestinal perforation, Hemorrhage

469

470 **7 DRUG INTERACTIONS**

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

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

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

482

483 **8 USE IN SPECIFIC POPULATIONS**

484 **8.1 Pregnancy**

485 *Pregnancy Category C*

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

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

496 **8.3 Nursing Mothers**

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

504 **8.4 Pediatric Use**

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

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

510 Juvenile cynomolgus monkeys with open growth plates exhibited physal dysplasia following 4 to
511 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure).
512 The incidence and severity of physal dysplasia were dose-related and were partially reversible upon
513 cessation of treatment.

514 **8.5 Geriatric Use**

515 In Study 1, severe adverse events that occurred at a higher incidence ($\geq 2\%$) in patients aged
516 ≥ 65 years as compared to younger patients were asthenia, sepsis, deep thrombophlebitis,
517 hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhea, constipation,
518 anorexia, leukopenia, anemia, dehydration, hypokalemia, and hyponatremia. The effect of Avastin
519 on overall survival was similar in elderly patients as compared to younger patients.

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

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

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

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

535 **8.6 Females of Reproductive Potential**

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

539 In a prospectively designed substudy of 179 premenopausal women randomized to receive
540 chemotherapy with or without Avastin, the incidence of ovarian failure was higher in the Avastin
541 arm (34%) compared to the control arm (2%). After discontinuation of Avastin and chemotherapy,

542 recovery of ovarian function occurred in 22% (7/32) of these Avastin-treated patients.
543 [See *Warnings and Precautions (5.10)*, *Adverse Reactions (6.1)*.]
544

545 **10 OVERDOSAGE**

546 The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of
547 16 patients and with severe headache in three of 16 patients.
548

549 **11 DESCRIPTION**

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

557 Avastin is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for
558 intravenous infusion. Avastin is supplied in 100 mg and 400 mg preservative-free, single-use vials
559 to deliver 4 mL or 16 mL of Avastin (25 mg/mL). The 100 mg product is formulated in 240 mg
560 α,α -trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium
561 phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The 400 mg
562 product is formulated in 960 mg α,α -trehalose dihydrate, 92.8 mg sodium phosphate (monobasic,
563 monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water
564 for Injection, USP.
565

566 **12 CLINICAL PHARMACOLOGY**

567 **12.1 Mechanism of Action**

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

573 **12.3 Pharmacokinetics**

574 The pharmacokinetic profile of bevacizumab was assessed using an assay that measures total
575 serum bevacizumab concentrations (i.e., the assay did not distinguish between free bevacizumab and
576 bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of
577 491 patients who received 1 to 20 mg/kg of Avastin weekly, every 2 weeks, or every 3 weeks, the
578 estimated half-life of bevacizumab was approximately 20 days (range 11–50 days). The predicted
579 time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg of
580 bevacizumab every 2 weeks was 2.8.

581 The clearance of bevacizumab varied by body weight, gender, and tumor burden. After correcting
582 for body weight, males had a higher bevacizumab clearance (0.262 L/day vs. 0.207 L/day) and a
583 larger V_c (3.25 L vs. 2.66 L) than females. Patients with higher tumor burden (at or above median
584 value of tumor surface area) had a higher bevacizumab clearance (0.249 L/day vs. 0.199 L/day) than
585 patients with tumor burdens below the median. In Study 1, there was no evidence of lesser efficacy
586 (hazard ratio for overall survival) in males or patients with higher tumor burden treated with Avastin
587 as compared to females and patients with low tumor burden. The relationship between bevacizumab
588 exposure and clinical outcomes has not been explored.
589

590 **13 NONCLINICAL TOXICOLOGY**

591 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

602 **13.2 Animal Toxicology and/or Pharmacology**

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

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

614 **13.3 Reproductive and Developmental Toxicology**

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

622 **14 CLINICAL STUDIES**

623 **14.1 Metastatic Colorectal Cancer (mCRC)**

624 *Study 1*

625 In this double-blind, active-controlled study, patients were randomized (1:1:1) to IV bolus-IFL
626 (irinotecan 125 mg/m², 5-FU 500 mg/m², and leucovorin (LV) 20 mg/m² given once weekly for
627 4 weeks every 6 weeks) plus placebo (Arm 1), bolus-IFL plus Avastin (5 mg/kg every 2 weeks)
628 (Arm 2), or 5-FU/LV plus Avastin (5 mg/kg every 2 weeks) (Arm 3). Enrollment in Arm 3 was
629 discontinued, as pre-specified, when the toxicity of Avastin in combination with the bolus-IFL
630 regimen was deemed acceptable. The main outcome measure was overall survival (OS).

