

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 3.2% 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. (5.3)
- **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. (5.4)

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
- Persistent, recurrent, or metastatic carcinoma of the cervix (2.2)
- 15 mg/kg IV every 3 weeks with paclitaxel/cisplatin or paclitaxel/topotecan
- Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer (2.2)
- 10 mg/kg IV every 2 weeks with paclitaxel, pegylated liposomal doxorubicin or weekly topotecan
 - 15 mg/kg IV every 3 weeks with topotecan given every 3 weeks

-----RECENT MAJOR CHANGES-----

Warnings and Precautions, Arterial Thromboembolic Events (5.5)	12/2013
Warnings and Precautions, Proteinuria (5.9)	12/2013
Indications and Usage (1.5)	08/2014
Indications and usage (1.6)	11/2014
Dosage and Administration (2.2)	11/2014
Warnings and Precautions, Gastrointestinal Perforations and Fistulae (5.1)	11/2014
Warnings and Precautions, Non-Gastrointestinal Fistulae (5.2)	11/2014
Warnings and Precautions, Hemorrhage (5.4)	08/2014
Warnings and Precautions, Venous Thromboembolic Events (5.6)	08/2014
Warnings and Precautions, Posterior Reversible Encephalopathy Syndrome (PRES) (5.8)	08/2014

-----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)
- Cervical cancer, in combination with paclitaxel and cisplatin or paclitaxel and topotecan in persistent, recurrent, or metastatic disease. (1.5)
- Platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan (1.5)

-----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-----

- Perforation or Fistula: Discontinue Avastin if perforation or fistula occurs. (5.1, 5.2)
- Arterial Thromboembolic Events (e.g., myocardial infarction, cerebral infarction): Discontinue Avastin for severe ATE. (5.5)
- Venous Thromboembolic Events: Discontinue Avastin for life-threatening VTE (5.6)
- Hypertension: Monitor blood pressure and treat hypertension. Temporarily suspend Avastin if not medically controlled. Discontinue Avastin for hypertensive crisis or hypertensive encephalopathy. (5.7)
- Posterior Reversible Encephalopathy Syndrome (PRES): Discontinue Avastin. (5.8)
- Proteinuria: Monitor urine protein. Discontinue Avastin for nephrotic syndrome. Temporarily suspend Avastin for moderate proteinuria. (5.9)
- Infusion Reactions: Stop Avastin for severe infusion reactions. (5.10)
- Ovarian Failure: Inform females of reproductive potential of the risk of ovarian failure with Avastin (5.11)

-----ADVERSE REACTIONS-----

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

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

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing Mothers: Discontinue nursing or discontinue drug. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2014

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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 3.2% . 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 occur 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.

44 1.5 Persistent, Recurrent, or Metastatic Carcinoma of the Cervix

45 Avastin in combination with paclitaxel and cisplatin or paclitaxel and topotecan is indicated for
46 the treatment of persistent, recurrent, or metastatic carcinoma of the cervix. *[See Clinical Studies*
47 *(14.6).]*

1.6 Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Avastin in combination with paclitaxel, pegylated liposomal doxorubicin or topotecan is indicated for the treatment of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who received no more than 2 prior chemotherapy regimens.

2 DOSAGE AND ADMINISTRATION

2.1 Administration

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

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

2.2 Recommended Doses and Schedules

Patients should continue treatment until disease progression or unacceptable toxicity.

Metastatic Colorectal Cancer (mCRC)

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

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

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

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

Glioblastoma

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

Metastatic Renal Cell Carcinoma (mRCC)

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

Cervical Cancer

The recommended dose of Avastin is 15 mg/kg every 3 weeks as an intravenous infusion administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin, or paclitaxel and topotecan.

Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

The recommended dose is 10mg/kg every 2 weeks in combination with one of the following intravenous chemotherapy regimens: paclitaxel, pegylated liposomal doxorubicin, or topotecan (weekly); or 15 mg/kg every 3 weeks in combination with topotecan (every 3 weeks).

2.3 Preparation for Administration

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

DO NOT ADMINISTER OR MIX WITH DEXTROSE SOLUTION.

2.4 Dose Modifications

There are no recommended dose reductions.

Discontinue Avastin for:

- Gastrointestinal perforations (gastrointestinal perforations, fistula formation in the gastrointestinal tract, intra-abdominal abscess), fistula formation involving an internal organ [See *Boxed Warning, Warnings and Precautions (5.1, 5.2).*]
- Wound dehiscence and wound healing complications requiring medical intervention [See *Warnings and Precautions (5.3).*]
- Serious hemorrhage (i.e., requiring medical intervention) [See *Boxed Warning, Warnings and Precautions (5.4).*]
- Severe arterial thromboembolic events [See *Warnings and Precautions (5.5).*]
- Life-threatening (Grade 4) venous thromboembolic events, including pulmonary embolism [See *Warnings and Precautions (5.6).*]
- Hypertensive crisis or hypertensive encephalopathy [See *Warnings and Precautions (5.7).*]
- Posterior Reversible Encephalopathy Syndrome (PRES) [See *Warnings and Precautions (5.8).*]
- Nephrotic syndrome [See *Warnings and Precautions (5.9).*]

Temporarily suspend Avastin for:

- At least 4 weeks prior to elective surgery [See *Warnings and Precautions (5.3).*]
- Severe hypertension not controlled with medical management [See *Warnings and Precautions (5.7).*]
- Moderate to severe proteinuria [See *Warnings and Precautions (5.9).*]
- Severe infusion reactions [See *Warnings and Precautions (5.10).*]

3 DOSAGE FORMS AND STRENGTHS

100 mg per 4 mL single-use vial

400 mg per 16 mL single-use vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Gastrointestinal Perforations and Fistulae

Serious and sometimes fatal gastrointestinal perforation occurs at a higher incidence in Avastin treated patients compared to controls. The incidence of gastrointestinal perforation ranged from 0.3 to 3.2% across clinical studies. [See *Adverse Reactions (6.1).*] From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (Study 9), gastrointestinal perforations were reported in 3.2% of Avastin treated patients, all of whom had a history of prior pelvic radiation. Fatal outcome was reported in <1% of Avastin-treated patients. In a platinum-resistant ovarian cancer trial (Study 10), the incidence of GI perforation was 1.7% (3/179). In this trial, patients with evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction were excluded.

The typical presentation may include abdominal pain, nausea, emesis, constipation, and fever. Perforation can be complicated by intra-abdominal abscess, fistula formation, and the need for diverting ostomies. The majority of cases occurred within the first 50 days of initiation of Avastin. Avoid use of Avastin in patients with ovarian cancer who have evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction. Permanently discontinue Avastin in patients with gastrointestinal perforation.

In Avastin clinical trials, gastrointestinal fistulae have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer and ovarian cancer. In a cervical cancer trial (Study 9), the incidence of gastrointestinal-vaginal fistulae was 8.3% in Avastin-treated patients and 0.9%

147 | in control patients, all of whom had a history of prior pelvic radiation. Patients who develop GI
148 | vaginal fistulas may also have bowel obstructions and require surgical intervention as well as
149 | diverting ostomies. [See *Boxed Warning, Dosage and Administration (2.4).*]

150 | **5.2 Non-Gastrointestinal Fistulae**

151

152 | Serious and sometimes fatal fistula formation involving tracheo-esophageal, bronchopleural,
153 | biliary, vaginal, renal and bladder sites occurs at a higher incidence in Avastin-treated patients
154 | compared to controls. Uncommon (<1%) reports of fistulae that involve areas of the body other
155 | than the gastrointestinal tract were observed in clinical trials across various indications and have also
156 | been reported in post-marketing experience. Most events occurred within the first 6 months of
157 | Avastin therapy.

158 | From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (Study 9),
159 | 1.8% of Avastin-treated patients and 1.4% of control patients were reported to have had non-
160 | gastrointestinal vaginal, vesical, or female genital tract fistulae.

