

## 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: November 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 (14.4).]*

### 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  
150 was  $\leq 0.3\%$  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  
200 hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen  
201 desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. In clinical  
202 studies, infusion reactions with the first dose of Avastin were uncommon ( $< 3\%$ ) and severe  
203 reactions occurred in 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 4198 patients with CRC, non-squamous NSCLC,  
241 glioblastoma, or mCRC trials including controlled (Studies 1, 2, 4, and 7) or uncontrolled, single arm  
242 (Study 5) treated at the recommended dose and schedule for a median of 8 to 23 doses of Avastin.  
243 [See *Clinical Studies (14)*.] The population was aged 18-88 years (median 60 years), 43.6% male  
244 and 83.8% white. The population included 1783 first- and second-line mCRC patients who received  
245 a median of 10 doses of Avastin, 480 first-line metastatic NSCLC patients who received a median of  
246 8 doses of Avastin, 163 glioblastoma patients who received a median of 9 doses of Avastin, and  
247 337 mCRC patients who received a median of 16 doses of Avastin. These data also reflect exposure  
248 to Avastin in 363 patients with metastatic breast cancer (MBC) who received a median of 9.5 doses  
249 of Avastin, 669 female adjuvant CRC patients who received a median of 23 doses of Avastin and  
250 exposure to Avastin in 403 previously untreated patients with diffuse large B-cell lymphoma  
251 (DLBCL) who received a median of 8 doses of Avastin. Avastin is not approved for use in MBC,  
252 adjuvant CRC, or DLBCL.

253 *Surgery and Wound Healing Complications*

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

259 In Study 5, events of post-operative wound healing complications (craniotomy site wound  
260 dehiscence and cerebrospinal fluid leak) occurred in patients with previously treated glioblastoma:  
261 3/84 patients in the Avastin alone arm and 1/79 patients in the Avastin plus irinotecan arm.  
262 [See *Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.2)*.]

263 *Hemorrhage*

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

271 *Venous Thromboembolic Events*

272 The overall incidence of Grade 3–4 venous thromboembolic events in Study 1 was 15.1% in  
273 patients receiving bolus-IFL plus Avastin and 13.6% in patients receiving bolus-IFL plus placebo.  
274 In Study 1, more patients in the Avastin containing arm experienced deep venous thrombosis (34 vs.  
275 19 patients ) and intra-abdominal venous thrombosis (10 vs. 5 patients).

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

282 In a second, randomized, 4-arm study in 1401 patients with mCRC, prospectively evaluating the  
283 incidence of VTE (all grades), the overall incidence of first VTE was higher in the Avastin  
284 containing arms (13.5%) than the chemotherapy alone arms (9.6%). Among the 116 patients treated

285 with anticoagulants following an initial VTE event (73 in the Avastin plus chemotherapy arms and  
286 43 in the chemotherapy alone arms), the overall incidence of subsequent VTEs was also higher  
287 among the Avastin treated patients (31.5% vs. 25.6%). In this subgroup of patients treated with  
288 anticoagulants, the overall incidence of bleeding, the majority of which were Grade 1, was higher in  
289 the Avastin treated arms than the chemotherapy arms (27.4% vs. 20.9%). [See *Dosage and*  
290 *Administration (2.4).*]

### 291 *Neutropenia and Infection*

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

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

### 307 *Proteinuria*

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

### 315 *Congestive Heart Failure (CHF)*

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

323 In previously untreated patients with diffuse large B-cell lymphoma (DLBCL), an indication for  
324 which Avastin is not approved, the incidence of CHF and decline in left-ventricular ejection fraction  
325 (LVEF) were significantly increased in the Avastin plus R-CHOP (rituximab, cyclophosphamide,  
326 doxorubicin, vincristine, and prednisone) arm (n=403) compared to the placebo plus R-CHOP arm  
327 (n=379); both regimens were given for 6 to 8 cycles. At the completion of R-CHOP therapy, the  
328 incidence of CHF was 10.9% in the Avastin plus R-CHOP arm compared to 5.0% in the R-CHOP  
329 alone arm [relative risk (95% CI) of 2.2 (1.3, 3.7)]. The incidence of a LVEF event, defined as a  
330 decline from baseline of 20% or more in LVEF or a decline from baseline of 10% or more to a  
331 LVEF value of less than 50%, was also increased in the Avastin plus R-CHOP arm (10.4%)  
332 compared to the R-CHOP alone arm (5.0%). Time to onset of left-ventricular dysfunction or CHF

