

Docket No. FDA-2010-N-0621

**Joint Statement of Undisputed Facts and Select Issues in Dispute
of the FDA Center for Drug Evaluation and Research and Genentech, Inc.**

Pursuant to the letter of February 23, 2011 from Dr. Karen Midthun, Presiding Officer for the June 28-29, 2011 hearing regarding the proposed withdrawal of the breast cancer indication for Avastin, directing counsel for Genentech, Inc. (“Genentech”) and the Center for Drug Evaluation and Research (“CDER”) (jointly “the parties”) to consult together and to prepare a joint statement of those facts that are not in dispute and of those issues that are disputed, the parties hereby submit the following joint statement.

There are facts and information upon which the parties do not agree and have not included in this document. The parties may present these additional facts and information in their respective Summaries of Arguments and Evidence to be submitted May 5, 2011 and at the hearing in this matter.

STATEMENT OF UNDISPUTED FACTS

Avastin (Bevacizumab)

1. Avastin (bevacizumab) is a recombinant, humanized monoclonal (IgG1) antibody that binds to and inhibits the biological activity of human vascular endothelial growth factor (“VEGF”) in *in vitro* and *in vivo* assay systems. Avastin has been tested in clinical trials in multiple tumor types.
2. CDER originally approved Avastin on February 26, 2004, as a first-line treatment in combination with intravenous 5-fluorouracil-based chemotherapy in patients with metastatic carcinoma of the colon and rectum. Since that time, CDER has approved Avastin for

non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease; glioblastoma, as a single agent for adult patients with progressive disease following prior therapy (accelerated approval); and metastatic renal cell carcinoma with interferon alfa. CDER does not propose to withdraw or modify any of these approved indications for Avastin.

3. The full indication for Avastin's approval in metastatic breast cancer ("MBC") is provided in Attachment 1. CDER has proposed to withdraw approval of the MBC indication.

Metastatic Breast Cancer

4. There is unmet medical need for additional safe and effective therapies for MBC.

5. MBC is an incurable disease. According to the American Cancer Society, it is estimated that more than 40,000 women in the United States died from MBC in 2009, and that over 90% of patients ultimately die from the disease.

6. MBC is a heterogeneous disease for which no single therapeutic approach is appropriate for all patients. Rather, the appropriate treatment strategy for a particular patient depends on multiple individualized factors, including tumor burden and related symptoms, underlying tumor biology (including presence or absence of hormone receptors and HER2 status), age and medical co-morbidities, and prior treatment in the adjuvant setting.

7. Approximately 70-75% of primary breast cancers are HER2-negative. Patients whose tumors over-express the HER2 protein or have more than two copies of the HER2 gene (gene-amplified) are considered to have HER2-positive MBC. Patients whose tumors do not over-express the HER2 protein or are not gene-amplified are considered to have HER2-negative MBC.

8. Treatment options for patients with MBC include the use of single-agent or combination chemotherapy, hormonal therapy, and biological therapy. Avastin is a biological therapy.

The E2100 Study

9. Genentech's sBLA submission 125085/91 included one randomized, controlled, open-label trial in the first-line treatment of MBC, E2100.¹ The E2100 study was a multicenter Phase III study led by the National Cancer Institute Therapy Evaluation Program and coordinated by the Eastern Cooperative Oncology Group ("ECOG").

10. The E2100 study investigated the combination of paclitaxel and Avastin compared to paclitaxel alone. The study enrolled 722 patients, predominantly in the United States.

11. The primary endpoint in the E2100 study was progression-free survival ("PFS").²

12. Secondary efficacy endpoints that were included in the trial were overall survival ("OS")³ and objective response rate ("ORR").⁴ The planned sample size of the E2100 study (685 patients) provided approximately 80% power after 481 deaths were observed to show a 7-month improvement in median survival (HR = 0.77) and approximately 25% power to determine a 3-month difference in median survival.

¹ "A Randomized Phase III Trial of Paclitaxel versus Paclitaxel Plus Bevacizumab (rhuMAB VEGF) As First-line Therapy for Locally Recurrent or Metastatic Breast Cancer."

² PFS is defined as time from randomization to the time of the first documented disease progression or death, whichever occurs first.

³ OS is defined as the time from randomization until death from any cause.

⁴ Objective response ("OR") is defined as a complete or partial response determined by two consecutive investigator's assessments that are four or more weeks apart. ORR is defined as the percentage of subjects who had objective responses.

13. The attached table (Attachment 2) accurately summarizes efficacy data from the E2100 study.

14. At CDER's request, because this was an open-label study, the PFS results of the E2100 study were subject to independent review.

