

## 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)	10/2012
Indications and Usage, Metastatic Breast Cancer (1.3) – Removed	12/2011
Dosage and Administration, Recommended Doses and Schedules: Metastatic Breast Cancer (2.2) - Removed	12/2011

### 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)
  - 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

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](http://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: October 2012

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

### 29 **1.2 Non-Squamous Non-Small Cell Lung Cancer (NSCLC)**

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

### 32 **1.3 Glioblastoma**

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

35 The effectiveness of Avastin in glioblastoma is based on an improvement in objective response  
36 rate. There are no data demonstrating an improvement in disease-related symptoms or increased  
37 survival with Avastin. [See *Clinical Studies (14.3)*.]

### 38 **1.4 Metastatic Renal Cell Carcinoma (mRCC)**

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

## 42 2 DOSAGE AND ADMINISTRATION

### 43 **2.1 Administration**

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

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

## 51 **2.2 Recommended Doses and Schedules**

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

### 53 *Metastatic Colorectal Cancer (mCRC)*

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

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

### 58 *Non-Squamous Non-Small Cell Lung Cancer (NSCLC)*

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

### 61 *Glioblastoma*

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

### 63 *Metastatic Renal Cell Carcinoma (mRCC)*

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

## 65 **2.3 Preparation for Administration**

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

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

## 72 **2.4 Dose Modifications**

73 There are no recommended dose reductions.

74 Discontinue Avastin for:

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

87 Temporarily suspend Avastin for:

- 88 • At least 4 weeks prior to elective surgery [See *Warnings and Precautions (5.2).*]
- 89 • Severe hypertension not controlled with medical management [See *Warnings and Precautions*  
90 *(5.6).*]
- 91 • Moderate to severe proteinuria pending further evaluation [See *Warnings and Precautions*  
92 *(5.8).*]
- 93 • Severe infusion reactions [See *Warnings and Precautions (5.9).*]

94

95 **3 DOSAGE FORMS AND STRENGTHS**

96 100 mg per 4 mL single-use vial  
97 400 mg per 16 mL single-use vial

98

99 **4 CONTRAINDICATIONS**

100 None.

101

102 **5 WARNINGS AND PRECAUTIONS**

103 **5.1 Gastrointestinal Perforations**

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

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

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

112 **5.2 Surgery and Wound Healing Complications**

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

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

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

126 **5.3 Hemorrhage**

127 Avastin can result in two distinct patterns of bleeding: minor hemorrhage, most commonly  
128 Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal  
129 hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage,  
130 epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin  
131 compared to patients receiving only chemotherapy. Across indications, the incidence of Grade  $\geq 3$   
132 hemorrhagic events among patients receiving Avastin ranged from 1.2 to 4.6%. [See *Adverse  
133 Reactions (6.1)*.]

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

137 In clinical studies in non-small cell lung cancer where patients with CNS metastases who  
138 completed radiation and surgery more than 4 weeks prior to the start of Avastin were evaluated with  
139 serial CNS imaging, symptomatic Grade 2 CNS hemorrhage was documented in one of  
140 83 Avastin-treated patients (rate 1.2%, 95% CI 0.06%–5.93%).

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

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

#### 146 **5.4 Non-Gastrointestinal Fistula Formation**

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

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

#### 153 **5.5 Arterial Thromboembolic Events**

154 Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction,  
155 transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a  
156 higher incidence in patients receiving Avastin compared to those in the control arm. Across  
157 indications, the incidence of Grade  $\geq 3$  ATE in the Avastin containing arms was 2.6% compared to  
158 0.8% in the control arms. Among patients receiving Avastin in combination with chemotherapy, the  
159 risk of developing ATE during therapy was increased in patients with a history of arterial  
160 thromboembolism, or age greater than 65 years. [See *Use in Specific Populations (8.5).*]

161 The safety of resumption of Avastin therapy after resolution of an ATE has not been studied.  
162 Discontinue Avastin in patients who experience a severe ATE. [See *Dosage and Administration*  
163 *(2.4).*]

#### 164 **5.6 Hypertension**

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

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

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

#### 174 **5.7 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**

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

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

#### 184 **5.8 Proteinuria**

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

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

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

## 198 **5.9 Infusion Reactions**

199 Infusion reactions reported in the clinical trials and post-marketing experience include hypertension,  
200 hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation,  
201 Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. In clinical studies, infusion  
202 reactions with the first dose of Avastin were uncommon ( $< 3\%$ ) and severe reactions occurred in  
203 0.2% of patients.

