

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AVASTIN safely and effectively. See full prescribing information for AVASTIN.

AVASTIN® (bevacizumab)  
Solution for intravenous infusion  
Initial U.S. Approval: 2004

### WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND HEALING COMPLICATIONS, and HEMORRHAGE

See full prescribing information for complete boxed warning.

- **Gastrointestinal Perforation:** Occurs in up to 2.4% of Avastin-treated patients. Discontinue Avastin for gastrointestinal perforation. (5.1)
- **Surgery and Wound Healing Complications:** Discontinue in patients with wound dehiscence. Discontinue at least 28 days prior to elective surgery. Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. (5.2)
- **Hemorrhage:** Severe or fatal hemorrhage, hemoptysis, gastrointestinal bleeding, CNS hemorrhage, and vaginal bleeding are increased in Avastin-treated patients. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis. (5.3)

### RECENT MAJOR CHANGES

Indications and Usage (1.1)	1/2013
Dosage and Administration (2.2)	1/2013
Indications and Usage, Limitation of Use (1.1)	10/2012
Warnings and Precautions, Surgery and Wound Healing Complications (5.2)	3/2013

### INDICATIONS AND USAGE

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

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

Limitation of Use: Avastin is not indicated for adjuvant treatment of colon cancer. (1.1)

### DOSAGE AND ADMINISTRATION

- Do not administer as an IV push or bolus. (2.1)
  - Do not initiate Avastin for 28 days following major surgery and until surgical wound is fully healed. (2.1)
- Metastatic colorectal cancer (2.2)
- 5 mg/kg IV every 2 weeks with bolus-IFL
  - 10 mg/kg IV every 2 weeks with FOLFOX4
  - 5 mg/kg IV every 2 weeks or 7.5 mg/kg IV every 3 weeks with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy after progression on a first-line Avastin containing regimen
- Non-squamous non-small cell lung cancer (2.2)
- 15 mg/kg IV every 3 weeks with carboplatin/paclitaxel
- Glioblastoma (2.2)
- 10 mg/kg IV every 2 weeks
- Metastatic renal cell carcinoma (mRCC) (2.2)
- 10 mg/kg IV every 2 weeks with interferon alfa

### DOSAGE FORMS AND STRENGTHS

- 100 mg/4 mL, single use vial (3)
- 400 mg/16 mL, single use vial (3)

### CONTRAINDICATIONS

None (4)

### WARNINGS AND PRECAUTIONS

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

### ADVERSE REACTIONS

Most common adverse reactions incidence (> 10% and at least twice the control arm rate) are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech, Inc. at 1-888-835-2555 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](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: 3/2013

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## 1 FULL PRESCRIBING INFORMATION

### 2 **WARNING: GASTROINTESTINAL PERFORATIONS, SURGERY AND WOUND** 3 **HEALING COMPLICATIONS, and HEMORRHAGE**

#### 4 **Gastrointestinal Perforations**

5 **The incidence of gastrointestinal perforation, some fatal, in Avastin-treated patients ranges**  
6 **from 0.3 to 2.4%. Discontinue Avastin in patients with gastrointestinal perforation.**

7 **[See *Dosage and Administration (2.4)*, *Warnings and Precautions (5.1)*.]**

#### 8 **Surgery and Wound Healing Complications**

9 **The incidence of wound healing and surgical complications, including serious and fatal**  
10 **complications, is increased in Avastin-treated patients. Discontinue Avastin in patients with**  
11 **wound dehiscence. The appropriate interval between termination of Avastin and subsequent**  
12 **elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has**  
13 **not been determined. Discontinue at least 28 days prior to elective surgery. Do not initiate**  
14 **Avastin for at least 28 days after surgery and until the surgical wound is fully healed.**

15 **[See *Dosage and Administration (2.4)*, *Warnings and Precautions (5.2)*, *Adverse Reactions (6.1)*.]**

#### 16 **Hemorrhage**

17 **Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, central nervous**  
18 **systems (CNS) hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more**  
19 **frequently in patients receiving Avastin. Do not administer Avastin to patients with serious**  
20 **hemorrhage or recent hemoptysis. [See *Dosage and Administration (2.4)*, *Warnings and***  
21 ***Precautions (5.3)*, *Adverse Reactions (6.1)*.]**

## 23 1 INDICATIONS AND USAGE

### 24 **1.1 Metastatic Colorectal Cancer (mCRC)**

25 Avastin is indicated for the first- or second-line treatment of patients with metastatic carcinoma of  
26 the colon or rectum in combination with intravenous 5-fluorouracil-based chemotherapy.