161

162 | Permanently discontinue Avastin in patients with tracheoesophageal (TE) fistula or any Grade 4
163 | fistula. Discontinue Avastin in patients with fistula formation involving an internal organ. [See
164 | *Dosage and Administration (2.4).*]

165 | **5.3 Surgery and Wound Healing Complications**

166 | Avastin impairs wound healing in animal models. [See *Nonclinical Toxicology (13.2).*] In clinical
167 | trials, administration of Avastin was not allowed until at least 28 days after surgery. In a controlled
168 | clinical trial, the incidence of wound healing complications, including serious and fatal
169 | complications, in patients with mCRC who underwent surgery during the course of Avastin
170 | treatment was 15% and in patients who did not receive Avastin, was 4%. [See *Adverse Reactions*
171 | *(6.1).*]

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

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

179 | Necrotizing fasciitis including fatal cases, has been reported in patients treated with Avastin;
180 | usually secondary to wound healing complications, gastrointestinal perforation or fistula formation.
181 | Discontinue Avastin therapy in patients who develop necrotizing fasciitis. [See *Adverse Reactions*
182 | *(6.3).*]

183 | **5.4 Hemorrhage**

184 | Avastin can result in two distinct patterns of bleeding: minor hemorrhage, most commonly
185 | Grade 1 epistaxis; and serious, and in some cases fatal, hemorrhagic events. Severe or fatal
186 | hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage,
187 | epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving Avastin
188 | compared to patients receiving only chemotherapy. Across indications, the incidence of Grade ≥ 3
189 | hemorrhagic events among patients receiving Avastin ranged from 0.4 to 6.9 %. [See *Adverse*
190 | *Reactions (6.1).*]

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

194 | In clinical studies in non-small cell lung cancer where patients with CNS metastases who
195 | completed radiation and surgery more than 4 weeks prior to the start of Avastin were evaluated with

196 serial CNS imaging, symptomatic Grade 2 CNS hemorrhage was documented in one of
197 83 Avastin-treated patients (rate 1.2%, 95% CI 0.06%–5.93%).

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

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

203 **5.5 Arterial Thromboembolic Events**

204 Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction,
205 transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a
206 higher incidence in patients receiving Avastin compared to those in the control arm. Across
207 indications, the incidence of Grade ≥ 3 ATE in the Avastin containing arms was 2.6% compared to
208 0.8% in the control arms. Among patients receiving Avastin in combination with chemotherapy, the
209 risk of developing ATE during therapy was increased in patients with a history of arterial
210 thromboembolism, diabetes, or age greater than 65 years. [See *Use in Specific Populations (8.5).*]

211 The safety of resumption of Avastin therapy after resolution of an ATE has not been studied.
212 Discontinue Avastin in patients who experience a severe ATE. [See *Dosage and Administration*
213 *(2.4).*]

214 **5.6 Venous Thromboembolic Events**

215 Patients treated for persistent, recurrent, or metastatic cervical cancer with Avastin may be at
216 increased risk of venous thromboembolic events (VTE).

217 From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (Study 9),
218 Grade ≥ 3 VTE were reported in 10.6% of patients treated with chemotherapy and Avastin compared
219 with 5.4% in patients receiving chemotherapy alone. Permanently discontinue Avastin in patients
220 with life-threatening (Grade 4) VTE, including pulmonary embolism. [See *Dosage and*
221 *Administration (2.4), Adverse Reactions (6.1).*]

222 **5.7 Hypertension**

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

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

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

232 **5.8 Posterior Reversible Encephalopathy Syndrome (PRES)**

233 PRES has been reported with an incidence of $< 0.5\%$ in clinical studies. The onset of symptoms
234 occurred from 16 hours to 1 year after initiation of Avastin. PRES is a neurological disorder which
235 can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic
236 disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging (MRI) is
237 necessary to confirm the diagnosis of PRES.

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

242 **5.9 Proteinuria**

243 The incidence and severity of proteinuria is increased in patients receiving Avastin as compared to
244 controls. Nephrotic syndrome occurred in $< 1\%$ of patients receiving Avastin in clinical trials, in

245 some instances with fatal outcome. [See *Adverse Reactions (6.1)*.] In a published case series, kidney
246 biopsy of six patients with proteinuria showed findings consistent with thrombotic microangiopathy.

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

250 Suspend Avastin administration for ≥ 2 grams of proteinuria/24 hours and resume when
251 proteinuria is < 2 gm/24 hours. Discontinue Avastin in patients with nephrotic syndrome. [See
252 *Dosage and Administration (2.4)*.] Data from a postmarketing safety study showed poor correlation
253 between UPCR (Urine Protein/Creatinine Ratio) and 24 hour urine protein (Pearson Correlation 0.39
254 (95% CI 0.17, 0.57). [See *Use in Specific Populations (8.5)*.]

255 **5.10 Infusion Reactions**

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

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

263 **5.11 Ovarian Failure**

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

269

270 **6 ADVERSE REACTIONS**

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

- 273 • Gastrointestinal Perforations and Fistulae [See *Boxed Warning, Dosage and Administration (2.4),*
274 *Warnings and Precautions (5.1)*.]
- 275 • Non-Gastrointestinal Fistulae [See *Dosage and Administration (2.4), Warnings and Precautions*
276 *(5.2)*.]
- 277 • Surgery and Wound Healing Complications [See *Boxed Warning, Dosage and Administration*
278 *(2.4), Warnings and Precautions (5.3)*.]
- 279 • Hemorrhage [See *Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions*
280 *(5.4)*.]
- 281 • Arterial Thromboembolic Events [See *Dosage and Administration (2.4), Warnings and*
282 *Precautions (5.5)*.]
- 283 • Venous Thromboembolic Events [See *Dosage and Administration (2.4), Warnings and*
284 *Precautions (5.6)*.]
- 285 • Hypertensive Crisis [See *Dosage and Administration (2.4), Warnings and Precautions (5.7)*.]
- 286 • Posterior Reversible Encephalopathy Syndrome [See *Dosage and Administration (2.4),*
287 *Warnings and Precautions (5.8)*.]
- 288 • Proteinuria [See *Dosage and Administration (2.4), Warnings and Precautions (5.9)*.]
- 289 • Infusion Reactions [See *Dosage and Administration (2.4), Warnings and Precautions (5.10)*.]
- 290 • Ovarian Failure [See *Warnings and Precautions (5.11), Use in Specific Populations (8.6)*.]

291 The most common adverse reactions observed in Avastin patients at a rate $> 10\%$ and at least
292 twice the control arm rate, are epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration,
293 dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis. Some of the
294 adverse reactions are commonly seen with chemotherapy; however, Avastin may exacerbate these
295 reactions when combined with chemotherapeutic agents. Examples include palmar-plantar

296 erythrodysesthesia syndrome with pegylated liposomal doxorubicin or capecitabine peripheral
297 sensory neuropathy with paclitaxel or oxaliplatin, and nail disorders or alopecia with paclitaxel.
298 Across all studies, Avastin was discontinued in 8.4 to 21% of patients because of adverse
299 reactions.

300 **6.1 Clinical Trial Experience**

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

304 The data below reflect exposure to Avastin in 4996 patients with CRC, non-squamous NSCLC,
305 glioblastoma, mRCC, or cervical cancer or platinum-resistant recurrent epithelial ovarian, fallopian
306 tube or primary peritoneal cancer including controlled (Studies 1, 2, 4, 5, 8 9 and 10) or
307 uncontrolled, single arm trials (Study 6) treated at the recommended dose and schedule for a median
308 of 6 to 23 doses of Avastin. [*See Clinical Studies (14).*] The population was aged 18-89 years
309 (median 60 years), 42% male and 86% White. The population included 2184 first- and second-line
310 mCRC patients who received a median of 10 doses of Avastin, 480 first-line metastatic NSCLC
311 patients who received a median of 8 doses of Avastin, 163 glioblastoma patients who received a
312 median of 9 doses of Avastin, 337 mRCC patients who received a median of 16 doses of Avastin,
313 218 cervical cancer patients who received a median of 6 doses of Avastin and 179 platinum-resistant
314 recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer patients who received a
315 median of 6 doses of Avastin. These data also reflect exposure to Avastin in 363 patients with
316 metastatic breast cancer (MBC) who received a median of 9.5 doses of Avastin, 1338 adjuvant CRC
317 patients, including 669 female patients, who received a median of 23 doses of Avastin, and 403
318 previously untreated patients with diffuse large B-cell lymphoma (DLBCL) who received a median
319 of 8 doses of Avastin. Avastin is not approved for use in MBC, adjuvant CRC, or DLBCL.