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

## 206 **5.10 Ovarian Failure**

207 The incidence of ovarian failure was higher (34% vs. 2%) in premenopausal women receiving  
208 Avastin in combination with mFOLFOX chemotherapy as compared to those receiving mFOLFOX  
209 chemotherapy alone for adjuvant treatment for colorectal cancer, a use for which Avastin is not  
210 approved. Inform females of reproductive potential of the risk of ovarian failure prior to starting  
211 treatment with Avastin. [See *Adverse Reactions* (6.1), *Use in Specific Populations* (8.6).]  
212

## 213 **6 ADVERSE REACTIONS**

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

- 216 • Gastrointestinal Perforations [See *Boxed Warning, Dosage and Administration* (2.4), *Warnings*  
217 *and Precautions* (5.1).]
- 218 • Surgery and Wound Healing Complications [See *Boxed Warning, Dosage and Administration*  
219 *(2.4), Warnings and Precautions* (5.2).]
- 220 • Hemorrhage [See *Boxed Warning, Dosage and Administration* (2.4), *Warnings and Precautions*  
221 *(5.3)*.]
- 222 • Non-Gastrointestinal Fistula Formation [See *Dosage and Administration* (2.4), *Warnings and*  
223 *Precautions* (5.4).]
- 224 • Arterial Thromboembolic Events [See *Dosage and Administration* (2.4), *Warnings and*  
225 *Precautions* (5.5).]
- 226 • Hypertensive Crisis [See *Dosage and Administration* (2.4), *Warnings and Precautions* (5.6).]
- 227 • Reversible Posterior Leukoencephalopathy Syndrome [See *Dosage and Administration* (2.4),  
228 *Warnings and Precautions* (5.7).]
- 229 • Proteinuria [See *Dosage and Administration* (2.4), *Warnings and Precautions* (5.8).]
- 230 • Ovarian Failure [See *Warnings and Precautions* (5.10), *Use in Specific Populations* (8.6).]

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

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

236 **6.1 Clinical Trial Experience**

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

240 The data below reflect exposure to Avastin in 3795 patients with CRC, non-squamous NSCLC,  
241 MBC, glioblastoma, or mRCC trials including controlled (Studies 1, 2, 4, and 7) or uncontrolled,  
242 single arm (Study 5) treated at the recommended dose and schedule for a median of 8 to 23 doses of  
243 Avastin. [See *Clinical Studies (14)*.] Data also reflect exposure to Avastin in 363 patients with  
244 metastatic breast cancer (MBC) who received a median of 9.5 doses of Avastin, an indication for  
245 which Avastin is not approved. The population was aged 18-88 years (median 59), 43.2% male and  
246 85.3% white. The population included 1783 first- and second-line mCRC patients who received a  
247 median of 10 doses of Avastin, 669 female adjuvant CRC patients who received a median of  
248 23 doses of Avastin, 480 first-line metastatic NSCLC patients who received a median of 8 doses of  
249 Avastin, 163 glioblastoma patients who received a median of 9 doses of Avastin, and 337 mRCC  
250 patients who received a median of 16 doses of Avastin.

251 *Surgery and Wound Healing Complications*

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

257 In Study 5, events of post-operative wound healing complications (craniotomy site wound  
258 dehiscence and cerebrospinal fluid leak) occurred in patients with previously treated glioblastoma:  
259 3/84 patients in the Avastin alone arm and 1/79 patients in the Avastin plus irinotecan arm.  
260 [See *Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.2)*.]

261 *Hemorrhage*

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

269 *Venous Thromboembolic Events*

270 The overall incidence of Grade 3–4 venous thromboembolic events in Study 1 was 15.1% in  
271 patients receiving bolus-IFL plus Avastin and 13.6% in patients receiving bolus-IFL plus placebo.  
272 In Study 1, more patients in the Avastin containing arm experienced deep venous thrombosis (34 vs.  
273 19 patients ) and intra-abdominal venous thrombosis (10 vs. 5 patients).