27 Avastin, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based  
28 chemotherapy, is indicated for the second-line treatment of patients with metastatic colorectal cancer  
29 who have progressed on a first-line Avastin-containing regimen.

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

### 32 **1.2 Non-Squamous Non-Small Cell Lung Cancer (NSCLC)**

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

### 35 **1.3 Glioblastoma**

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

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

### 41 **1.4 Metastatic Renal Cell Carcinoma (mRCC)**

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

## 45 **2 DOSAGE AND ADMINISTRATION**

### 46 **2.1 Administration**

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

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

### 54 **2.2 Recommended Doses and Schedules**

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

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

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

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

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

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

#### 67 *Glioblastoma*

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

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

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

### 71 **2.3 Preparation for Administration**

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

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

### 78 **2.4 Dose Modifications**

79 There are no recommended dose reductions.

80 Discontinue Avastin for:

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

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

100

### 101 **3 DOSAGE FORMS AND STRENGTHS**

- 102 100 mg per 4 mL single-use vial  
103 400 mg per 16 mL single-use vial

104

### 105 **4 CONTRAINDICATIONS**

106 None.

107

### 108 **5 WARNINGS AND PRECAUTIONS**

#### 109 **5.1 Gastrointestinal Perforations**

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

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

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

#### 118 **5.2 Surgery and Wound Healing Complications**

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

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

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

132 Necrotizing fasciitis including fatal cases, has been reported in patients treated with Avastin;  
133 usually secondary to wound healing complications, gastrointestinal perforation or fistula formation.  
134 Discontinue Avastin therapy in patients who develop necrotizing fasciitis. [See *Adverse Reactions*  
135 *(6.3).*]

#### 136 **5.3 Hemorrhage**

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

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

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

147 In clinical studies in non-small cell lung cancer where patients with CNS metastases who  
148 completed radiation and surgery more than 4 weeks prior to the start of Avastin were evaluated with  
149 serial CNS imaging, symptomatic Grade 2 CNS hemorrhage was documented in one of  
150 83 Avastin-treated patients (rate 1.2%, 95% CI 0.06%–5.93%).

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

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

#### 156 **5.4 Non-Gastrointestinal Fistula Formation**

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

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

#### 163 **5.5 Arterial Thromboembolic Events**

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

171 The safety of resumption of Avastin therapy after resolution of an ATE has not been studied.  
172 Discontinue Avastin in patients who experience a severe ATE. [See *Dosage and Administration*  
173 *(2.4).*]

#### 174 **5.6 Hypertension**

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

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

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

#### 184 **5.7 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)**

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

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

### 194 **5.8 Proteinuria**

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

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

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

### 208 **5.9 Infusion Reactions**

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

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

### 216 **5.10 Ovarian Failure**

217 The incidence of ovarian failure was higher (34% vs. 2%) in premenopausal women receiving  
218 Avastin in combination with mFOLFOX chemotherapy as compared to those receiving mFOLFOX  
219 chemotherapy alone for adjuvant treatment for colorectal cancer, a use for which Avastin is not  
220 approved. Inform females of reproductive potential of the risk of ovarian failure prior to starting  
221 treatment with Avastin. [See *Adverse Reactions* (6.1), *Use in Specific Populations* (8.6).]  
222

## 223 **6 ADVERSE REACTIONS**

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

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

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

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

## 246 **6.1 Clinical Trial Experience**

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

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

### 263 *Surgery and Wound Healing Complications*

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

269 In Study 6, events of post-operative wound healing complications (craniotomy site wound  
270 dehiscence and cerebrospinal fluid leak) occurred in patients with previously treated glioblastoma:  
271 3/84 patients in the Avastin alone arm and 1/79 patients in the Avastin plus irinotecan arm.  
272 [See *Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.2)*.]