320 *Surgery and Wound Healing Complications*

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

326 In Study 6, events of post-operative wound healing complications (craniotomy site wound
327 dehiscence and cerebrospinal fluid leak) occurred in patients with previously treated glioblastoma:
328 3/84 patients in the Avastin alone arm and 1/79 patients in the Avastin plus irinotecan arm.
329 [*See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.3).*]

330 *Hemorrhage*

331 The incidence of epistaxis was higher (35% vs. 10%) in patients with mCRC receiving bolus-IFL
332 plus Avastin compared with patients receiving bolus-IFL plus placebo. All but one of these events
333 were Grade 1 in severity and resolved without medical intervention. Grade 1 or 2 hemorrhagic
334 events were more frequent in patients receiving bolus-IFL plus Avastin when compared to those
335 receiving bolus-IFL plus placebo and included gastrointestinal hemorrhage (24% vs. 6%), minor
336 gum bleeding (2% vs. 0), and vaginal hemorrhage (4% vs. 2%). [*See Boxed Warning, Dosage and*
337 *Administration (2.4), Warnings and Precautions (5.4).*]

338 *Venous Thromboembolic Events*

339 The overall incidence of Grade 3–4 venous thromboembolic events in Study 1 was 15.1% in
340 patients receiving bolus-IFL plus Avastin and 13.6% in patients receiving bolus-IFL plus placebo.
341 In Study 1, more patients in the Avastin containing arm experienced deep venous thrombosis (34 vs.
342 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

343 The risk of developing a second thromboembolic event while on Avastin and oral anticoagulants
344 was evaluated in two randomized studies. In Study 1, 53 patients (14%) on the bolus-IFL plus

345 Avastin arm and 30 patients (8%) on the bolus-IFL plus placebo arm received full dose warfarin
346 following a venous thromboembolic event (VTE). Among these patients, an additional
347 thromboembolic event occurred in 21% (11/53) of patients receiving bolus-IFL plus Avastin and 3%
348 (1/30) of patients receiving bolus-IFL alone.

349 In a second, randomized, 4-arm study in 1401 patients with mCRC, prospectively evaluating the
350 incidence of VTE (all grades), the overall incidence of first VTE was higher in the Avastin
351 containing arms (13.5%) than the chemotherapy alone arms (9.6%). Among the 116 patients treated
352 with anticoagulants following an initial VTE event (73 in the Avastin plus chemotherapy arms and
353 43 in the chemotherapy alone arms), the overall incidence of subsequent VTEs was also higher
354 among the Avastin treated patients (31.5% vs. 25.6%). In this subgroup of patients treated with
355 anticoagulants, the overall incidence of bleeding, the majority of which were Grade 1, was higher in
356 the Avastin treated arms than the chemotherapy arms (27.4% vs. 20.9%).

357 From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (Study 9),
358 Grade 3 or 4 VTE have been reported in 10.6% of patients treated with chemotherapy and Avastin
359 compared with 5.4% in patients receiving chemotherapy alone. There were no patients with Grade 5
360 VTE. [See *Dosage and Administration* (2.4), *Warnings and Precautions* (5.6).]

361 *Neutropenia and Infection*

362 The incidences of neutropenia and febrile neutropenia are increased in patients receiving Avastin
363 plus chemotherapy compared to chemotherapy alone. In Study 1, the incidence of Grade 3 or 4
364 neutropenia was increased in mCRC patients receiving IFL plus Avastin (21%) compared to patients
365 receiving IFL alone (14%). In Study 5, the incidence of Grade 4 neutropenia was increased in
366 NSCLC patients receiving paclitaxel/carboplatin (PC) plus Avastin (26.2%) compared with patients
367 receiving PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC plus Avastin vs.
368 1.8% for PC alone). There were 19 (4.5%) infections with Grade 3 or 4 neutropenia in the PC plus
369 Avastin arm of which 3 were fatal compared to 9 (2%) neutropenic infections in patients receiving
370 PC alone, of which none were fatal. During the first 6 cycles of treatment, the incidence of serious
371 infections including pneumonia, febrile neutropenia, catheter infections and wound infections was
372 increased in the PC plus Avastin arm [58 patients (13.6%)] compared to the PC alone arm
373 [29 patients (6.6%)].

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

377 *Proteinuria*

378 Grade 3–4 proteinuria ranged from 0.7 to 7.4% in Studies 1, 2, 4, 5, 8 and 10. The overall
379 incidence of proteinuria (all grades) was only adequately assessed in Study 8, in which the incidence
380 was 20%. Median onset of proteinuria was 5.6 months (range 15 days to 37 months) after initiation
381 of Avastin. Median time to resolution was 6.1 months (95% CI 2.8 months, 11.3 months).
382 Proteinuria did not resolve in 40% of patients after median follow up of 11.2 months and required
383 permanent discontinuation of Avastin in 30% of the patients who developed proteinuria (Study 8).

384 In an exploratory, pooled analysis of 8,273 patients treated in 7 randomized clinical trials, 5.4%
385 (271 of 5037) of patients receiving Avastin in combination with chemotherapy experienced
386 Grade ≥ 2 proteinuria. The Grade ≥ 2 proteinuria resolved in 74.2% (201 of 271) of patients.
387 Avastin was re-initiated in 41.7% (113 of 271) of patients. Of the 113 patients who re-initiated
388 Avastin, 47.8% (54 of 113) experienced a second episode of Grade ≥ 2 proteinuria. [See *Warnings*
389 *and Precautions* (5.9).]

390 *Congestive Heart Failure (CHF)*

391 The incidence of Grade ≥ 3 left ventricular dysfunction was 1.0% in patients receiving Avastin
392 compared to 0.6% in the control arm across indications. In patients with metastatic breast cancer
393 (MBC), an indication for which Avastin is not approved, the incidence of Grade 3–4 CHF was

394 increased in patients in the Avastin plus paclitaxel arm (2.2%) as compared to the control arm
395 (0.3%). Among patients receiving prior anthracyclines for MBC, the rate of CHF was 3.8% for
396 patients receiving Avastin as compared to 0.6% for patients receiving paclitaxel alone. The safety of
397 continuation or resumption of Avastin in patients with cardiac dysfunction has not been studied.

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

410 *Ovarian Failure*

411 The incidence of new cases of ovarian failure (defined as amenorrhoea lasting 3 or more months,
412 FSH level ≥ 30 mIU/mL and a negative serum β -HCG pregnancy test) was prospectively evaluated
413 in a subset of 179 women receiving mFOLFOX chemotherapy alone (n=84) or with Avastin
414 (n=95). New cases of ovarian failure were identified in 34% (32/95) of women receiving Avastin in
415 combination with chemotherapy compared with 2% (2/84) of women receiving chemotherapy alone
416 [relative risk of 14 (95% CI 4, 53)]. After discontinuation of Avastin treatment, recovery of ovarian
417 function at all time points during the post-treatment period was demonstrated in 22% (7/32) of the
418 Avastin-treated women. Recovery of ovarian function is defined as resumption of menses, a positive
419 serum β -HCG pregnancy test, or a FSH level < 30 mIU/mL during the post-treatment period. Long
420 term effects of Avastin exposure on fertility are unknown. [See *Warnings and Precautions (5.11)*,
421 *Use in Specific Populations (8.6)*.]

422 *Post-Treatment Vascular Events*

423 In an open-label, randomized, controlled trial of Avastin in adjuvant colorectal cancer, an indication
424 for which Avastin is not approved, the overall incidence rate of post-treatment Grade ≥ 3 vascular
425 events was 3.1% (41 of 1338) among patients receiving mFOLFOX6 plus Avastin, compared to
426 1.6% (21 of 1349) among patients receiving mFOLFOX6 alone. Post-treatment vascular events
427 included arterial and venous thromboembolic events, ischemic events, and vascular aneurysms.

428 *Metastatic Colorectal Cancer (mCRC)*

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

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

436

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

	Arm 1 IFL+Placebo (n=396)	Arm 2 IFL+Avastin (n=392)
NCI-CTC Grade 3-4 Events	74%	87%
<u>Body as a Whole</u>		
Asthenia	7%	10%
Abdominal Pain	5%	8%
Pain	5%	8%
<u>Cardiovascular</u>		
Hypertension	2%	12%
Deep Vein Thrombosis	5%	9%
Intra-Abdominal Thrombosis	1%	3%
Syncope	1%	3%
<u>Digestive</u>		
Diarrhea	25%	34%
Constipation	2%	4%
<u>Hemic/Lymphatic</u>		
Leukopenia	31%	37%
Neutropenia ^a	14%	21%

^a Central laboratories were collected on Days 1 and 21 of each cycle.
 Neutrophil counts are available in 303 patients in Arm 1 and 276 in Arm 2.

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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 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%

444

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

446 Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events related to treatment
 447 were collected in Study 2. The most frequent adverse events (selected Grade 3-5 non-hematologic
 448 and Grade 4-5 hematologic adverse events) occurring at a higher incidence ($\geq 2\%$) in 287 patients
 449 receiving FOLFOX4 plus Avastin compared to 285 patients receiving FOLFOX4 alone were fatigue
 450 (19% vs. 13%), diarrhea (18% vs. 13%), sensory neuropathy (17% vs. 9%), nausea (12% vs. 5%),
 451 vomiting (11% vs. 4%), dehydration (10% vs. 5%), hypertension (9% vs. 2%), abdominal pain (8%
 452 vs. 5%), hemorrhage (5% vs. 1%), other neurological (5% vs. 3%), ileus (4% vs. 1%) and headache
 453 (3% vs. 0%). These data are likely to under-estimate the true adverse event rates due to the reporting
 454 mechanisms used in Study 2.