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

635 The addition of Avastin resulted in an improvement in survival across subgroups defined by age
636 (< 65 yrs, ≥ 65 yrs) and gender. Results are presented in Table 4 and Figure 1.

637

Table 4
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.

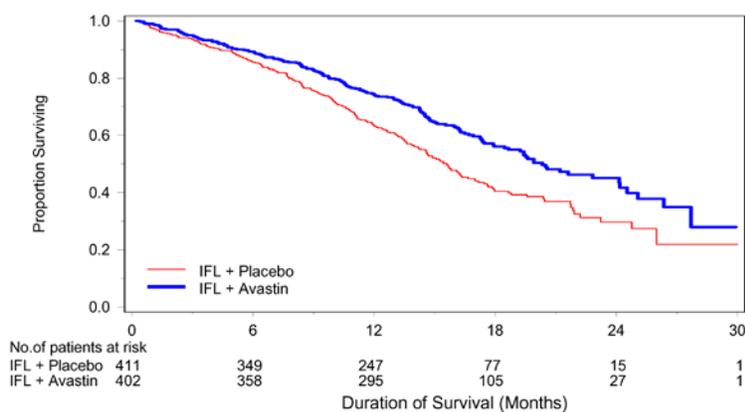
^b p<0.01 by χ^2 test.

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Figure 1
Duration of Survival in Study 1



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

646 *Study 2*

647 Study 2 was a randomized, open-label, active-controlled trial in patients who were previously
648 treated with irinotecan \pm 5-FU for initial therapy for metastatic disease or as adjuvant therapy.
649 Patients were randomized (1:1:1) to IV FOLFOX4 (Day 1: oxaliplatin 85 mg/m² and LV 200 mg/m²
650 concurrently, then 5-FU 400 mg/m² bolus followed by 600 mg/m² continuously; Day 2: LV
651 200 mg/m², then 5-FU 400 mg/m² bolus followed by 600 mg/m² continuously; repeated every

652 2 weeks), FOLFOX4 plus Avastin (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1), or
653 Avastin monotherapy(10 mg/kg every 2 weeks). The main outcome measure was OS.

654 The Avastin monotherapy arm was closed to accrual after enrollment of 244 of the planned
655 290 patients following a planned interim analysis by the data monitoring committee based on
656 evidence of decreased survival compared to FOLFOX4 alone.

657 Of the 829 patients randomized to the three arms, the median age was 61 years, 40% were female,
658 87% were Caucasian, 49% had an ECOG performance status of 0, 26% received prior radiation
659 therapy, and 80% received prior adjuvant chemotherapy, 99% received prior irinotecan, with or
660 without 5-FU as therapy for metastatic disease, and 1% received prior irinotecan and 5-FU as
661 adjuvant therapy.

662 The addition of Avastin to FOLFOX4 resulted in significantly longer survival as compared to
663 FOLFOX4 alone (median OS 13.0 months vs. 10.8 months; hazard ratio 0.75 [95% CI 0.63, 0.89],
664 $p=0.001$ stratified log rank test) with clinical benefit seen in subgroups defined by age (<65 yrs,
665 ≥ 65 yrs) and gender. PFS and ORR based on investigator assessment were higher in the Avastin
666 plus FOLFOX4 arm.

667 *Study 3*

668 The activity of Avastin in combination with bolus or infusional 5-FU/LV was evaluated in a
669 single arm study enrolling 339 patients with mCRC with disease progression following both
670 irinotecan- and oxaliplatin-containing chemotherapy regimens. Seventy-three percent of patients
671 received concurrent bolus 5-FU/LV. One objective partial response was verified in the first
672 100 evaluable patients for an overall response rate of 1% (95% CI 0–5.5%).