333 was 1–6 months after initiation of therapy in at least 85% of the patients and was resolved in 62% of  
334 the patients experiencing CHF in the Avastin arm compared to 82% in the control arm.

#### 335 *Ovarian Failure*

336 The incidence of new cases of ovarian failure (defined as amenorrhoea lasting 3 or more months,  
337 FSH level  $\geq 30$  mIU/mL and a negative serum  $\beta$ -HCG pregnancy test) was prospectively evaluated  
338 in a subset of 179 women receiving mFOLFOX chemotherapy alone (n=84) or with Avastin  
339 (n=95). New cases of ovarian failure were identified in 34% (32/95) of women receiving Avastin in  
340 combination with chemotherapy compared with 2% (2/84) of women receiving chemotherapy alone  
341 [relative risk of 14 (95% CI 4, 53)]. After discontinuation of Avastin treatment, recovery of ovarian  
342 function at all time points during the post-treatment period was demonstrated in 22% (7/32) of the  
343 Avastin-treated women. Recovery of ovarian function is defined as resumption of menses, a positive  
344 serum  $\beta$ -HCG pregnancy test, or a FSH level  $< 30$  mIU/mL during the post-treatment period. Long  
345 term effects of Avastin exposure on fertility are unknown. [See *Warnings and Precautions (5.10)*,  
346 *Use in Specific Populations (8.6)*.]

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

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

351 All Grade 3–4 adverse events and selected Grade 1–2 adverse events (hypertension, proteinuria,  
352 thromboembolic events) were collected in the entire study population. Severe and life-threatening  
353 (Grade 3–4) adverse events, which occurred at a higher incidence ( $\geq 2\%$ ) in patients receiving  
354 bolus-IFL plus Avastin as compared to bolus-IFL plus placebo, are presented in Table 1.  
355

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

|                            | Arm 1<br>IFL□ + Placebo<br>(n=396) | Arm 2<br>IFL□ + Avastin<br>(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.

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

**Table 2**  
 NCI-CTC Grade 1-4 Adverse Events in Study 1  
 (Occurring at Higher Incidence [ $\geq 5\%$ ] in IFL+Avastin vs. IFL)

|                             | Arm 1<br>IFL+Placebo<br>(n=98) | Arm 2<br>IFL+Avastin<br>(n=102) | Arm 3<br>5-FU/LV+Avastin<br>(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<br>IFL+Placebo<br>(n=98) | Arm 2<br>IFL+Avastin<br>(n=102) | Arm 3<br>5-FU/LV□+Avastin<br>(n=109) |
|-----------------------|--------------------------------|---------------------------------|--------------------------------------|
| <u>Special Senses</u> |                                |                                 |                                      |
| Taste Disorder        | 9%                             | 14%                             | 21%                                  |
| <u>Urogenital</u>     |                                |                                 |                                      |
| Proteinuria           | 24%                            | 36%                             | 36%                                  |

363

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

365 Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events related to treatment  
 366 were collected in Study 2. The most frequent adverse events (selected Grade 3-5 non-hematologic  
 367 and Grade 4-5 hematologic adverse events) occurring at a higher incidence ( $\geq 2\%$ ) in 287 patients  
 368 receiving FOLFOX4 plus Avastin compared to 285 patients receiving FOLFOX4 alone were fatigue  
 369 (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%),  
 370 vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8%  
 371 vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache  
 372 (3% vs. 0%). These data are likely to under-estimate the true adverse event rates due to the reporting  
 373 mechanisms used in Study 2.