274 The risk of developing a second thromboembolic event while on Avastin and oral anticoagulants  
275 was evaluated in two randomized studies. In Study 1, 53 patients (14%) on the bolus-IFL plus  
276 Avastin arm and 30 patients (8%) on the bolus-IFL plus placebo arm received full dose warfarin  
277 following a venous thromboembolic event (VTE). Among these patients, an additional  
278 thromboembolic event occurred in 21% (11/53) of patients receiving bolus-IFL plus Avastin and 3%  
279 (1/30) of patients receiving bolus-IFL alone.

280 In a second, randomized, 4-arm study in 1401 patients with mCRC, prospectively evaluating the  
281 incidence of VTE (all grades), the overall incidence of first VTE was higher in the Avastin  
282 containing arms (13.5%) than the chemotherapy alone arms (9.6%). Among the 116 patients treated  
283 with anticoagulants following an initial VTE event (73 in the Avastin plus chemotherapy arms and

284 43 in the chemotherapy alone arms), the overall incidence of subsequent VTEs was also higher  
285 among the Avastin treated patients (31.5% vs. 25.6%). In this subgroup of patients treated with  
286 anticoagulants, the overall incidence of bleeding, the majority of which were Grade 1, was higher in  
287 the Avastin treated arms than the chemotherapy arms (27.4% vs. 20.9%). [See *Dosage and*  
288 *Administration* (2.4).]

### 289 *Neutropenia and Infection*

290 The incidences of neutropenia and febrile neutropenia are increased in patients receiving Avastin  
291 plus chemotherapy compared to chemotherapy alone. In Study 1, the incidence of Grade 3 or 4  
292 neutropenia was increased in mCRC patients receiving IFL plus Avastin (21%) compared to patients  
293 receiving IFL alone (14%). In Study 4, the incidence of Grade 4 neutropenia was increased in  
294 NSCLC patients receiving paclitaxel/carboplatin (PC) plus Avastin (26.2%) compared with patients  
295 receiving PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC plus Avastin vs.  
296 1.8% for PC alone). There were 19 (4.5%) infections with Grade 3 or 4 neutropenia in the PC plus  
297 Avastin arm of which 3 were fatal compared to 9 (2%) neutropenic infections in patients receiving  
298 PC alone, of which none were fatal. During the first 6 cycles of treatment, the incidence of serious  
299 infections including pneumonia, febrile neutropenia, catheter infections and wound infections was  
300 increased in the PC plus Avastin arm [58 patients (13.6%)] compared to the PC alone arm  
301 [29 patients (6.6%)].

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

### 305 *Proteinuria*

306 Grade 3–4 proteinuria ranged from 0.7 to 7.4% in Studies 1, 2, 4 and 7. The overall incidence of  
307 proteinuria (all grades) was only adequately assessed in Study 7, in which the incidence was 20%.  
308 Median onset of proteinuria was 5.6 months (range 15 days to 37 months) after initiation of Avastin.  
309 Median time to resolution was 6.1 months (95% CI 2.8 months, 11.3 months). Proteinuria did not  
310 resolve in 40% of patients after median follow up of 11.2 months and required permanent  
311 discontinuation of Avastin in 30% of the patients who developed proteinuria (Study 7).  
312 [See *Warnings and Precautions* (5.8).]

### 313 *Congestive Heart Failure*

314 The incidence of Grade  $\geq 3$  left ventricular dysfunction was 1.0% in patients receiving Avastin  
315 compared to 0.6% in the control arm across indications. In patients with metastatic breast cancer  
316 MBC, an indication for which Avastin is not approved, the incidence of Grade 3–4 congestive heart  
317 failure (CHF) was increased in patients in the Avastin plus paclitaxel arm (2.2%) as compared to the  
318 control arm (0.3%). Among patients receiving prior anthracyclines for MBC, the rate of CHF was  
319 3.8% for patients receiving Avastin as compared to 0.6% for patients receiving paclitaxel alone.  
320 The safety of continuation or resumption of Avastin in patients with cardiac dysfunction has not  
321 been studied.