673 *Study 4*

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

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

685 Of the 820 patients randomized, the majority of patients were male (64%) and the median age was
686 63.0 years (range 21 to 84 years). At baseline, 52% of patients were ECOG performance status (PS)
687 1, 44% were ECOG PS 0, 58% received irinotecan-based therapy as first-line treatment, 55%
688 progressed on first-line treatment within 9 months, and 77% received their last dose of Avastin as
689 first-line treatment within 42 days of being randomized. Second-line chemotherapy regimens were
690 generally balanced between each treatment arm.

691 The addition of Avastin to fluoropyrimidine-based chemotherapy resulted in a statistically
692 significant prolongation of survival and PFS; there was no significant difference in overall response
693 rate, a key secondary outcome measure. Results are presented in Table 5 and Figure 2.

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Table 5
Study 4 Efficacy Results

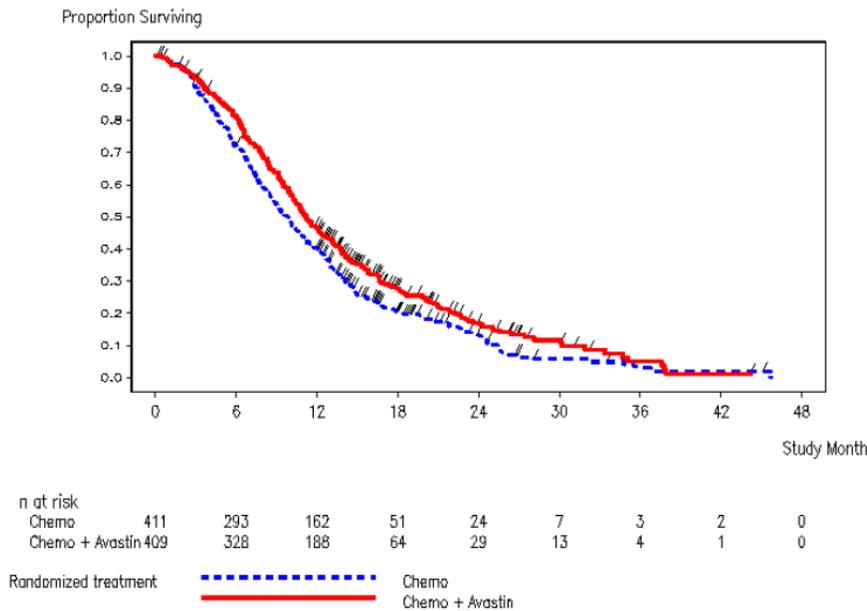
	Chemotherapy	Avastin + Chemotherapy
Number of Patients	411	409
Overall Survival^a		
Median (months)	9.8	11.2
Hazard ratio (95% CI)	0.81 (0.69, 0.94)	
Progression-Free Survival^b		
Median (months)	4.0	5.7
Hazard ratio (95% CI)	0.68 (0.59, 0.78)	

^a p = 0.0057 by unstratified log rank test.

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

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Figure 2
Duration of Survival in Study 4



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14.2 Lack of Efficacy in Adjuvant Treatment of Colon Cancer

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

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

The main efficacy outcome of the study was disease free survival (DFS) in patients with stage III colon cancer. Addition of Avastin to chemotherapy did not improve DFS. As compared to the

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715 control arm, the proportion of stage III patients with disease recurrence or with death due to disease
716 progression were numerically higher in the FOLFOX4 plus Avastin and in the XELOX plus Avastin
717 arms. The hazard ratios for DFS were 1.17 (95% CI: 0.98–1.39) for the FOLFOX4 plus Avastin
718 versus FOLFOX4 and 1.07 (95% CI: 0.90–1.28) for the XELOX plus Avastin versus FOLFOX4.
719 The hazard ratios for overall survival were 1.31 (95% CI=1.03, 1.67) and 1.27 (95% CI=1.00, 1.62)
720 for the comparison of Avastin plus FOLFOX4 versus FOLFOX4 and Avastin plus XELOX versus
721 FOLFOX4, respectively. Similar lack of efficacy for DFS were observed in the Avastin-containing
722 arms compared to control in the high-risk stage II cohort.