### 273 *Hemorrhage*

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

### 281 *Venous Thromboembolic Events*

282 The overall incidence of Grade 3–4 venous thromboembolic events in Study 1 was 15.1% in  
283 patients receiving bolus-IFL plus Avastin and 13.6% in patients receiving bolus-IFL plus placebo.  
284 In Study 1, more patients in the Avastin containing arm experienced deep venous thrombosis (34 vs.  
285 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

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



290 thromboembolic event occurred in 21% (11/53) of patients receiving bolus-IFL plus Avastin and 3%  
291 (1/30) of patients receiving bolus-IFL alone.

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

### 301 *Neutropenia and Infection*

302 The incidences of neutropenia and febrile neutropenia are increased in patients receiving Avastin  
303 plus chemotherapy compared to chemotherapy alone. In Study 1, the incidence of Grade 3 or 4  
304 neutropenia was increased in mCRC patients receiving IFL plus Avastin (21%) compared to patients  
305 receiving IFL alone (14%). In Study 5, the incidence of Grade 4 neutropenia was increased in  
306 NSCLC patients receiving paclitaxel/carboplatin (PC) plus Avastin (26.2%) compared with patients  
307 receiving PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC plus Avastin vs.  
308 1.8% for PC alone). There were 19 (4.5%) infections with Grade 3 or 4 neutropenia in the PC plus  
309 Avastin arm of which 3 were fatal compared to 9 (2%) neutropenic infections in patients receiving  
310 PC alone, of which none were fatal. During the first 6 cycles of treatment, the incidence of serious  
311 infections including pneumonia, febrile neutropenia, catheter infections and wound infections was  
312 increased in the PC plus Avastin arm [58 patients (13.6%)] compared to the PC alone arm  
313 [29 patients (6.6%)].

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

### 317 *Proteinuria*

318 Grade 3–4 proteinuria ranged from 0.7 to 7.4% in Studies 1, 2, 4, 5 and 8. The overall incidence  
319 of proteinuria (all grades) was only adequately assessed in Study 8, in which the incidence was 20%.  
320 Median onset of proteinuria was 5.6 months (range 15 days to 37 months) after initiation of Avastin.  
321 Median time to resolution was 6.1 months (95% CI 2.8 months, 11.3 months). Proteinuria did not  
322 resolve in 40% of patients after median follow up of 11.2 months and required permanent  
323 discontinuation of Avastin in 30% of the patients who developed proteinuria (Study 8).  
324 [See *Warnings and Precautions* (5.8).]

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

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

333 In previously untreated patients with diffuse large B-cell lymphoma (DLBCL), an indication for  
334 which Avastin is not approved, the incidence of CHF and decline in left-ventricular ejection fraction  
335 (LVEF) were significantly increased in the Avastin plus R-CHOP (rituximab, cyclophosphamide,  
336 doxorubicin, vincristine, and prednisone) arm (n=403) compared to the placebo plus R-CHOP arm  
337 (n=379); both regimens were given for 6 to 8 cycles. At the completion of R-CHOP therapy, the  
338 incidence of CHF was 10.9% in the Avastin plus R-CHOP arm compared to 5.0% in the R-CHOP

339 alone arm [relative risk (95% CI) of 2.2 (1.3, 3.7)]. The incidence of a LVEF event, defined as a  
340 decline from baseline of 20% or more in LVEF or a decline from baseline of 10% or more to a  
341 LVEF value of less than 50%, was also increased in the Avastin plus R-CHOP arm (10.4%)  
342 compared to the R-CHOP alone arm (5.0%). Time to onset of left-ventricular dysfunction or CHF  
343 was 1-6 months after initiation of therapy in at least 85% of the patients and was resolved in 62% of  
344 the patients experiencing CHF in the Avastin arm compared to 82% in the control arm.