15. The ECOG dataset results as reported by the authors were published in the peer-reviewed *New England Journal of Medicine*. The PFS results from the independent review were published in the *Journal of Clinical Oncology*.

16. At the time of Avastin's 2008 approval for its MBC indication, the degree of improvement in median PFS observed in the E2100 study, 5.5 months with an HR of 0.48, was considered to represent a direct clinical benefit for MBC patients.

The AVADO and RIBBON1 Studies

17. The AVADO study (BO17708) compared Avastin at two doses, plus docetaxel to docetaxel alone. The RIBBON1 study (AVF3694g) consisted of two independently powered comparisons under a single protocol: Avastin plus taxane/anthracycline compared with taxane/anthracycline alone (where the taxane was docetaxel or nab-paclitaxel), and Avastin plus capecitabine to capecitabine alone.

18. PFS was the primary efficacy endpoint in the AVADO and RIBBON1 studies. OS and ORR were secondary endpoints.

19. The attached table (Attachment 2) accurately summarizes efficacy data from the AVADO and RIBBON1 studies.

20. A post hoc exploratory pooled analysis of the OS data from the E2100, AVADO, and RIBBON1 studies yielded an estimated hazard ratio ("HR") of 0.97 (95% confidence interval 0.86, 1.08), p=0.56.

The Safety Profile of Avastin in First-Line MBC

21. The safety profile of Avastin is described in the FDA-approved prescribing information, provided as Attachment 1.
22. The attached prescribing information is a fair and accurate description of the safety profile of Avastin.
23. The safety data observed in the E2100, AVADO, and RIBBON1 studies were consistent with the safety profile of Avastin described in its approved prescribing information.

Avastin MBC Regulatory History at FDA

24. On October 28, 2004, Genentech and CDER discussed the E2100 study design by teleconference.
25. At a January 10, 2006 Type B teleconference to discuss Genentech's proposal to use RIBBON1 and RIBBON2 to support approval in combination with broader chemotherapy, CDER recommended that Genentech consider separate studies with the individual chemotherapy agents. CDER stated in its minutes that "the treatment effect will vary according to the chemotherapy regimen used, however, the treatment effect must be efficacious for the combinations of Bevacizumab and chemotherapy used."
26. In a supplemental BLA submission dated May 23, 2006 (sBLA 125085/91), Genentech requested approval of Avastin, in combination with taxane-based chemotherapy, for the treatment of patients who have not received chemotherapy (first-line) for their locally recurrent or metastatic breast cancer.
27. Results of the E2100 trial were presented to the Oncologic Drugs Advisory Committee ("ODAC") on December 5, 2007. A transcript and summary meeting minutes are available on FDA's web site:

<http://www.fda.gov/ohrms/dockets/ac/cder07.htm#OncologicDrugs>. These materials faithfully and accurately report on the meeting.

28. ODAC members voted as follows at the December 5, 2007 meeting:

- Are the data provided sufficient to establish a favorable risk/benefit analysis for the use of bevacizumab plus paclitaxel for first-line treatment of patients with metastatic breast cancer? (Voting Question)

Vote: Yes = 4 No = 5 Abstain = 0

29. In a letter dated February 20, 2008, Genentech requested accelerated approval for use of Avastin in combination with paclitaxel for the first-line treatment of HER2-negative MBC.

30. On February 22, 2008, CDER approved Avastin for use in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer under the Agency's accelerated approval regulations.

31. During CDER's review of sBLA 125085/91, Genentech proposed and CDER agreed that the AVADO and RIBBON1 trials could serve as the required trial(s) to verify and describe the clinical benefit.

32. Prior to granting accelerated approval, CDER viewed 24 PowerPoint slides summarizing the AVADO data, including the final PFS and the interim OS results. In the slides provided, the final PFS data showed an improvement in median PFS of 0.8 months (8.0 months in the control arm vs. 8.8 months in the Avastin 15 mg/kg arm), with stratified HR of 0.64 (0.50, 0.82) (p=0.0003). The interim OS results showed a stratified HR of 0.65 (0.42, 1.02) (p=0.057).

33. CDER's February 22, 2008 approval letter stated that approval was contingent upon successful completion of and submission of efficacy supplements containing the final reports and revised labeling for clinical studies AVADO and RIBBON1.