723 In a second study, 2710 patients with stage II and III colon cancer who had undergone surgery with
724 curative intent, were randomized to receive either Avastin administered at a dose equivalent to
725 2.5 mg/kg/week in combination with mFOLFOX6 (N=1354) or mFOLFOX6 alone (N=1356). The
726 median age was 57 years, 50% were male and 87% Caucasian. Seventy-five percent had stage III
727 disease. The main efficacy outcome was DFS among stage III patients. The hazard ratio for DFS
728 was 0.92 (95% CI: 0.77, 1.10). Overall survival, an additional efficacy outcome, was not
729 significantly improved with the addition of Avastin to mFOLFOX6 (HR=0.96, 95% CI=[0.75,1.22]).

730 **14.3 Unresectable Non-Squamous Non-Small Cell Lung Cancer (NSCLC)**

731 *Study 5*

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

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

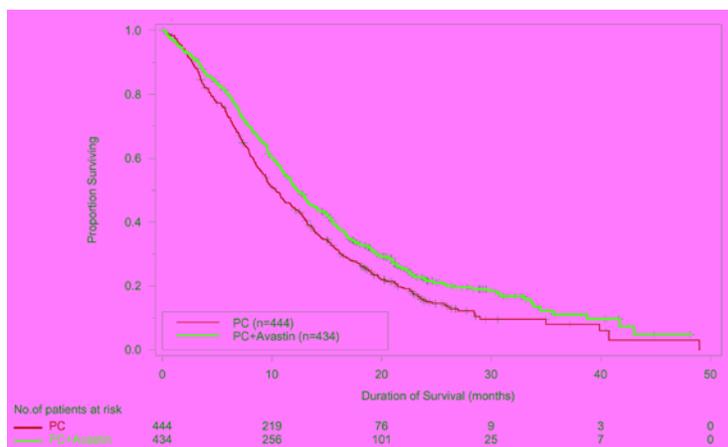
744 Of the 878 patients randomized, the median age was 63, 46% were female, 43% were \geq age 65,
745 and 28% had $\geq 5\%$ weight loss at study entry. Eleven percent had recurrent disease and of the 89%
746 with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had
747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

748 The results are presented in Figure 3. OS was statistically significantly higher among patients
749 receiving PC plus Avastin compared with those receiving PC alone; median OS was 12.3 months vs.
750 10.3 months [hazard ratio 0.80 (repeated 95% CI 0.68, 0.94), final p- value 0.013, stratified log-rank
751 test]. Based on investigator assessment which was not independently verified, patients were
752 reported to have longer PFS with Avastin in combination with PC compared to PC alone.

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Figure 3
Duration of Survival in Study 5



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758 In an exploratory analyses across patient subgroups, the impact of Avastin on OS was less robust
759 in the following: women [HR=0.99 (95% CI: 0.79, 1.25)], age \geq 65 years [HR=0.91 (95% CI:
760 0.72, 1.14)] and patients with \geq 5% weight loss at study entry [HR=0.96 (95% CI: 0.73, 1.26)].

761 The safety and efficacy of Avastin in patients with locally advanced, metastatic or recurrent
762 non-squamous NSCLC, who had not received prior chemotherapy was studied in another
763 randomized, double-blind, placebo controlled, three-arm study of Avastin in combination with
764 cisplatin and gemcitabine (CG) versus placebo and CG. A total of 1043 patients were randomized
765 1:1:1 to receive placebo plus CG, Avastin 7.5 mg/kg plus CG or Avastin 15.0 mg/kg plus CG.
766 The median age was 58 years, 36% were female, and 29% were \geq age 65. Eight percent had
767 recurrent disease and 77% had Stage IV disease. Progression-free survival, the main efficacy
768 outcome measure, was significantly higher in both Avastin containing arms compared to the placebo
769 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
770 (95% CI 0.68; 0.98), $p=0.0301$ for the Avastin 15.0 mg/kg plus CG arm]. The addition of Avastin
771 to CG chemotherapy failed to demonstrate an improvement in the duration of overall survival, an
772 additional efficacy outcome measure, [HR 0.93 (95% CI 0.78; 1.11), $p=0.4203$ for the Avastin
773 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
774 plus CG arm].