### 322 *Ovarian Failure*

323 The incidence of new cases of ovarian failure (defined as amenorrhoea lasting 3 or more months,  
324 FSH level  $\geq 30$  mIU/mL and a negative serum  $\beta$ -HCG pregnancy test) was prospectively evaluated in  
325 a subset of 179 women receiving mFOLFOX chemotherapy alone (n=84 or with Avastin (n=95).  
326 New cases of ovarian failure were identified in 34% (32/95) of women receiving Avastin in  
327 combination with chemotherapy compared with 2% (2/84) of women receiving chemotherapy alone  
328 [relative risk of 14 (95% CI 4, 53)]. After discontinuation of Avastin treatment, recovery of ovarian  
329 function at all time points during the post-treatment period was demonstrated in 22% (7/32) of the  
330 Avastin-treated women. Recovery of ovarian function is defined as resumption of menses, a positive  
331 serum  $\beta$ -HCG pregnancy test, or a FSH level  $< 30$  mIU/mL during the post-treatment period. Long

332 term effects of Avastin exposure on fertility are unknown. [See *Warnings and Precautions (5.10)*,  
333 *Use in Specific Populations (8.6)*.]

334 *Metastatic Colorectal Cancer (mCRC)*

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

338 All Grade 3–4 adverse events and selected Grade 1–2 adverse events (hypertension, proteinuria,  
339 thromboembolic events) were collected in the entire study population. Severe and life-threatening  
340 (Grade 3–4) adverse events, which occurred at a higher incidence ( $\geq 2\%$ ) in patients receiving  
341 bolus-IFL plus Avastin as compared to bolus-IFL plus placebo, are presented in Table 1.  
342

**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 <sup>a</sup>	14%	21%

<sup>a</sup> 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.

343  
344 Grade 1–4 adverse events which occurred at a higher incidence ( $\geq 5\%$ ) in patients receiving  
345 bolus-IFL plus Avastin as compared to the bolus-IFL plus placebo arm are presented in Table 2.  
346 Grade 1–4 adverse events were collected for the first approximately 100 patients in each of the three  
347 treatment arms who were enrolled until enrollment in Arm 3 (5-FU/LV + Avastin) was discontinued.  
348

**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%

350

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

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

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

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

370 *Glioblastoma*

371 All adverse events were collected in 163 patients enrolled in Study 5 who either received Avastin  
 372 alone or Avastin plus irinotecan. All patients received prior radiotherapy and temozolomide.  
 373 Avastin was administered at 10 mg/kg every 2 weeks alone or in combination with irinotecan.  
 374 Avastin was discontinued due to adverse events in 4.8% of patients treated with Avastin alone.

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

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

385 (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic event (7%), arterial  
 386 thromboembolic event (3%), wound-healing complications (3%), proteinuria (1%), and  
 387 gastrointestinal perforation (2%).

388 *Metastatic Renal Cell Carcinoma (mRCC)*

389 All grade adverse events were collected in Study 7. Grade 3–5 adverse events occurring at a  
 390 higher incidence ( $\geq 2\%$ ) in 337 patients receiving interferon alfa (IFN- $\alpha$ ) plus Avastin compared to  
 391 304 patients receiving IFN- $\alpha$  plus placebo arm were fatigue (13% vs. 8%), asthenia (10% vs. 7%),  
 392 proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis),  
 393 and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured,  
 394 gastric ulcer hemorrhage, gingival bleeding, haemoptysis, hemorrhage intracranial, large intestinal  
 395 hemorrhage, respiratory tract hemorrhage, and traumatic hematoma).

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

398

**Table 3**  
 NCI-CTC Grades 1–5 Adverse Events in Study 7 (Occurring at  
 Higher Incidence [ $\geq 5\%$ ] in IFN- $\alpha$  + Avastin vs. IFN- $\alpha$  + Placebo)

System Organ Class/Preferred term <sup>a</sup>	IFN- $\alpha$ +Placebo (n=304)	IFN- $\alpha$ + 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%

<sup>a</sup>Adverse events were encoded using MedDRA, Version 10.1.