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

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

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

462 Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected in
 463 Study 5. Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events (occurring at a
 464 higher incidence ($\geq 2\%$) in 427 patients receiving PC plus Avastin compared with 441 patients
 465 receiving PC alone were neutropenia (27% vs. 17%), fatigue (16% vs. 13%), hypertension (8% vs.
 466 0.7%), infection without neutropenia (7% vs. 3%), venous thrombus/embolism (5% vs. 3%), febrile
 467 neutropenia (5% vs. 2%), pneumonitis/pulmonary infiltrates (5% vs. 3%), infection with Grade 3 or
 468 4 neutropenia (4% vs. 2%), hyponatremia (4% vs. 1%), headache (3% vs. 1%) and proteinuria (3%
 469 vs. 0%).

470 *Glioblastoma*

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

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

480 In patients receiving Avastin alone or Avastin plus irinotecan (N= 163), the incidence of
481 Avastin-related adverse events (Grade 1–4) were bleeding/hemorrhage (40%), epistaxis (26%), CNS
482 hemorrhage (5%), hypertension (32%), venous thromboembolic event (8%), arterial thromboembolic
483 event (6%), wound-healing complications (6%), proteinuria (4%), gastrointestinal perforation (2%),
484 and PRES (1%). The incidence of Grade 3–5 events in these 163 patients were bleeding/hemorrhage
485 (2%), CNS hemorrhage (1%), hypertension (5%), venous thromboembolic event (7%), arterial
486 thromboembolic event (3%), wound-healing complications (3%), proteinuria (1%), and
487 gastrointestinal perforation (2%).

488 *Metastatic Renal Cell Carcinoma (mRCC)*

489 All grade adverse events were collected in Study 8. Grade 3–5 adverse events occurring at a
490 higher incidence ($\geq 2\%$) in 337 patients receiving interferon alfa (IFN- α) plus Avastin compared to
491 304 patients receiving IFN- α plus placebo arm were fatigue (13% vs. 8%), asthenia (10% vs. 7%),
492 proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis),
493 and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured,
494 gastric ulcer hemorrhage, gingival bleeding, haemoptysis, hemorrhage intracranial, large intestinal
495 hemorrhage, respiratory tract hemorrhage, and traumatic hematoma).

496 Grade 1–5 adverse events occurring at a higher incidence ($\geq 5\%$) in patients receiving IFN- α plus
497 Avastin compared to the IFN- α plus placebo arm are presented in Table 3.
498

Table 3
 NCI-CTC Grades 1–5 Adverse Events in Study 8 (Occurring at
 Higher Incidence [$\geq 5\%$] in IFN- α + Avastin vs. IFN- α + Placebo)

System Organ Class/Preferred term ^a	IFN- α + Placebo (n=304)	IFN- α + Avastin (n=337)
<u>Gastrointestinal disorders</u>		
Diarrhea	16%	21%
<u>General disorders and administration site conditions</u>		
Fatigue	27%	33%
<u>Investigations</u>		
Weight decreased	15%	20%
<u>Metabolism and nutrition disorders</u>		
Anorexia	31%	36%
<u>Musculoskeletal and connective tissue disorders</u>		
Myalgia	14%	19%
Back pain	6%	12%
<u>Nervous system disorders</u>		
Headache	16%	24%
<u>Renal and urinary disorders</u>		
Proteinuria	3%	20%
<u>Respiratory, thoracic and mediastinal disorders</u>		
Epistaxis	4%	27%
Dysphonia	0%	5%
<u>Vascular disorders</u>		
Hypertension	9%	28%

^a Adverse events were encoded using MedDRA, Version 10.1.

499

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

505 *Persistent, Recurrent, or Metastatic Carcinoma of the Cervix*

506 All grade adverse reactions were collected in Study 9.

507 Grade 1-4 adverse reactions occurring where the incidence difference is $\geq 5\%$ in patients receiving
 508 Avastin plus chemotherapy compared to chemotherapy alone are presented in Table 4.

509

Table 4
 NCI-CTC Grades 1-4 and 3-4 Adverse Reactions in Study 9
 (Incidence Difference of $\geq 5\%$ Between Treatment Arms in Chemo + Avastin vs. Chemo Alone)

	Grade 1-4 reactions		Grade 3-4 reactions	
	Chemo Alone (n=222)	Chemo+Avastin (n=218)	Chemo Alone (n=222)	Chemo+Avastin (n=218)
<u>Metabolism and Nutrition Disorders</u>				
Decreased Appetite	26%	34%		
Hyperglycemia	19%	26%		
Hypomagnesemia	15%	24%		
Hyponatremia	10%	19%		
Hypoalbuminemia	11%	16%		
<u>General Disorders and Administration Site Conditions</u>				
Fatigue	75%	80%		
Edema Peripheral	22%	15%		
<u>Investigations</u>				
Weight Decreased	7%	21%		
Blood Creatinine Increased	10%	16%		
<u>Infections and Infestations</u>				
Urinary Tract Infection	14%	22%		
Infection	5%	10%		
<u>Vascular Disorders</u>				
Hypertension	6%	29%	0.5%	11.5%
Thrombosis	3%	10%	2.7%	8.3%
<u>Nervous System Disorders</u>				
Headache	13%	22%		
Dysarthria	1%	8%		
<u>Gastrointestinal Disorders</u>				
Stomatitis	10%	15%		
Proctalgia	1%	6%		
Anal Fistula	—	6%		
<u>Blood and Lymphatic System Disorders</u>				
Neutropenia	6%	12%		
Lymphopenia	5%	12%		
<u>Psychiatric Disorders</u>				
Anxiety	10%	17%		
<u>Reproductive System and Breast Disorders</u>				
Pelvic Pain	8%	14%		
<u>Respiratory, Thoracic and Mediastinal Disorders</u>				
Epistaxis	1%	17%		
<u>Renal and Urinary Disorders</u>				
Proteinuria	3%	10%		

510

511 Grade 3 or 4 adverse reactions occurring at a higher incidence ($\geq 2\%$) in 218 patients receiving
512 chemotherapy plus Avastin compared to 222 patients receiving chemotherapy alone were abdominal
513 pain (11.9% vs. 9.9%), diarrhea (5.5% vs. 2.7%), anal fistula (3.7% vs. 0%), proctalgia (2.8% vs.
514 0%), urinary tract infection (8.3% vs. 6.3%), cellulitis (3.2% vs. 0.5%), fatigue (14.2% vs. 9.9%),
515 hypokalemia (7.3% vs. 4.5%), hyponatremia (3.7% vs. 1.4%), dehydration (4.1% vs. 0.5%),
516 neutropenia (7.8% vs. 4.1%), lymphopenia (6.0% vs. 3.2%), back pain (5.5% vs. 3.2%), and pelvic
517 pain (5.5% vs. 1.4%).

518

519 There were no Grade 5 adverse reactions occurring at a higher incidence ($\geq 2\%$) in patients
520 receiving chemotherapy plus Avastin compared to patients receiving chemotherapy alone.

521

522 *Platinum-Resistant Recurrent Epithelia Ovarian, Fallopian Tube, or Primary Peritoneal Cancer*

523 Patients with evidence of recto-sigmoid involvement by pelvic examination or bowel involvement
524 on CT scan or clinical symptoms of bowel obstruction were excluded in this study.

525 Grade 2-4 adverse events occurring at a higher incidence ($\geq 5\%$) in patients receiving Avastin plus
526 chemotherapy compared to patients receiving chemotherapy alone are presented in Table 5.