#### 345 *Ovarian Failure*

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

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

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

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

365

**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.

366  
 367 Grade 1–4 adverse events which occurred at a higher incidence ( $\geq 5\%$ ) in patients receiving  
 368 bolus-IFL plus Avastin as compared to the bolus-IFL plus placebo arm are presented in Table 2.  
 369 Grade 1–4 adverse events were collected for the first approximately 100 patients in each of the three  
 370 treatment arms who were enrolled until enrollment in Arm 3 (5-FU/LV + Avastin) was discontinued.  
 371

**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%

373

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

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

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

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

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

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

399 *Glioblastoma*

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

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

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

417 *Metastatic Renal Cell Carcinoma (mRCC)*

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

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

427

**Table 3**  
NCI-CTC Grades 1–5 Adverse Events in Study 8 (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.

428  
429 The following adverse events were reported at a 5-fold greater incidence in the IFN- $\alpha$  plus  
430 Avastin arm compared to IFN- $\alpha$  alone and not represented in Table 3: gingival bleeding (13 patients  
431 vs. 1 patient); rhinitis (9 vs.0 ); blurred vision (8 vs. 0); gingivitis (8 vs. 1); gastroesophageal reflux  
432 disease (8 vs.1 ); tinnitus (7 vs. 1); tooth abscess (7 vs.0); mouth ulceration (6 vs. 0); acne (5 vs. 0);  
433 deafness (5 vs. 0); gastritis (5 vs. 0); gingival pain (5 vs. 0) and pulmonary embolism (5 vs. 1).

## 434 6.2 Immunogenicity

435 As with all therapeutic proteins, there is a potential for an immune response to Avastin.  
436 In clinical trials of adjuvant colon carcinoma, 14 of 2233 evaluable patients (0.63%) tested positive  
437 for treatment-emergent anti-bevacizumab antibodies detected by an electrochemiluminescent (ECL)  
438 based assay. Among these 14 patients, three tested positive for neutralizing antibodies against  
439 bevacizumab using an enzyme-linked immunosorbent assay (ELISA). The clinical significance of  
440 these anti-product antibody responses to bevacizumab is unknown.

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

444 incidence of antibodies to Avastin with the incidence of antibodies to other products may be  
445 misleading.

### 446 **6.3 Postmarketing Experience**

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

450 *Body as a Whole:* Polyserositis

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

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

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

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

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

457 *Hemic and lymphatic:* Pancytopenia

458 *Hepatobiliary disorders:* Gallbladder perforation

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

461 *Musculoskeletal:* Osteonecrosis of the jaw

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

463 *Respiratory:* Nasal septum perforation, dysphonia

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

465 Arterial thromboembolic events, Hypertension, Gastrointestinal perforation, Hemorrhage

466

## 467 **7 DRUG INTERACTIONS**

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

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

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

479

## 480 **8 USE IN SPECIFIC POPULATIONS**

### 481 **8.1 Pregnancy**

482 *Pregnancy Category C*

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



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

### 493 **8.3 Nursing Mothers**

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

### 501 **8.4 Pediatric Use**

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

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

507 Juvenile cynomolgus monkeys with open growth plates exhibited physal dysplasia following 4 to  
508 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure).  
509 The incidence and severity of physal dysplasia were dose-related and were partially reversible upon  
510 cessation of treatment.

### 511 **8.5 Geriatric Use**

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

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

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

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

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

### 532 **8.6 Females of Reproductive Potential**

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

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

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

541

## 542 **10 OVERDOSAGE**

543 The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of  
544 16 patients and with severe headache in three of 16 patients.