399

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

## 405 **6.2 Immunogenicity**

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

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

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

## 417 **6.3 Postmarketing Experience**

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

421 *Body as a Whole:* Polyserositis

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

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

424 Permanent loss of vision; Endophthalmitis (infectious and sterile); Intraocular inflammation; Retinal  
425 detachment; Increased intraocular pressure; Hemorrhage including conjunctival, vitreous  
426 hemorrhage or retinal hemorrhage; Vitreous floaters; Ocular hyperemia; Ocular pain or discomfort

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

428 *Hemic and lymphatic:* Pancytopenia

429 *Musculoskeletal:* Osteonecrosis of the jaw

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

431 *Respiratory:* Nasal septum perforation, dysphonia

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

433 Arterial thromboembolic events, Hypertension, Gastrointestinal perforation, Hemorrhage

434

## 435 **7 DRUG INTERACTIONS**

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

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

445 In Study 7, there was no difference in the mean exposure of interferon alfa administered in  
446 combination with Avastin when compared to interferon alfa alone.

447

## 448 **8 USE IN SPECIFIC POPULATIONS**

### 449 **8.1 Pregnancy**

#### 450 *Pregnancy Category C*

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

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

### 461 **8.3 Nursing Mothers**

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

### 469 **8.4 Pediatric Use**

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

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

475 Juvenile cynomolgus monkeys with open growth plates exhibited physeal dysplasia following 4 to  
476 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure).  
477 The incidence and severity of physeal dysplasia were dose-related and were partially reversible upon  
478 cessation of treatment.

### 479 **8.5 Geriatric Use**

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

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

487 In Study 4, patients aged  $\geq 65$  years receiving carboplatin, paclitaxel, and Avastin had a greater  
488 relative risk for proteinuria as compared to younger patients. [See *Warnings and Precautions (5.8)*.]  
489

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

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

### 501 **8.6 Females of Reproductive Potential**

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

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

510

## 511 **10 OVERDOSAGE**

512 The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of  
513 16 patients and with severe headache in three of 16 patients.

514

## 515 **11 DESCRIPTION**

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

523 Avastin is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for  
524 intravenous infusion. Avastin is supplied in 100 mg and 400 mg preservative-free, single-use vials  
525 to deliver 4 mL or 16 mL of Avastin (25 mg/mL). The 100 mg product is formulated in 240 mg  
526  $\alpha, \alpha$ -trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium  
527 phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and Water for Injection, USP. The 400 mg  
528 product is formulated in 960 mg  $\alpha, \alpha$ -trehalose dihydrate, 92.8 mg sodium phosphate (monobasic,  
529 monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and Water  
530 for Injection, USP.

531

## 532 **12 CLINICAL PHARMACOLOGY**

### 533 **12.1 Mechanism of Action**

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

### 539 **12.3 Pharmacokinetics**

540 The pharmacokinetic profile of bevacizumab was assessed using an assay that measures total  
541 serum bevacizumab concentrations (i.e., the assay did not distinguish between free bevacizumab and  
542 bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of

543 491 patients who received 1 to 20 mg/kg of Avastin weekly, every 2 weeks, or every 3 weeks, the  
544 estimated half-life of bevacizumab was approximately 20 days (range 11–50 days). The predicted  
545 time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg of  
546 bevacizumab every 2 weeks was 2.8.

547 The clearance of bevacizumab varied by body weight, gender, and tumor burden. After correcting  
548 for body weight, males had a higher bevacizumab clearance (0.262 L/day vs. 0.207 L/day) and a  
549 larger  $V_c$  (3.25 L vs. 2.66 L) than females. Patients with higher tumor burden (at or above median  
550 value of tumor surface area) had a higher bevacizumab clearance (0.249 L/day vs. 0.199 L/day) than  
551 patients with tumor burdens below the median. In Study 1, there was no evidence of lesser efficacy  
552 (hazard ratio for overall survival) in males or patients with higher tumor burden treated with Avastin  
553 as compared to females and patients with low tumor burden. The relationship between bevacizumab  
554 exposure and clinical outcomes has not been explored.  
555