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

375 Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected in  
 376 Study 4. Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events (occurring at a  
 377 higher incidence ( $\geq 2\%$ ) in 427 patients receiving PC plus Avastin compared with 441 patients  
 378 receiving PC alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs.  
 379 0.7%), infection without neutropenia (7% vs. 3%), venous thrombus/embolism (5% vs. 3%), febrile  
 380 neutropenia (5% vs. 2%), pneumonitis/pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or  
 381 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3%  
 382 vs. 0%).

383 *Glioblastoma*

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

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

393 In patients receiving Avastin alone or Avastin plus irinotecan (N=163), the incidence of  
 394 Avastin-related adverse events (Grade 1-4) were bleeding/hemorrhage (40%), epistaxis (26%), CNS  
 395 hemorrhage (5%), hypertension (32%), venous thromboembolic event (8%), arterial thromboembolic  
 396 event (6%), wound-healing complications (6%), proteinuria (4%), gastrointestinal perforation (2%),  
 397 and RPLS (1%). The incidence of Grade 3-5 events in these 163 patients were bleeding/hemorrhage  
 398 (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic event (7%), arterial

399 thromboembolic event (3%), wound-healing complications (3%), proteinuria (1%), and  
400 gastrointestinal perforation (2%).

401 *Metastatic Renal Cell Carcinoma (mRCC)*

402 All grade adverse events were collected in Study 7. Grade 3–5 adverse events occurring at a  
403 higher incidence ( $\geq 2\%$ ) in 337 patients receiving interferon alfa (IFN- $\alpha$ ) plus Avastin compared to  
404 304 patients receiving IFN- $\alpha$  plus placebo arm were fatigue (13% vs. 8%), asthenia (10% vs. 7%),  
405 proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis),  
406 and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured,  
407 gastric ulcer hemorrhage, gingival bleeding, haemoptysis, hemorrhage intracranial, large intestinal  
408 hemorrhage, respiratory tract hemorrhage, and traumatic hematoma).

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

411

**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<br>(n=304) | IFN- $\alpha$ +<br>Avastin<br>(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.

412

413 The following adverse events were reported at a 5-fold greater incidence in the IFN- $\alpha$  plus  
414 Avastin arm compared to IFN- $\alpha$  alone and not represented in Table 3: gingival bleeding (13 patients

415 vs. 1 patient); rhinitis (9 vs.0 ); blurred vision (8 vs. 0); gingivitis (8 vs. 1); gastroesophageal reflux  
416 disease (8 vs.1 ); tinnitus (7 vs. 1); tooth abscess (7 vs.0); mouth ulceration (6 vs. 0); acne (5 vs. 0);  
417 deafness (5 vs. 0); gastritis (5 vs. 0); gingival pain (5 vs. 0) and pulmonary embolism (5 vs. 1).

## 418 **6.2 Immunogenicity**

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

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

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

## 430 **6.3 Postmarketing Experience**

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

434 *Body as a Whole:* Polyserositis

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

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

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

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

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

441 *Hemic and lymphatic:* Pancytopenia

442 *Hepatobiliary disorders:* Gallbladder perforation

443 *Musculoskeletal:* Osteonecrosis of the jaw

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

445 *Respiratory:* Nasal septum perforation, dysphonia

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

447 Arterial thromboembolic events, Hypertension, Gastrointestinal perforation, Hemorrhage

448

## 449 **7 DRUG INTERACTIONS**

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

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

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

461

462 **8 USE IN SPECIFIC POPULATIONS**

463 **8.1 Pregnancy**

464 *Pregnancy Category C*

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

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

475 **8.3 Nursing Mothers**

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

483 **8.4 Pediatric Use**

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

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

489 Juvenile cynomolgus monkeys with open growth plates exhibited physal dysplasia following 4 to  
490 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure).  
491 The incidence and severity of physal dysplasia were dose-related and were partially reversible upon  
492 cessation of treatment.