545

## 546 **11 DESCRIPTION**

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

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

562

## 563 **12 CLINICAL PHARMACOLOGY**

### 564 **12.1 Mechanism of Action**

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

### 570 **12.3 Pharmacokinetics**

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

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

586

## 587 **13 NONCLINICAL TOXICOLOGY**

### 588 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

### 599 **13.2 Animal Toxicology and/or Pharmacology**

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

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

### 611 **13.3 Reproductive and Developmental Toxicology**

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

## 619 **14 CLINICAL STUDIES**

### 620 **14.1 Metastatic Colorectal Cancer (mCRC)**

#### 621 *Study 1*

622 In this double-blind, active-controlled study, patients were randomized (1:1:1) to IV bolus-IFL  
623 (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  
624 4 weeks every 6 weeks) plus placebo (Arm 1), bolus-IFL plus Avastin (5 mg/kg every 2 weeks)  
625 (Arm 2), or 5-FU/LV plus Avastin (5 mg/kg every 2 weeks) (Arm 3). Enrollment in Arm 3 was  
626 discontinued, as pre-specified, when the toxicity of Avastin in combination with the bolus-IFL  
627 regimen was deemed acceptable. The main outcome measure was overall survival (OS).

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

632 The addition of Avastin resulted in an improvement in survival across subgroups defined by age  
633 (<65 yrs, ≥65 yrs) and gender. Results are presented in Table 4 and Figure 1.

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**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.

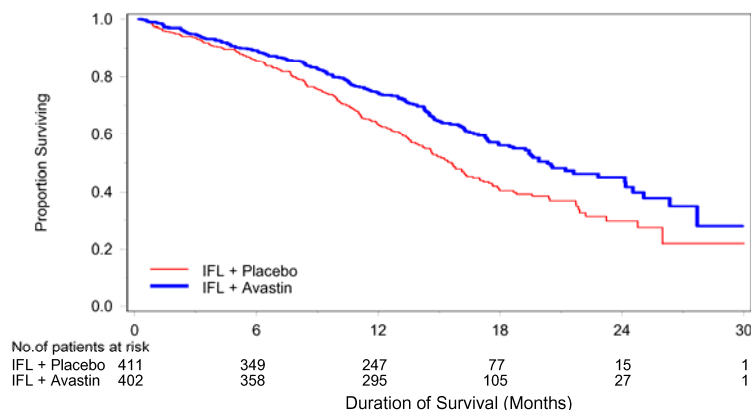
<sup>b</sup> p<0.01 by  $\chi^2$  test.

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



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643 *Study 2*

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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 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

649 2 weeks), FOLFOX4 plus Avastin (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1), or  
650 Avastin monotherapy(10 mg/kg every 2 weeks). The main outcome measure was OS.

651 The Avastin monotherapy arm was closed to accrual after enrollment of 244 of the planned  
652 290 patients following a planned interim analysis by the data monitoring committee based on  
653 evidence of decreased survival compared to FOLFOX4 alone.

654 Of the 829 patients randomized to the three arms, the median age was 61 years, 40% were female,  
655 87% were Caucasian, 49% had an ECOG performance status of 0, 26% received prior radiation  
656 therapy, and 80% received prior adjuvant chemotherapy, 99% received prior irinotecan, with or  
657 without 5-FU as therapy for metastatic disease, and 1% received prior irinotecan and 5-FU as  
658 adjuvant therapy.

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

#### 664 *Study 3*

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

#### 670 *Study 4*

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

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

682 Of the 820 patients randomized, the majority of patients were male (64%) and the median age was  
683 63.0 years (range 21 to 84 years). At baseline, 52% of patients were ECOG performance status (PS)  
684 1, 44% were ECOG PS 0, 58% received irinotecan-based therapy as first-line treatment, 55%  
685 progressed on first-line treatment within 9 months, and 77% received their last dose of Avastin as  
686 first-line treatment within 42 days of being randomized. Second-line chemotherapy regimens were  
687 generally balanced between each treatment arm.