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Table 5
Grade 2–4 Adverse Events Occurring at Higher Incidence [$\geq 5\%$] in Chemo + Avastin vs. Chemo
Safety–Evaluable Patients

System Organ Class Preferred Term	Chemo (n=181)	Chemo+Avastin (n=179)
Blood And Lymphatic System Disorders		
Neutropenia	25.4%	30.7%
General Disorders And Administration Site Conditions		
Mucosal Inflammation	5.5%	12.8%
Infections And Infestations		
Infection	4.4%	10.6%
Nervous System Disorders		
Peripheral Sensory Neuropathy	7.2%	17.9%
Renal And Urinary Disorders		
Proteinuria	0.6%	12.3%
Respiratory, Thoracic and Mediastinal Disorders		
Epistaxis	0.0%	5.0%
Skin And Subcutaneous Tissue Disorders		
Palmar–Plantar Erythrodysaesthesia Syndrome	5.0%	10.6%
Vascular Disorders		
Hypertension	5.5%	19.0%

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Grade 3–4 adverse events occurring at a higher incidence ($\geq 2\%$) in 179 patients receiving Avastin plus chemotherapy compared to 181 patients receiving chemotherapy alone were hypertension (6.7% vs. 1.1%) and palmar-plantar erythrodysaesthesia syndrome (4.5% vs. 1.7%). There were no Grade 5 events occurring at a higher incidence ($\geq 2\%$) in patients receiving Avastin plus chemotherapy compared to patients receiving chemotherapy alone.

540 **6.2 Immunogenicity**

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

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

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

552 **6.3 Postmarketing Experience**

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

556 *Body as a Whole:* Polyserositis

557 *Cardiovascular:* Pulmonary hypertension, PRES, Mesenteric venous occlusion

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

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

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

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

563 *Hemic and lymphatic:* Pancytopenia

564 *Hepatobiliary disorders:* Gallbladder perforation

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

567 *Musculoskeletal:* Osteonecrosis of the jaw

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

569 *Respiratory:* Nasal septum perforation, dysphonia

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

571 Arterial thromboembolic events, Hypertension, Gastrointestinal perforation, Hemorrhage

572

573 **7 DRUG INTERACTIONS**

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

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

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

585

586 **8 USE IN SPECIFIC POPULATIONS**

587 **8.1 Pregnancy**

588 *Pregnancy Category C*

589 There are no adequate or well controlled studies of bevacizumab in pregnant women. While it is
590 not known if bevacizumab crosses the placenta, human IgG is known to cross the placenta.

591 Reproduction studies in rabbits treated with approximately 1 to 12 times the recommended human
592 dose of bevacizumab demonstrated teratogenicity, including an increased incidence of specific gross
593 and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested. Other
594 observed effects included decreases in maternal and fetal body weights and an increased number of
595 fetal resorptions. [See *Nonclinical Toxicology (13.3).*]

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

599 **8.3 Nursing Mothers**

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

607 **8.4 Pediatric Use**

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

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

613 Juvenile cynomolgus monkeys with open growth plates exhibited physeal dysplasia following 4 to
614 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure).
615 The incidence and severity of physeal dysplasia were dose-related and were partially reversible upon
616 cessation of treatment.

617 **8.5 Geriatric Use**

618 In Study 1, severe adverse events that occurred at a higher incidence ($\geq 2\%$) in patients aged
619 ≥ 65 years as compared to younger patients were asthenia, sepsis, deep thrombophlebitis,
620 hypertension, hypotension, myocardial infarction, congestive heart failure, diarrhea, constipation,
621 anorexia, leukopenia, anemia, dehydration, hypokalemia, and hyponatremia. The effect of Avastin
622 on overall survival was similar in elderly patients as compared to younger patients.

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

625 In Study 5, patients aged ≥ 65 years receiving carboplatin, paclitaxel, and Avastin had a greater
626 relative risk for proteinuria as compared to younger patients. [See *Warnings and Precautions (5.9).*]

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

632 In an exploratory, pooled analysis of 1745 patients treated in five randomized, controlled studies,
633 there were 618 (35%) patients aged ≥ 65 years and 1127 patients < 65 years of age. The overall

634 incidence of arterial thromboembolic events was increased in all patients receiving Avastin with
635 chemotherapy as compared to those receiving chemotherapy alone, regardless of age. However, the
636 increase in arterial thromboembolic events incidence was greater in patients aged ≥ 65 years (8.5%
637 vs. 2.9%) as compared to those < 65 years (2.1% vs. 1.4%). [See *Warnings and Precautions* (5.5).]

638 **8.6 Females of Reproductive Potential**

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

642 In a prospectively designed substudy of 179 premenopausal women randomized to receive
643 chemotherapy with or without Avastin, the incidence of ovarian failure was higher in the Avastin
644 arm (34%) compared to the control arm (2%). After discontinuation of Avastin and chemotherapy,
645 recovery of ovarian function occurred in 22% (7/32) of these Avastin-treated patients.
646 [See *Warnings and Precautions* (5.11), *Adverse Reactions* (6.1).]

647

648 **10 OVERDOSAGE**

649 The highest dose tested in humans (20 mg/kg IV) was associated with headache in nine of
650 16 patients and with severe headache in three of 16 patients.

651

652 **11 DESCRIPTION**

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

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

668

669 **12 CLINICAL PHARMACOLOGY**

670 **12.1 Mechanism of Action**

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

676 **12.3 Pharmacokinetics**

677 The pharmacokinetic profile of bevacizumab was assessed using an assay that measures total
678 serum bevacizumab concentrations (i.e., the assay did not distinguish between free bevacizumab and
679 bevacizumab bound to VEGF ligand). Based on a population pharmacokinetic analysis of
680 491 patients who received 1 to 20 mg/kg of Avastin weekly, every 2 weeks, or every 3 weeks, the
681 estimated half-life of bevacizumab was approximately 20 days (range 11–50 days). The predicted

682 time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg of
683 bevacizumab every 2 weeks was 2.8.

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

692

693 **13 NONCLINICAL TOXICOLOGY**

694 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

705 **13.2 Animal Toxicology and/or Pharmacology**

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

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

717 **13.3 Reproductive and Developmental Toxicology**

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

724

725 **14 CLINICAL STUDIES**

726 **14.1 Metastatic Colorectal Cancer (mCRC)**

727 *Study 1*

728 In this double-blind, active-controlled study, patients were randomized (1:1:1) to IV bolus-IFL
729 (irinotecan 125 mg/m², 5-FU 500 mg/m², and leucovorin (LV) 20 mg/m² given once weekly for

730 4 weeks every 6 weeks) plus placebo (Arm 1), bolus-IFL plus Avastin (5 mg/kg every 2 weeks)
 731 (Arm 2), or 5-FU/LV plus Avastin (5 mg/kg every 2 weeks) (Arm 3). Enrollment in Arm 3 was
 732 discontinued, as pre-specified, when the toxicity of Avastin in combination with the bolus-IFL
 733 regimen was deemed acceptable. The main outcome measure was overall survival (OS).

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

738 The addition of Avastin resulted in an improvement in survival across subgroups defined by age
 739 (<65 yrs, ≥65 yrs) and gender. Results are presented in Table 6 and Figure 1.
 740

Table 6
 Study 1 Efficacy Results

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

^a p<0.001 by stratified log rank test.

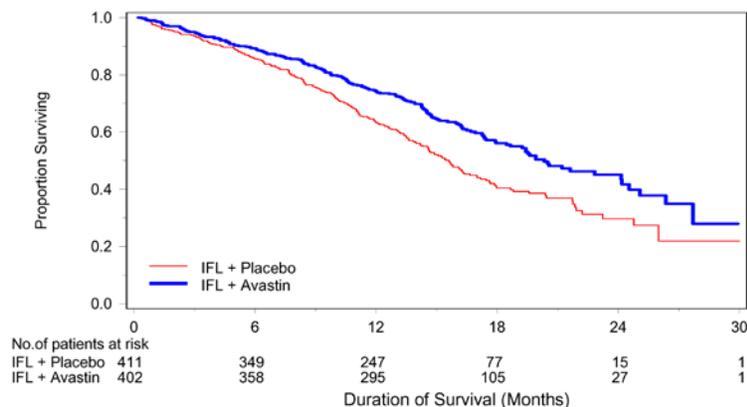
^b p<0.01 by χ^2 test.

741

742

743

Figure 1
 Duration of Survival in Study 1



744

745

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

749 *Study 2*

750 Study 2 was a randomized, open-label, active-controlled trial in patients who were previously
751 treated with irinotecan ± 5-FU for initial therapy for metastatic disease or as adjuvant therapy.
752 Patients were randomized (1:1:1) to IV FOLFOX4 (Day 1: oxaliplatin 85 mg/m² and LV 200 mg/m²
753 concurrently, then 5-FU 400 mg/m² bolus followed by 600 mg/m² continuously; Day 2: LV
754 200 mg/m², then 5-FU 400 mg/m² bolus followed by 600 mg/m² continuously; repeated every
755 2 weeks), FOLFOX4 plus Avastin (10 mg/kg every 2 weeks prior to FOLFOX4 on Day 1), or
756 Avastin monotherapy (10 mg/kg every 2 weeks). The main outcome measure was OS.