## 556 **13 NONCLINICAL TOXICOLOGY**

### 557 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

### 568 **13.2 Animal Toxicology and/or Pharmacology**

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

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

### 580 **13.3 Reproductive and Developmental Toxicology**

581 Pregnant rabbits dosed with 1 to 12 times the human dose of bevacizumab every three days during  
582 the period of organogenesis (gestation day 6–18) exhibited teratogenic effects, decreases in maternal  
583 and fetal body weights, and increased number of fetal resorptions. Teratogenic effects included:  
584 reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws;  
585 meningocele; fontanel, rib and hindlimb deformities; corneal opacity; and absent hindlimb  
586 phalanges. There are no data available regarding the level of bevacizumab exposure in the offspring.  
587

588 **14 CLINICAL STUDIES**

589 **14.1 Metastatic Colorectal Cancer (mCRC)**

590 *Study 1*

591 In this double-blind, active-controlled study, patients were randomized (1:1:1) to IV bolus-IFL  
 592 (irinotecan 125 mg/m<sup>2</sup>, 5-FU 500 mg/m<sup>2</sup>, and leucovorin (LV) 20 mg/m<sup>2</sup> given once weekly for  
 593 4 weeks every 6 weeks) plus placebo (Arm 1), bolus-IFL plus Avastin (5 mg/kg every 2 weeks)  
 594 (Arm 2), or 5-FU/LV plus Avastin (5 mg/kg every 2 weeks) (Arm 3). Enrollment in Arm 3 was  
 595 discontinued, as pre-specified, when the toxicity of Avastin in combination with the bolus-IFL  
 596 regimen was deemed acceptable. The main outcome measure was overall survival (OS).

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

601 The addition of Avastin resulted in an improvement in survival across subgroups defined by age  
 602 (<65 yrs, ≥65 yrs) and gender. Results are presented in Table 4 and Figure 1.

603

**Table 4**  
 Study 1 Efficacy Results

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

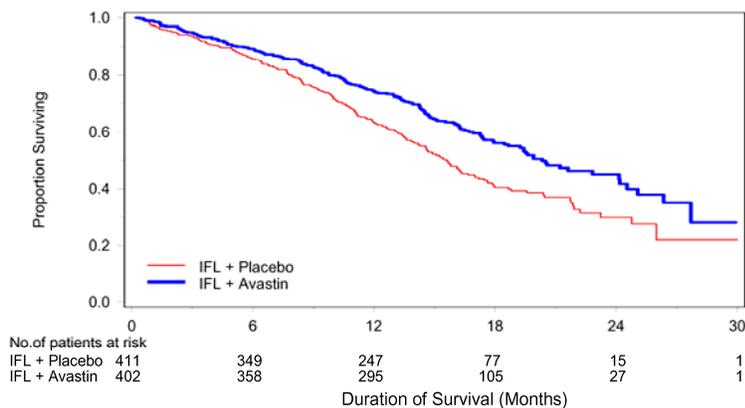
<sup>a</sup> p<0.001 by stratified log rank test.

<sup>b</sup> p<0.01 by  $\chi^2$  test.

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**Figure 1**  
Duration of Survival in Study 1



607  
608

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

### Study 2

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

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

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

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

### Study 3

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

639

## 640 **14.2 Lack of Efficacy in Adjuvant Treatment of Colon Cancer**

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

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

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

660 In a second study, 2710 patients with stage II and III colon cancer who had undergone surgery with  
661 curative intent, were randomized to receive either Avastin administered at a dose equivalent to  
662 2.5 mg/kg/week in combination with mFOLFOX6 (N=1356) or mFOLFOX6 alone (N=1354). The  
663 median age was 57 years, 50% were male and 87% Caucasian. Seventy-five percent had stage III  
664 disease. The main efficacy outcome was DFS among stage III patients. The hazard ratio for DFS  
665 was 0.92 (95% CI: 0.77, 1.10). Overall survival, an additional efficacy outcome, was not  
666 significantly improved with the addition of Avastin to mFOLFOX6 (HR=0.96, 95% CI=[0.75,1.22].  
667