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

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**Table 5**  
Study 4 Efficacy Results

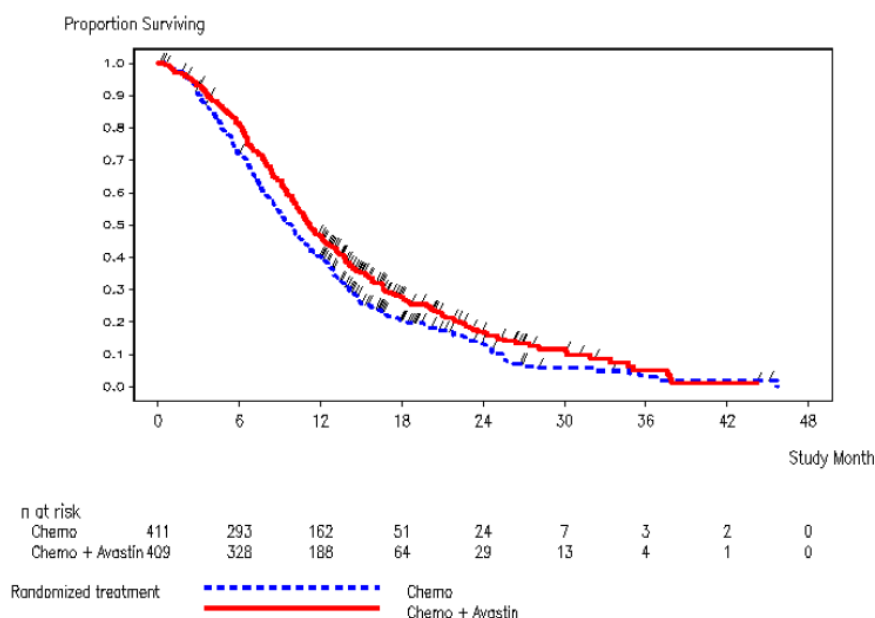
	Chemotherapy	Avastin + Chemotherapy
Number of Patients	411	409
<b>Overall Survival<sup>a</sup></b>		
Median (months)	9.8	11.2
Hazard ratio (95% CI)	0.81 (0.69, 0.94)	
<b>Progression-Free Survival<sup>b</sup></b>		
Median (months)	4.0	5.7
Hazard ratio (95% CI)	0.68 (0.59, 0.78)	

<sup>a</sup> p = 0.0057 by unstratified log rank test.

<sup>b</sup> p-value < 0.0001 by unstratified log rank test.

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



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

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

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

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

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

720 In a second study, 2710 patients with stage II and III colon cancer who had undergone surgery with  
721 curative intent, were randomized to receive either Avastin administered at a dose equivalent to  
722 2.5 mg/kg/week in combination with mFOLFOX6 (N=1354) or mFOLFOX6 alone (N=1356). The  
723 median age was 57 years, 50% were male and 87% Caucasian. Seventy-five percent had stage III  
724 disease. The main efficacy outcome was DFS among stage III patients. The hazard ratio for DFS  
725 was 0.92 (95% CI: 0.77, 1.10). Overall survival, an additional efficacy outcome, was not  
726 significantly improved with the addition of Avastin to mFOLFOX6 (HR=0.96, 95% CI=[0.75,1.22]).

### 727 **14.3 Unresectable Non–Squamous Non–Small Cell Lung Cancer (NSCLC)**

#### 728 *Study 5*

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

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

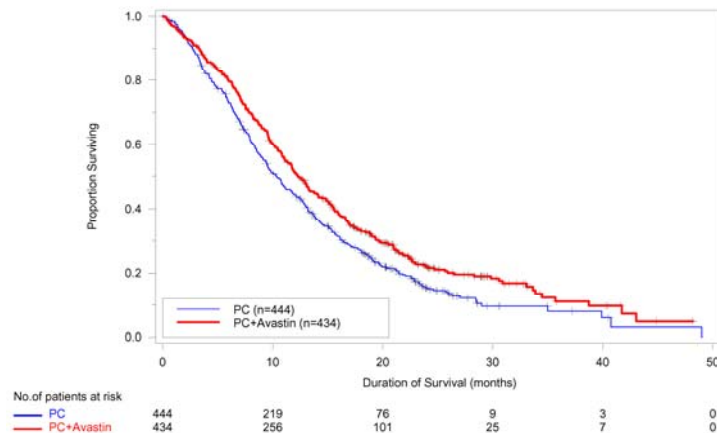
741 Of the 878 patients randomized, the median age was 63, 46% were female, 43% were ≥ age 65,  
742 and 28% had ≥5% weight loss at study entry. Eleven percent had recurrent disease and of the 89%  
743 with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had  
744 Stage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