757 The Avastin monotherapy arm was closed to accrual after enrollment of 244 of the planned
758 290 patients following a planned interim analysis by the data monitoring committee based on
759 evidence of decreased survival compared to FOLFOX4 alone.

760 Of the 829 patients randomized to the three arms, the median age was 61 years, 40% were female,
761 87% were Caucasian, 49% had an ECOG performance status of 0, 26% received prior radiation
762 therapy, and 80% received prior adjuvant chemotherapy, 99% received prior irinotecan, with or
763 without 5-FU as therapy for metastatic disease, and 1% received prior irinotecan and 5-FU as
764 adjuvant therapy.

765 The addition of Avastin to FOLFOX4 resulted in significantly longer survival as compared to
766 FOLFOX4 alone (median OS 13.0 months vs. 10.8 months; hazard ratio 0.75 [95% CI 0.63, 0.89],
767 p=0.001 stratified log rank test) with clinical benefit seen in subgroups defined by age (<65 yrs,
768 ≥65 yrs) and gender. PFS and ORR based on investigator assessment were higher in the Avastin
769 plus FOLFOX4 arm.

770 *Study 3*

771 The activity of Avastin in combination with bolus or infusional 5-FU/LV was evaluated in a
772 single arm study enrolling 339 patients with mCRC with disease progression following both
773 irinotecan- and oxaliplatin-containing chemotherapy regimens. Seventy-three percent of patients
774 received concurrent bolus 5-FU/LV. One objective partial response was verified in the first
775 100 evaluable patients for an overall response rate of 1% (95% CI 0–5.5%).

776 *Study 4*

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

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

788 Of the 820 patients randomized, the majority of patients were male (64%) and the median age was
789 63.0 years (range 21 to 84 years). At baseline, 52% of patients were ECOG performance status (PS)
790 1, 44% were ECOG PS 0, 58% received irinotecan-based therapy as first-line treatment, 55%
791 progressed on first-line treatment within 9 months, and 77% received their last dose of Avastin as
792 first-line treatment within 42 days of being randomized. Second-line chemotherapy regimens were
793 generally balanced between each treatment arm.

794 The addition of Avastin to fluoropyrimidine-based chemotherapy resulted in a statistically
 795 significant prolongation of survival and PFS; there was no significant difference in overall response
 796 rate, a key secondary outcome measure. Results are presented in Table 7 and Figure 2.
 797

798 **Table 7**
 799 Study 4 Efficacy Results
 800

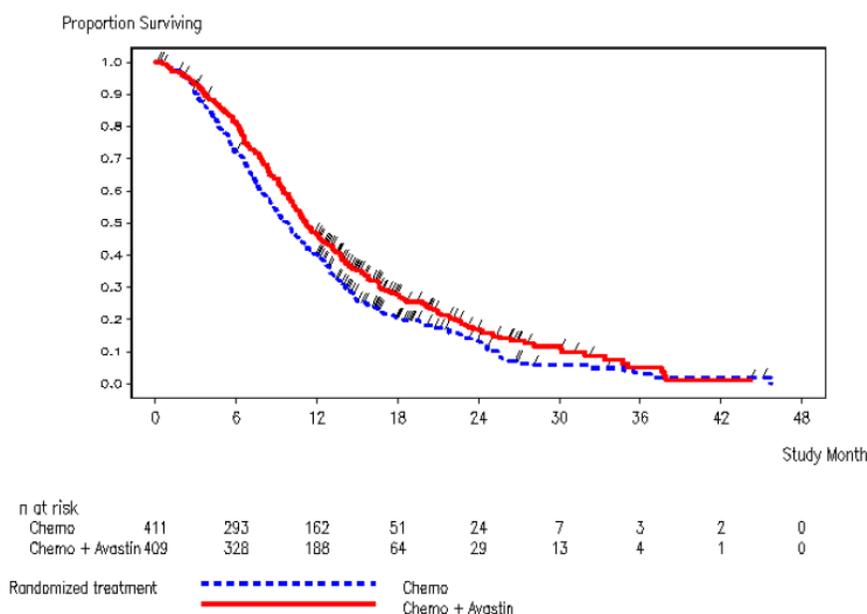
	Chemotherapy	Avastin + Chemotherapy
Number of Patients	411	409
Overall Survival^a		
Median (months)	9.8	11.2
Hazard ratio (95% CI)	0.81 (0.69, 0.94)	
Progression-Free Survival^b		
Median (months)	4.0	5.7
Hazard ratio (95% CI)	0.68 (0.59, 0.78)	

^a p = 0.0057 by unstratified log rank test.

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

801
 802
 803

Figure 2
 Duration of Survival in Study 4



804
 805

14.2 Lack of Efficacy in Adjuvant Treatment of Colon Cancer

806 Lack of efficacy of Avastin as an adjunct to standard chemotherapy for the adjuvant treatment of
 807 colon cancer was determined in two randomized, open-label, multicenter clinical trials.
 808

809 The first study conducted in 3451 patients with high risk stage II and III colon cancer, who had
 810 undergone surgery for colon cancer with curative intent, was a 3-arm study of Avastin administered
 811 at a dose equivalent to 2.5 mg/kg/week on either a 2-weekly schedule in combination with
 812 FOLFOX4, or on a 3-weekly schedule in combination with XELOX and FOLFOX4 alone. Patients
 813 were randomized as follows: 1151 patients to FOLFOX4 arm, 1155 to FOLFOX4 plus Avastin arm,

814 and 1145 to XELOX plus Avastin arm. The median age was 58 years, 54% were male, 84% were
815 Caucasian and 29% were \geq age 65. Eighty-three percent had stage III disease.

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

826 In a second study, 2710 patients with stage II and III colon cancer who had undergone surgery with
827 curative intent, were randomized to receive either Avastin administered at a dose equivalent to
828 2.5 mg/kg/week in combination with mFOLFOX6 (N=1354) or mFOLFOX6 alone (N=1356). The
829 median age was 57 years, 50% were male and 87% Caucasian. Seventy-five percent had stage III
830 disease. The main efficacy outcome was DFS among stage III patients. The hazard ratio for DFS
831 was 0.92 (95% CI: 0.77, 1.10). Overall survival, an additional efficacy outcome, was not
832 significantly improved with the addition of Avastin to mFOLFOX6 (HR=0.96, 95% CI=[0.75,1.22]).

833 **14.3 Unresectable Non–Squamous Non–Small Cell Lung Cancer (NSCLC)**

834 *Study 5*

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

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

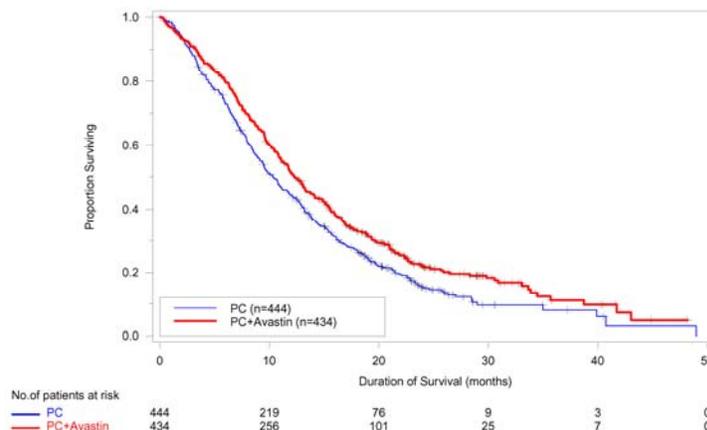
847 Of the 878 patients randomized, the median age was 63, 46% were female, 43% were \geq age 65,
848 and 28% had \geq 5% weight loss at study entry. Eleven percent had recurrent disease and of the 89%
849 with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had
850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

851 The results are presented in Figure 3. OS was statistically significantly higher among patients
852 receiving PC plus Avastin compared with those receiving PC alone; median OS was 12.3 months vs.
853 10.3 months [hazard ratio 0.80 (repeated 95% CI 0.68, 0.94), final p- value 0.013, stratified log-rank
854 test]. Based on investigator assessment which was not independently verified, patients were
855 reported to have longer PFS with Avastin in combination with PC compared to PC alone.

856

857
858

Figure 3
Duration of Survival in Study 5



859
860

861 In an exploratory analyses across patient subgroups, the impact of Avastin on OS was less robust
862 in the following: women [HR=0.99 (95% CI: 0.79, 1.25)], age ≥ 65 years [HR=0.91 (95% CI:
863 0.72, 1.14)] and patients with $\geq 5\%$ weight loss at study entry [HR=0.96 (95% CI: 0.73, 1.26)].