## 668 **14.3 Unresectable Non–Squamous Non–Small Cell Lung Cancer (NSCLC)**

### 669 *Study 4*

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

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

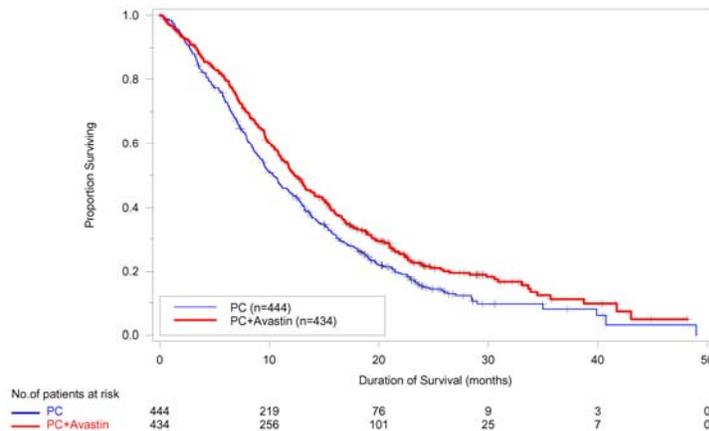
682 Of the 878 patients randomized, the median age was 63, 46% were female, 43% were  $\geq$  age 65,  
683 and 28% had  $\geq$ 5% weight loss at study entry. Eleven percent had recurrent disease and of the 89%  
684 with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76%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

686 The results are presented in Figure 2. OS was statistically significantly higher among patients  
687 receiving PC plus Avastin compared with those receiving PC alone; median OS was 12.3 months vs.

688 10.3 months [hazard ratio 0.80 (repeated 95% CI 0.68, 0.94), final p- value 0.013, stratified log-rank  
689 test]. Based on investigator assessment which was not independently verified, patients were  
690 reported to have longer PFS with Avastin in combination with PC compared to PC alone.  
691

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**Figure 2**  
Duration of Survival in Study 4



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696 In an exploratory analyses across patient subgroups, the impact of Avastin on OS was less robust  
697 in the following: women [HR=0.99 (95% CI: 0.79, 1.25)], age  $\geq 65$  years [HR=0.91 (95% CI:  
698 0.72, 1.14)] and patients with  $\geq 5\%$  weight loss at study entry [HR=0.96 (95% CI: 0.73, 1.26)].

699 The safety and efficacy of Avastin in patients with locally advanced, metastatic or recurrent  
700 non-squamous NSCLC, who had not received prior chemotherapy was studied in another  
701 randomized, double-blind, placebo controlled, three-arm study of Avastin in combination with  
702 cisplatin and gemcitabine (CG) versus placebo and CG. A total of 1043 patients were randomized  
703 1:1:1 to receive placebo plus CG, Avastin 7.5 mg/kg plus CG or Avastin 15.0 mg/kg plus CG.  
704 The median age was 58 years, 36% were female, and 29% were  $\geq$  age 65. Eight percent had  
705 recurrent disease and 77% had Stage IV disease. Progression-free survival, the main efficacy  
706 outcome measure, was significantly higher in both Avastin containing arms compared to the placebo  
707 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  
708 (95% CI 0.68; 0.98),  $p=0.0301$  for the Avastin 15.0 mg/kg plus CG arm]. The addition of Avastin  
709 to CG chemotherapy failed to demonstrate an improvement in the duration of overall survival, an  
710 additional efficacy outcome measure, [HR 0.93 (95% CI 0.78; 1.11),  $p=0.4203$  for the Avastin  
711 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  
712 plus CG arm].

#### 713 14.4 Glioblastoma

##### 714 Study 5

715 The efficacy and safety of Avastin was evaluated in Study 5, an open-label, multicenter,  
716 randomized, non-comparative study of patients with previously treated glioblastoma. Patients  
717 received Avastin (10 mg/kg IV) alone or Avastin plus irinotecan every 2 weeks until disease  
718 progression or until unacceptable toxicity. All patients received prior radiotherapy (completed at  
719 least 8 weeks prior to receiving Avastin) and temozolomide. Patients with active brain hemorrhage  
720 were excluded.