493 **8.5 Geriatric Use**

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

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

501 In Study 4, patients aged  $\geq 65$  years receiving carboplatin, paclitaxel, and Avastin had a greater  
502 relative risk for proteinuria as compared to younger patients. [See *Warnings and Precautions (5.8)*.]  
503

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

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

### 515 **8.6 Females of Reproductive Potential**

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

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

524

## 525 **10 OVERDOSAGE**

526 The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of  
527 16 patients and with severe headache in three of 16 patients.

528

## 529 **11 DESCRIPTION**

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

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

545

## 546 **12 CLINICAL PHARMACOLOGY**

### 547 **12.1 Mechanism of Action**

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

### 553 **12.3 Pharmacokinetics**

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

557 491 patients who received 1 to 20 mg/kg of Avastin weekly, every 2 weeks, or every 3 weeks, the  
558 estimated half-life of bevacizumab was approximately 20 days (range 11–50 days). The predicted  
559 time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg of  
560 bevacizumab every 2 weeks was 2.8.

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

569

## 570 **13 NONCLINICAL TOXICOLOGY**

### 571 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

### 582 **13.2 Animal Toxicology and/or Pharmacology**

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

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

### 594 **13.3 Reproductive and Developmental Toxicology**

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

601

602 **14 CLINICAL STUDIES**

603 **14.1 Metastatic Colorectal Cancer (mCRC)**

604 *Study 1*

605 In this double-blind, active-controlled study, patients were randomized (1:1:1) to IV bolus-IFL  
606 (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  
607 4 weeks every 6 weeks) plus placebo (Arm 1), bolus-IFL plus Avastin (5 mg/kg every 2 weeks)  
608 (Arm 2), or 5-FU/LV plus Avastin (5 mg/kg every 2 weeks) (Arm 3). Enrollment in Arm 3 was  
609 discontinued, as pre-specified, when the toxicity of Avastin in combination with the bolus-IFL  
610 regimen was deemed acceptable. The main outcome measure was overall survival (OS).

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

615 The addition of Avastin resulted in an improvement in survival across subgroups defined by age  
616 (<65 yrs, ≥65 yrs) and gender. Results are presented in Table 4 and Figure 1.

617

**Table 4**  
Study 1 Efficacy Results

|  | IFL+Placebo | IFL+Avastin<br>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                           |

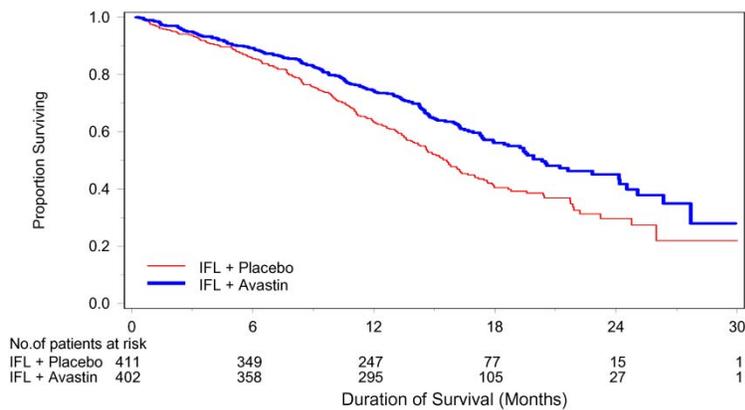
<sup>a</sup> p<0.001 by stratified log rank test.

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

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



621  
622

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%).