864 The safety and efficacy of Avastin in patients with locally advanced, metastatic or recurrent
865 non-squamous NSCLC, who had not received prior chemotherapy was studied in another
866 randomized, double-blind, placebo controlled, three-arm study of Avastin in combination with
867 cisplatin and gemcitabine (CG) versus placebo and CG. A total of 1043 patients were randomized
868 1:1:1 to receive placebo plus CG, Avastin 7.5 mg/kg plus CG or Avastin 15.0 mg/kg plus CG.
869 The median age was 58 years, 36% were female, and 29% were \geq age 65. Eight percent had
870 recurrent disease and 77% had Stage IV disease. Progression-free survival, the main efficacy
871 outcome measure, was significantly higher in both Avastin containing arms compared to the placebo
872 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
873 (95% CI 0.68; 0.98), $p=0.0301$ for the Avastin 15.0 mg/kg plus CG arm]. The addition of Avastin
874 to CG chemotherapy failed to demonstrate an improvement in the duration of overall survival, an
875 additional efficacy outcome measure, [HR 0.93 (95% CI 0.78; 1.11), $p=0.4203$ for the Avastin
876 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
877 plus CG arm].

878 **14.4 Glioblastoma**

879 *Study 6*

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

886 Of the 85 patients randomized to the Avastin arm, the median age was 54 years, 32% were
887 female, 81% were in first relapse, Karnofsky performance status was 90–100 for 45% and 70–80 for
888 55%.

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

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

894 *Study 7*

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

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

900 The efficacy of Avastin was supported by an objective response rate of 19.6% (95% CI 10.9%,
901 31.3%) using the same response criteria as in Study 6. Median duration of response was 3.9 months
902 (95% CI 2.4, 17.4).

903 **14.5 Metastatic Renal Cell Carcinoma (mRCC)**

904 *Study 8*

905 Patients with treatment-naïve mRCC were evaluated in a multicenter, randomized, double-blind,
906 international study comparing Avastin plus interferon alfa 2a (IFN- α 2a) versus placebo plus
907 IFN- α 2a. A total of 649 patients who had undergone a nephrectomy were randomized (1:1) to
908 receive either Avastin (10 mg/kg IV infusion every 2 weeks; n=327) or placebo (IV every 2 weeks;
909 n=322) in combination with IFN- α 2a (9 MIU subcutaneously three times weekly, for a maximum of
910 52 weeks). Patients were treated until disease progression or unacceptable toxicity. The main
911 outcome measure of the study was investigator-assessed PFS. Secondary outcome measures were
912 ORR and OS.

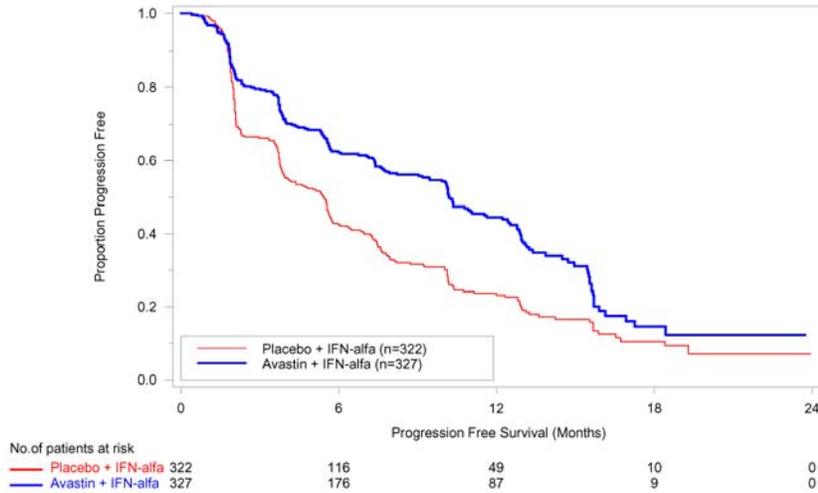
913 The median age was 60 years (range 18–82), 96% were white, and 70% were male. The study
914 population was characterized by Motzer scores as follows: 28% favorable (0), 56% intermediate
915 (1-2), 8% poor (3–5), and 7% missing.

916 The results are presented in Figure 4. PFS was statistically significantly prolonged among
917 patients receiving Avastin plus IFN- α 2a compared to those receiving IFN- α 2a alone; median PFS
918 was 10.2 months vs. 5.4 months [HR 0.60 (95% CI 0.49, 0.72), p-value <0.0001, stratified log-rank
919 test]. Among the 595 patients with measurable disease, ORR was also significantly higher (30% vs.
920 12%, p <0.0001, stratified CMH test). There was no improvement in OS based on the final analysis
921 conducted after 444 deaths, with a median OS of 23 months in the Avastin plus IFN- α 2a arm and
922 21 months in the IFN- α 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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927 **14.6 Persistent, Recurrent, or Metastatic Carcinoma of the Cervix**

928 *Study 9*

929 Patients with persistent, recurrent, or metastatic carcinoma of the cervix were evaluated in a
930 randomized, four-arm, multi-center trial comparing Avastin plus chemotherapy versus chemotherapy alone.
931 A total of 452 patients were randomized (1:1:1:1) to receive paclitaxel and Cisplatin with or
932 without Avastin, or paclitaxel and topotecan with or without Avastin.

933

934 The dosing regimens for Avastin, Paclitaxel, Cisplatin and Topotecan were as follows:

935

- 936 • Day 1: Paclitaxel 135 mg/m² IV over 24 hours, Day 2: cisplatin 50 mg/m² IV plus Avastin;
937 or Day 1: paclitaxel 175 mg/m² IV over 3 hours, Day 2: cisplatin 50 mg/m² IV plus Avastin ;
938 or Day 1: paclitaxel 175 mg/m² IV over 3 hours plus cisplatin 50 mg/m² IV plus Avastin
- 939 • Day 1: Paclitaxel 175 mg/m² over 3 hours plus Avastin, Days 1-3: topotecan 0.75 mg/m²
940 over 30 minutes

941 Patients were treated until disease progression or unacceptable adverse events precluded further
942 therapy. The main outcome measure of the study was overall survival (OS). Response rate (ORR)
943 was a secondary outcome measure.

944 The median age was 48 years (range: 20–85). Of the 452 patients randomized at baseline, 78% of
945 patients were Caucasian, 80% had received prior radiation, 74% had received prior chemotherapy
946 concurrent with radiation, and 32% had a platinum-free interval of less than 6 months. Patients had
947 a GOG Performance Status (PS) of 0 (58%) or 1 (42%). Demographic and disease characteristics
948 were balanced across arms.

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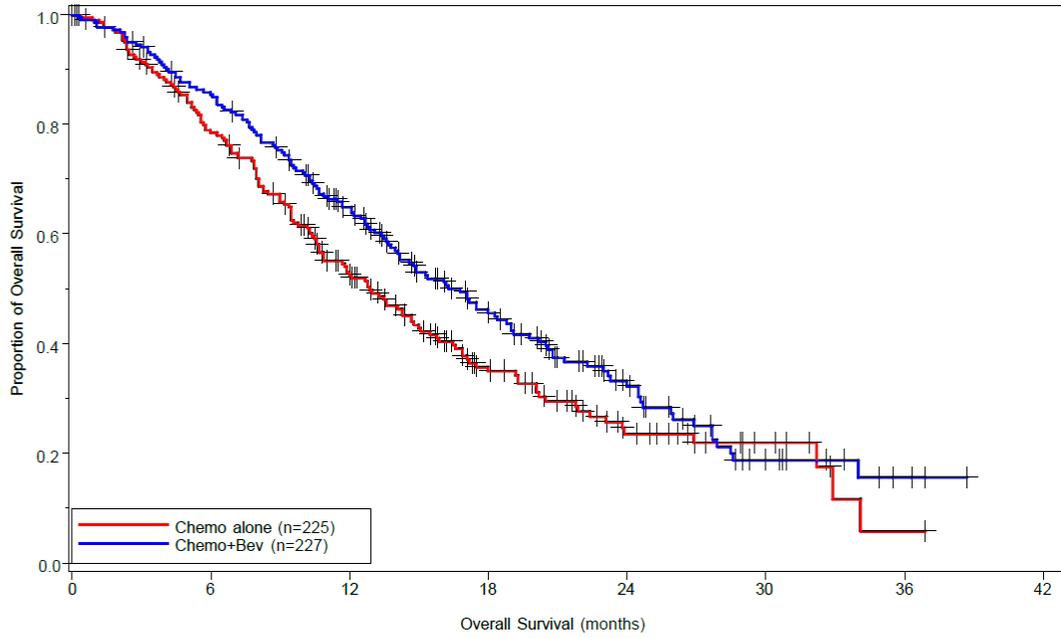
950 The study results for OS in patients who received chemotherapy plus Avastin as compared to
951 chemotherapy alone are presented in Table 8 and Figure 5.