721 Of the 85 patients randomized to the Avastin arm, the median age was 54 years, 32% were  
722 female, 81% were in first relapse, Karnofsky performance status was 90–100 for 45% and 70–80 for  
723 55%.

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

#### 729 *Study 6*

730 Study 6, was a single-arm, single institution trial with 56 patients with glioblastoma. All patients  
731 had documented disease progression after receiving temozolomide and radiation therapy. Patients  
732 received Avastin 10 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity.

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

735 The efficacy of Avastin was supported by an objective response rate of 19.6% (95% CI 10.9%,  
736 31.3%) using the same response criteria as in Study 5. Median duration of response was 3.9 months  
737 (95% CI 2.4, 17.4).

### 738 **14.5 Metastatic Renal Cell Carcinoma (mRCC)**

#### 739 *Study 7*

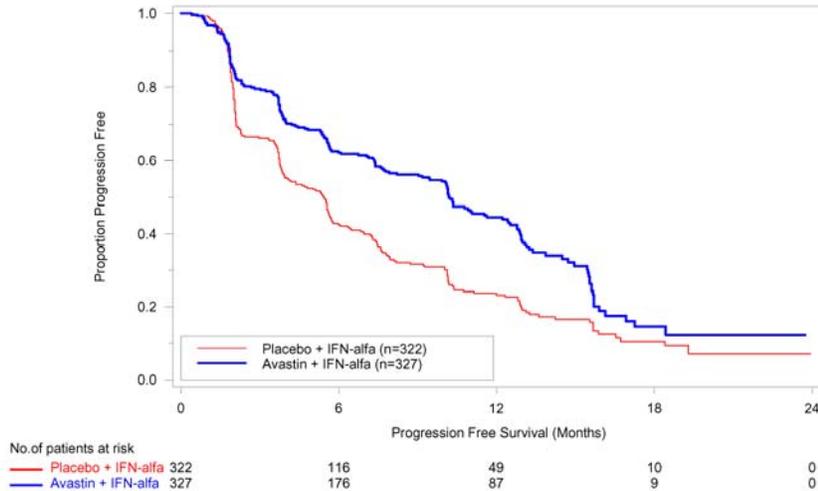
740 Patients with treatment-naïve mRCC were evaluated in a multicenter, randomized, double-blind,  
741 international study comparing Avastin plus interferon alfa 2a (IFN- $\alpha$ 2a) versus placebo plus  
742 IFN- $\alpha$ 2a. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to  
743 receive either Avastin (10 mg/kg IV infusion every 2 weeks; n=327) or placebo (IV every 2 weeks;  
744 n=322) in combination with IFN- $\alpha$ 2a (9 MIU subcutaneously three times weekly, for a maximum of  
745 52 weeks). Patients were treated until disease progression or unacceptable toxicity. The main  
746 outcome measure of the study was investigator-assessed PFS. Secondary outcome measures were  
747 ORR and OS.

748 The median age was 60 years (range 18–82), 96% were white, and 70% were male. The study  
749 population was characterized by Motzer scores as follows: 28% favorable (0), 56% intermediate  
750 (1-2), 8% poor (3–5), and 7% missing.

751 The results are presented in Figure 3. PFS was statistically significantly prolonged among  
752 patients receiving Avastin plus IFN- $\alpha$ 2a compared to those receiving IFN- $\alpha$ 2a alone; median PFS  
753 was 10.2 months vs. 5.4 months [HR 0.60 (95% CI 0.49, 0.72), p-value <0.0001, stratified log-rank  
754 test]. Among the 595 patients with measurable disease, ORR was also significantly higher (30% vs.  
755 12%, p <0.0001, stratified CMH test). There was no improvement in OS based on the final analysis  
756 conducted after 444 deaths, with a median OS of 23 months in the Avastin plus IFN- $\alpha$ 2a arm and  
757 21 months in the IFN- $\alpha$ 2a plus placebo arm [HR 0.86, (95% CI 0.72, 1.04)].  
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760

**Figure 3**  
Progression-Free Survival in Study 7



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762

### 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.

769

### 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.**

10136665

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080-4990

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