775 **14.4 Glioblastoma**

776 *Study 6*

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

783 Of the 85 patients randomized to the Avastin arm, the median age was 54 years, 32% were
784 female, 81% were in first relapse, Karnofsky performance status was 90–100 for 45% and 70–80 for
785 55%.

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

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

791 *Study 7*

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

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

797 The efficacy of Avastin was supported by an objective response rate of 19.6% (95% CI 10.9%,
798 31.3%) using the same response criteria as in Study 6. Median duration of response was 3.9 months
799 (95% CI 2.4, 17.4).

800 **14.5 Metastatic Renal Cell Carcinoma (mRCC)**

801 *Study 8*

802 Patients with treatment-naïve mRCC were evaluated in a multicenter, randomized, double-blind,
803 international study comparing Avastin plus interferon alfa 2a (IFN- α 2a) versus placebo plus
804 IFN- α 2a. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to
805 receive either Avastin (10 mg/kg IV infusion every 2 weeks; n=327) or placebo (IV every 2 weeks;
806 n=322) in combination with IFN- α 2a (9 MIU subcutaneously three times weekly, for a maximum of
807 52 weeks). Patients were treated until disease progression or unacceptable toxicity. The main
808 outcome measure of the study was investigator-assessed PFS. Secondary outcome measures were
809 ORR and OS.

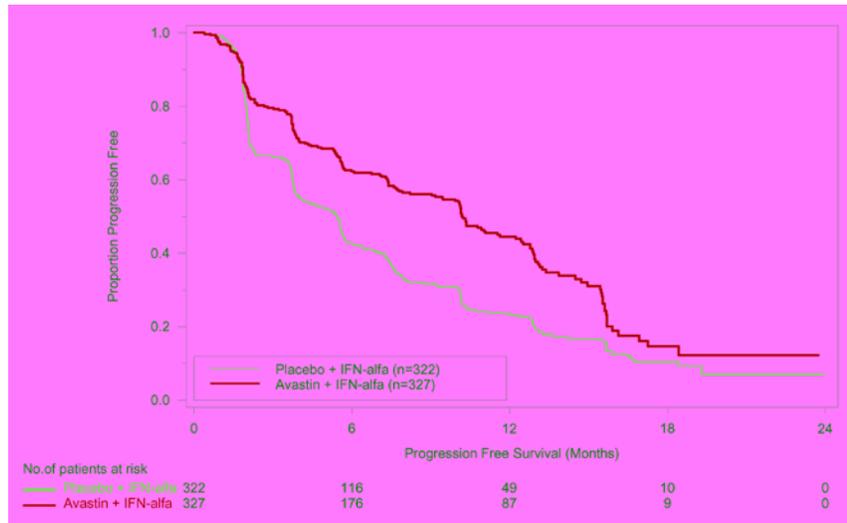
810 The median age was 60 years (range 18–82), 96% were white, and 70% were male. The study
811 population was characterized by Motzer scores as follows: 28% favorable (0), 56% intermediate
812 (1-2), 8% poor (3–5), and 7% missing.

813 The results are presented in Figure 4. PFS was statistically significantly prolonged among
814 patients receiving Avastin plus IFN- α 2a compared to those receiving IFN- α 2a alone; median PFS
815 was 10.2 months vs. 5.4 months [HR 0.60 (95% CI 0.49, 0.72), p-value <0.0001, stratified log-rank
816 test]. Among the 595 patients with measurable disease, ORR was also significantly higher (30% vs.
817 12%, p <0.0001, stratified CMH test). There was no improvement in OS based on the final analysis
818 conducted after 444 deaths, with a median OS of 23 months in the Avastin plus IFN- α 2a arm and
819 21 months in the IFN- α 2a plus placebo arm [HR 0.86, (95% CI 0.72, 1.04)].

820

821
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Figure 4
Progression-Free Survival in Study 8



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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.

831

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

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