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Figure 5
Study 9: Overall Survival for Chemotherapy vs. Chemotherapy plus Avastin

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Number at Risk:

Chemo alone

Chemo+Bev

225	171	102	49	21	8	1	0
227	188	128	73	35	12	3	0

958

Table 8
Study 9 Efficacy Results: Chemotherapy versus Chemotherapy + Avastin

	Chemotherapy (n=225)	Chemotherapy + Avastin (n=227)
Overall Survival		
Median (months) ^a	12.9	16.8
Hazard ratio [95% CI]	0.74 [0.58;0.94] (p-value ^b = 0.0132)	

^a Kaplan-Meier estimates.

^b log-rank test (stratified).

959 The overall response rate was also higher in patients who received chemotherapy plus Avastin [45%
960 (95% CI: 39, 52)] than in patients who received chemotherapy alone [34% (95% CI: 28,40)].

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Table 9**Study 9 Efficacy Results: Platinum Doublet versus Nonplatinum Doublet**

	Topotecan + Paclitaxel +/- Avastin (n=223)	Cisplatin + Paclitaxel +/- Avastin (n=229)
Overall Survival		
Median (months) ^a	13.3	15.5
Hazard ratio [95% CI]	1.15 [0.91, 1.46] p-value=0.23	

^a Kaplan-Meier estimates.

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The hazard ratio for OS with Cisplatin +Paclitaxel + Avastin as compared to Cisplatin +Paclitaxel alone was 0.72 (95% CI: 0.51,1.02). The hazard ratio for OS with Topotecan +Paclitaxel +Avastin as compared to Topotecan +Paclitaxel alone was 0.76 (95% CI: 0.55, 1.06).

14.7 Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Study 10

Avastin was evaluated in a multicenter, open-label, randomized, two-arm study (Study 10) comparing Avastin plus chemotherapy versus chemotherapy alone in patients with platinum-resistant, recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that recurred within < 6 months from the most recent platinum-based therapy (N=361). Patients had received no more than 2 prior chemotherapy regimens. Patients received one of the following intravenous chemotherapies at the discretion of the investigator: paclitaxel (80mg/m² on days 1, 8, 15 and 22 every 4 weeks; pegylated liposomal doxorubicin (PLD) 40mg/m² on day 1 every 4 weeks; or topotecan 4mg/m² on days 1, 8 and 15 every 4 weeks or 1.25m/m² on days 1-5 every 3 weeks). Patients were treated until disease progression, unacceptable toxicity, or withdrawal. Forty percent of patients on the chemotherapy alone arm received Avastin monotherapy upon progression.. The main outcome measure was investigator-assessed Progression-Free Survival (PFS). Secondary outcome measures were Objective Response Rate (ORR) and Overall Survival (OS).

The median age was 61 years (range 25–84 years) and 37% of patients were ≥ age 65. Seventy-nine percent had measurable disease at baseline, 87% had baseline CA-125 levels ≥ 2 × ULN and 31% had ascites at baseline. Seventy-three percent had a platinum-free interval (PFI) of 3–6 months and 27% had PFI of < 3 months. ECOG Performance Status was 0 for 59%, 1 for 34% and 2 for 7% of the patients.

The addition of Avastin to chemotherapy demonstrated a statistically significant improvement in investigator-assessed PFS, which was supported by a retrospective independent review analysis. Study results for the intent to treat (ITT) population are presented in Table 10 and Figure 6. Results for the separate chemotherapy cohorts are presented in Table 11.

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Table 10: Efficacy Results in Study 10 ITT Population

Efficacy Parameter	CT ^c (N=182)	CT ^c +Avastin (N=179)
<u>PFS per Investigator</u>		
Median (95% CI), in months	3.4 (2.1, 3.8)	6.8 (5.6, 7.8)
HR (95% CI) ^a		0.38 (0.30, 0.49)
p-value ^b		<0.0001
<u>Overall Survival</u>		
Median (95% CI), in months	13.3 (11.9, 16.4)	16.6 (13.7, 19.0)
HR (95% CI) ^a		0.89 (0.69, 1.14)
<u>Objective Response Rate</u>		
Number of Patients with Measurable Disease at Baseline	144	142
Rate, % (95% CI)	13% (7%, 18%)	28% (21%, 36%)
<u>Median of Response Duration</u>		
in months	5.4	9.4

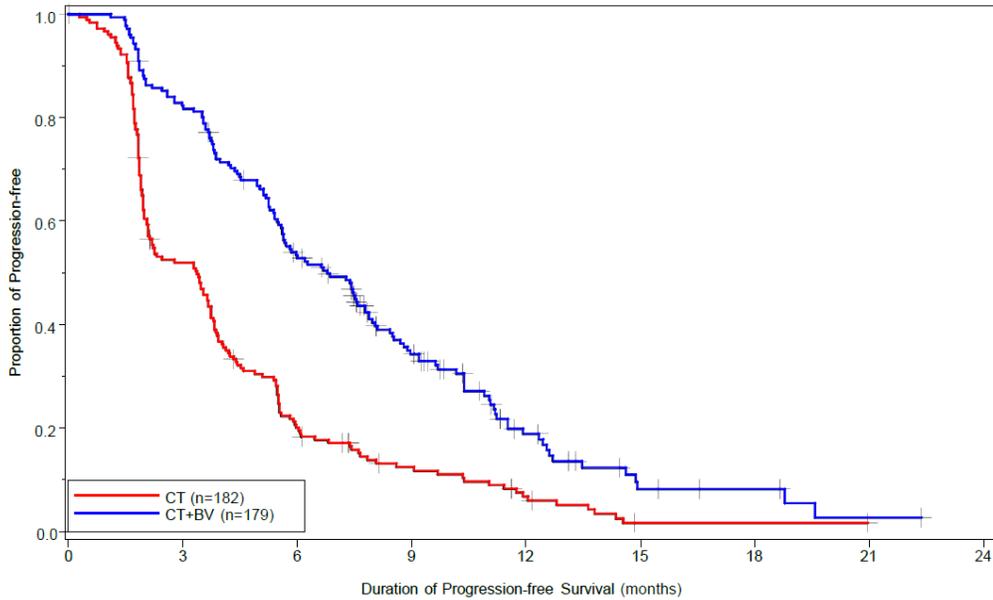
^a per stratified Cox proportional hazards model

^b per stratified logrank test

^c chemotherapy

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Figure 6
Investigator-Assessed Progression-Free Survival in Study 10 ITT Population



Number at Risk:

	0	3	6	9	12	15	18	21	24
CT	182	92	35	18	9	1	1	0	0
CT+BV	179	144	91	51	19	6	4	1	0

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Table 11 Study 10 Efficacy Results in Chemotherapy Cohorts

Efficacy Parameter	Paclitaxel		Topotecan		PLD	
	CT ^b (N=55)	CT ^b +Avastin (N=60)	CT ^b (N=63)	CT ^b +Avastin (N=57)	CT ^b (N=64)	CT ^b +Avastin (N=62)
<u>PFS per Investigator</u>						

Median (months) (95% CI)	3.9 (3.5, 5.5)	9.6 (7.8, 11.5)	2.1 (1.9, 2.3)	6.2 (5.3, 7.6)	3.5 (1.9, 3.9)	5.1 (3.9, 6.3)
HR (95% CI) ^a	0.47 (0.31, 0.72)		0.24 (0.15, 0.38)		0.47 (0.32, 0.71)	
Overall Survival						
Median (months) (95% CI)	13.2 (8.2, 19.7)	22.4 (16.7, 26.7)	13.3 (10.4, 18.3)	13.8 (11.0, 18.3)	14.1 (9.9, 17.8)	13.7 (11.0, 18.3)
HR (95% CI) ^a	0.64 (0.41, 1.01)		1.12 (0.73, 1.73)		0.94 (0.63, 1.42)	
Objective Response Rate						
Number of Patients with Measurable Disease at Baseline	43	45	50	46	51	51
Rate, % (95% CI)	30 (17, 44)	53 (39, 68)	2 (0, 6)	17 (6, 28)	8 (0, 15)	16 (6, 26)
Median of Response Duration (months)	6.8	11.6	NE	5.2	4.6	8.0

^a per stratified Cox proportional hazards model

^b chemotherapy

NE= Not Estimable

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.

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.

Avastin[®] (bevacizumab)

Manufactured by:

Genentech, Inc.

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080-4990

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