745 The results are presented in Figure 3. OS was statistically significantly higher among patients  
746 receiving PC plus Avastin compared with those receiving PC alone; median OS was 12.3 months vs.  
747 10.3 months [hazard ratio 0.80 (repeated 95% CI 0.68, 0.94), final p- value 0.013, stratified log-rank  
748 test]. Based on investigator assessment which was not independently verified, patients were  
749 reported to have longer PFS with Avastin in combination with PC compared to PC alone.

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**Figure 3**  
Duration of Survival in Study 5



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755 In an exploratory analyses across patient subgroups, the impact of Avastin on OS was less robust  
756 in the following: women [HR=0.99 (95% CI: 0.79, 1.25)], age  $\geq 65$  years [HR=0.91 (95% CI:  
757 0.72, 1.14)] and patients with  $\geq 5\%$  weight loss at study entry [HR=0.96 (95% CI: 0.73, 1.26)].

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

#### 772 **14.4 Glioblastoma**

##### 773 *Study 6*

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

780 Of the 85 patients randomized to the Avastin arm, the median age was 54 years, 32% were  
781 female, 81% were in first relapse, Karnofsky performance status was 90–100 for 45% and 70–80 for  
782 55%.

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



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

788 *Study 7*

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

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

794 The efficacy of Avastin was supported by an objective response rate of 19.6% (95% CI 10.9%,  
795 31.3%) using the same response criteria as in Study 6. Median duration of response was 3.9 months  
796 (95% CI 2.4, 17.4).

797 **14.5 Metastatic Renal Cell Carcinoma (mRCC)**

798 *Study 8*

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

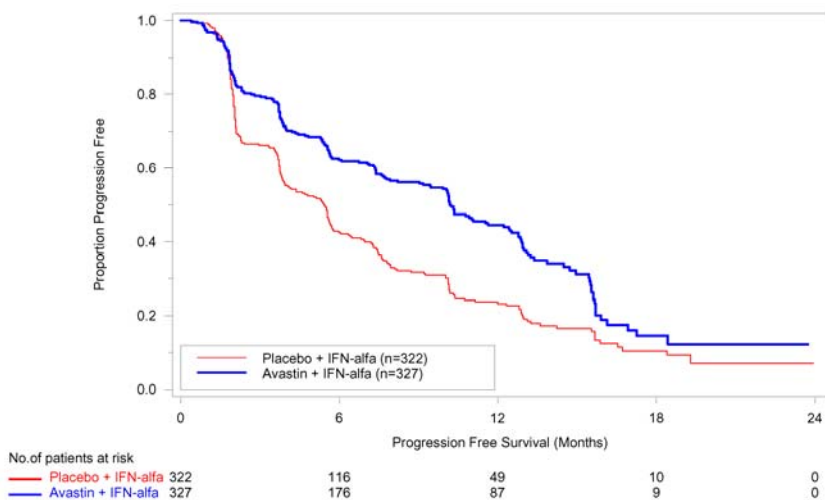
807 The median age was 60 years (range 18–82), 96% were white, and 70% were male. The study  
808 population was characterized by Motzer scores as follows: 28% favorable (0), 56% intermediate  
809 (1-2), 8% poor (3–5), and 7% missing.

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

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**Figure 4**  
Progression-Free Survival in Study 8



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## 16 HOW SUPPLIED/STORAGE AND HANDLING

Avastin vials [100 mg (NDC 50242-060-01) and 400 mg (NDC 50242-061-01)] are stable at 2–8°C (36–46°F). Avastin vials should be protected from light. **Do not freeze or shake.**

Diluted Avastin solutions may be stored at 2–8°C (36–46°F) for up to 8 hours. Store in the original carton until time of use. No incompatibilities between Avastin and polyvinylchloride or polyolefin bags have been observed.

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## 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.**

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