## 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.

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

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

674 In a second study, 2710 patients with stage II and III colon cancer who had undergone surgery with  
675 curative intent, were randomized to receive either Avastin administered at a dose equivalent to  
676 2.5 mg/kg/week in combination with mFOLFOX6 (N=1354) or mFOLFOX6 alone (N=1356). The  
677 median age was 57 years, 50% were male and 87% Caucasian. Seventy-five percent had stage III  
678 disease. The main efficacy outcome was DFS among stage III patients. The hazard ratio for DFS  
679 was 0.92 (95% CI: 0.77, 1.10). Overall survival, an additional efficacy outcome, was not  
680 significantly improved with the addition of Avastin to mFOLFOX6 (HR=0.96, 95% CI=[0.75,1.22].  
681

### 682 **14.3 Unresectable Non–Squamous Non–Small Cell Lung Cancer (NSCLC)**

#### 683 *Study 4*

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

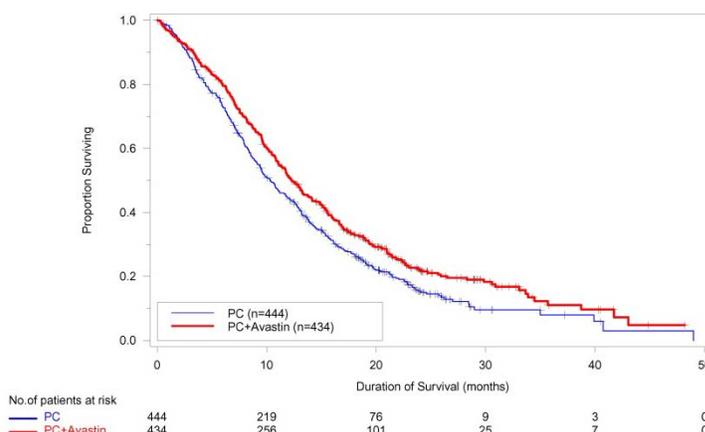
687 Chemotherapy-naïve patients with locally advanced, metastatic or recurrent non–squamous  
688 NSCLC were randomized (1:1) to receive six 21-day cycles of paclitaxel 200 mg/m<sup>2</sup> and carboplatin  
689 AUC=6.0, by IV on day 1 (PC) or PC in combination with Avastin 15 mg/kg by IV on day 1 (PC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

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

700 The results are presented in Figure 2. OS was statistically significantly higher among patients  
701 receiving PC plus Avastin compared with those receiving PC alone; median OS was 12.3 months vs.  
702 10.3 months [hazard ratio 0.80 (repeated 95% CI 0.68, 0.94), final p- value 0.013, stratified log-rank  
703 test]. Based on investigator assessment which was not independently verified, patients were  
704 reported to have longer PFS with Avastin in combination with PC compared to PC alone.  
705

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707

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



708  
709

710 In an exploratory analyses across patient subgroups, the impact of Avastin on OS was less robust  
711 in the following: women [HR=0.99 (95% CI: 0.79, 1.25)], age  $\geq$  65 years [HR=0.91 (95% CI:  
712 0.72, 1.14)] and patients with  $\geq$ 5% weight loss at study entry [HR=0.96 (95% CI: 0.73, 1.26)].

713 The safety and efficacy of Avastin in patients with locally advanced, metastatic or recurrent  
714 non-squamous NSCLC, who had not received prior chemotherapy was studied in another  
715 randomized, double-blind, placebo controlled, three-arm study of Avastin in combination with  
716 cisplatin and gemcitabine (CG) versus placebo and CG. A total of 1043 patients were randomized  
717 1:1:1 to receive placebo plus CG, Avastin 7.5 mg/kg plus CG or Avastin 15.0 mg/kg plus CG.  
718 The median age was 58 years, 36% were female, and 29% were  $\geq$  age 65. Eight percent had  
719 recurrent disease and 77% had Stage IV disease. Progression-free survival, the main efficacy  
720 outcome measure, was significantly higher in both Avastin containing arms compared to the placebo  
721 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  
722 (95% CI 0.68; 0.98),  $p=0.0301$  for the Avastin 15.0 mg/kg plus CG arm]. The addition of Avastin  
723 to CG chemotherapy failed to demonstrate an improvement in the duration of overall survival, an  
724 additional efficacy outcome measure, [HR 0.93 (95% CI 0.78; 1.11),  $p=0.4203$  for the Avastin  
725 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  
726 plus CG arm].