34. On February 26, 2009, there was a Type B meeting between CDER and Genentech.

35. On March 6, 2009, there was a follow-up call to the February 26, 2009 Type B meeting between CDER and Genentech.

36. Genentech submitted the results of the AVADO and RIBBON1 trials on November 16, 2009 in sBLA 125085/191 and sBLA 125084/192, respectively. The submissions requested expansion of Avastin's labeling to include an indication for use in combination with docetaxel chemotherapy and with taxane-based, anthracycline-based or capecitabine chemotherapy for the first-line treatment of HER2-negative MBC.

37. Results of the AVADO and RIBBON1 trials were presented to ODAC on July 20, 2010. Summary meeting minutes and a transcript are available on FDA's web site (<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm195226.htm>). These materials faithfully and accurately report on the meeting.

38. Based on their review of these trials, ODAC members voted as follows at the July 20, 2010 meeting:

- Does the addition of bevacizumab to docetaxel represent a favorable risk/benefit analysis for the initial treatment of patients with metastatic breast cancer?

Vote: Yes = 0 No = 13 Abstain = 0

- Does the addition of bevacizumab to taxanes, anthracyclines or capecitabine represent a favorable risk/benefit analysis for the initial treatment of patients with metastatic breast cancer?

Vote: Yes = 1 No = 12 Abstain = 0

- Taking into consideration the totality of findings, and the responses to Questions 1 and 2 above, do the AVADO and RIBBON1 results provide confirmatory evidence of clinical benefit of bevacizumab in combination with paclitaxel for the initial treatment of MBC?

Vote: Yes = 0 No = 13 Abstain = 0

- Should the indication for treatment of metastatic breast cancer be removed from the Avastin label?

Vote: Yes = 12 No = 1 Abstain = 0

39. Six of the 13 voting members of the July 2010 ODAC panel were members of the December 2007 ODAC panel, which had 9 voting members. Seven of the 13 voting members at the July 2010 ODAC were standing committee members, and six were temporary members for that meeting.

40. In response to feedback from the July 20, 2010 ODAC meeting, on August 16, 2010 Genentech submitted a summary of a proposed protocol for a study to characterize further the effect specifically of the combination of Avastin plus paclitaxel. The summary stated that the proposed study would include a prospective biomarker evaluation to try to identify those patients who are more likely to derive a more substantial benefit from Avastin.

41. On August 27, 2010, at CDER's request, Genentech ceased affirmative marketing of Avastin for MBC.

42. On December 16, 2010, CDER issued two complete response letters on Genentech's November 16, 2009 sBLA submissions of the AVADO and RIBBON1 results.

43. On December 16, 2010, CDER issued a Notice of Opportunity for a Hearing ("NOOH") on CDER's proposal to withdraw approval of Avastin's MBC indication.

44. The NOOH stated CDER's conclusion that AVADO and RIBBON1 failed to verify clinical benefit for Avastin in MBC and that Avastin is not safe or effective when used in accordance with its MBC indication.

45. On January 16, 2011, Genentech submitted data, analyses, and information in support of its position that Avastin should "retain accelerated approval" for

Avastin in combination with paclitaxel subject to Genentech's conduct of "a confirmatory study."

SELECT ISSUES IN DISPUTE

Despite diligent efforts on the part of both parties and their counsel, the parties have been unable to reach agreement on how to frame the central questions that must be answered to enable the Commissioner to render her decision in this case. Accordingly, each party intends to submit a separate document summarizing its understanding of the central questions to be presented and resolved. The parties have, however, identified several general topics that they agree will need to be addressed in connection with resolution of this matter, including the following:

1. The legal and regulatory standards applicable to the determinations to be made in this proceeding, including the application and interpretation of the accelerated approval regulations.
2. How CDER's and Genentech's analyses of the efficacy and safety data for Avastin differ as to their impact on the overall benefit-risk assessment of the product for its approved metastatic breast cancer indication.
3. Whether the data from studies conducted in patients with metastatic breast cancer outside the first-line setting that Genentech submitted to BLA 125085 and CDER considered are relevant to this proceeding.
4. Whether CDER's decisions on the approval of other products for the treatment of metastatic breast cancer or withdrawal of other oncology drug products are relevant to this proceeding.
5. Whether the actions or opinions of other regulatory and scientific bodies on Avastin for the treatment of metastatic breast cancer are relevant to this proceeding.

Respectfully submitted,

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April 7, 2011

ATTACHMENT 1

Avastin Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

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

See full prescribing information for complete boxed warning.