## 727 14.4 Glioblastoma

### 728 Study 5

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

735 Of the 85 patients randomized to the Avastin arm, the median age was 54 years, 32% were  
736 female, 81% were in first relapse, Karnofsky performance status was 90–100 for 45% and 70–80 for  
737 55%.

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

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

#### 743 *Study 6*

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

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

749 The efficacy of Avastin was supported by an objective response rate of 19.6% (95% CI 10.9%,  
750 31.3%) using the same response criteria as in Study 5. Median duration of response was 3.9 months  
751 (95% CI 2.4, 17.4).

### 752 **14.5 Metastatic Renal Cell Carcinoma (mRCC)**

#### 753 *Study 7*

754 Patients with treatment-naïve mRCC were evaluated in a multicenter, randomized, double-blind,  
755 international study comparing Avastin plus interferon alfa 2a (IFN- $\alpha$ 2a) versus placebo plus  
756 IFN- $\alpha$ 2a. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to  
757 receive either Avastin (10 mg/kg IV infusion every 2 weeks; n=327) or placebo (IV every 2 weeks;  
758 n=322) in combination with IFN- $\alpha$ 2a (9 MIU subcutaneously three times weekly, for a maximum of  
759 52 weeks). Patients were treated until disease progression or unacceptable toxicity. The main  
760 outcome measure of the study was investigator-assessed PFS. Secondary outcome measures were  
761 ORR and OS.

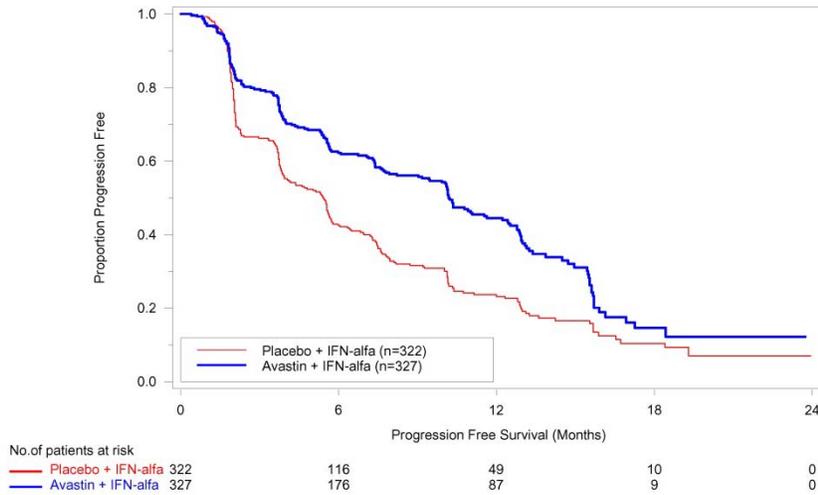
762 The median age was 60 years (range 18–82), 96% were white, and 70% were male. The study  
763 population was characterized by Motzer scores as follows: 28% favorable (0), 56% intermediate  
764 (1-2), 8% poor (3–5), and 7% missing.

765 The results are presented in Figure 3. PFS was statistically significantly prolonged among  
766 patients receiving Avastin plus IFN- $\alpha$ 2a compared to those receiving IFN- $\alpha$ 2a alone; median PFS  
767 was 10.2 months vs. 5.4 months [HR 0.60 (95% CI 0.49, 0.72), p-value <0.0001, stratified log-rank  
768 test]. Among the 595 patients with measurable disease, ORR was also significantly higher (30% vs.  
769 12%, p <0.0001, stratified CMH test). There was no improvement in OS based on the final analysis  
770 conducted after 444 deaths, with a median OS of 23 months in the Avastin plus IFN- $\alpha$ 2a arm and  
771 21 months in the IFN- $\alpha$ 2a plus placebo arm [HR 0.86, (95% CI 0.72, 1.04)].

772

773  
774

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



775  
776

### 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.

783

### 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.

796

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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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