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

RECENT MAJOR CHANGES

INDICATIONS AND USAGE

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

- Metastatic colorectal cancer, with intravenous 5-fluorouracil-based chemotherapy for first- or second-line treatment. (1.1)
- Non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease. (1.2)
- Metastatic breast cancer, with paclitaxel for treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer. (1.3)
 - Effectiveness based on improvement in progression-free survival. No data available demonstrating improvement in disease-related symptoms or survival with Avastin.
 - Not indicated for disease progression following anthracycline and taxane chemotherapy administered for metastatic disease.
- Glioblastoma, as a single agent for adult patients with progressive disease following prior therapy. (1.4)
 - 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 (1.5)

DOSAGE AND ADMINISTRATION

- Do not administer as an IV push or bolus. (2.1)

- Do not initiate Avastin for 28 days following major surgery and until surgical wound is fully healed. (2.1)

Metastatic colorectal cancer (2.2)

- 5 mg/kg IV every 2 weeks with bolus-IFL
- 10 mg/kg IV every 2 weeks with FOLFOX4

Non-squamous non-small cell lung cancer (2.2)

- 15 mg/kg IV every 3 weeks with carboplatin/paclitaxel

Metastatic breast cancer (2.2)

- 10 mg/kg IV every 2 weeks with paclitaxel

Glioblastoma (2.2)

- 10 mg/kg IV every 2 weeks

Metastatic renal cell carcinoma (mRCC) (2.2)

- 10 mg/kg IV every 2 weeks with interferon alfa

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

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

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, taking into account the importance of the drug to the mother. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: February 2011

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FULL PRESCRIBING INFORMATION

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

Gastrointestinal Perforations

The incidence of gastrointestinal perforation, some fatal, in Avastin-treated patients ranges from 0.3 to 2.4%. Discontinue Avastin in patients with gastrointestinal perforation. [See *Dosage and Administration (2.4)*, *Warnings and Precautions (5.1)*.]

Surgery and Wound Healing Complications

The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients. Discontinue Avastin in patients with wound dehiscence. The appropriate interval between termination of Avastin and subsequent elective surgery required to reduce the risks of impaired wound healing/wound dehiscence has not been determined. 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. [See *Dosage and Administration (2.4)*, *Warnings and Precautions (5.2)*, and *Adverse Reactions (6.1)*.]

Hemorrhage

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

1 INDICATIONS AND USAGE

1.1 Metastatic Colorectal Cancer (mCRC)

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

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

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

1.3 Metastatic Breast Cancer (MBC)

Avastin is indicated for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer in combination with paclitaxel.

The effectiveness of Avastin in MBC is based on an improvement in progression free survival. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin. [See *Clinical Studies (14.3)*.]

Avastin is not indicated for patients with breast cancer that has progressed following anthracycline and taxane chemotherapy administered for metastatic disease.

1.4 Glioblastoma

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

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

1.5 Metastatic Renal Cell Carcinoma (mRCC)

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

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.

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

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

Metastatic Breast Cancer (MBC)

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

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, 5.4).]
- Wound dehiscence and wound healing complications requiring medical intervention [See Warnings and Precautions (5.2).]
- Serious hemorrhage (i.e., requiring medical intervention) [See Boxed Warning, Warnings and Precautions (5.3).]
- Severe arterial thromboembolic events [See Warnings and Precautions (5.5).]
- Hypertensive crisis or hypertensive encephalopathy [See Warnings and Precautions (5.6).]
- Reversible posterior leukoencephalopathy syndrome (RPLS) [See Warnings and Precautions (5.7).]
- Nephrotic syndrome [See Warnings and Precautions (5.8).]

Temporarily suspend Avastin for:

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

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

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 2.4% across clinical studies. [*See Adverse Reactions (6.1).*]

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

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

5.2 Surgery and Wound Healing Complications

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

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

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

5.3 Hemorrhage

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

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

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

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

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

5.4 Non-Gastrointestinal Fistula Formation

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

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

5.5 Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, angina, and a variety of other ATE occurred at a higher incidence in patients receiving Avastin compared to those in the control arm. Across indications, the incidence of Grade ≥ 3 ATE in the Avastin containing arms was 2.4% compared to 0.7% in the control arms. Among patients receiving Avastin in combination with chemotherapy, the risk of developing ATE during therapy was increased in patients with a history of arterial thromboembolism, or age greater than 65 years. *[See Use in Specific Populations (8.5).]*

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

5.6 Hypertension

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

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

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

5.7 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

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

Discontinue Avastin in patients developing RPLS. Symptoms usually resolve or improve within days, although some patients have experienced ongoing neurologic sequelae. The safety of

reinitiating Avastin therapy in patients previously experiencing RPLS is not known. *[See Dosage and Administration (2.4).]*

5.8 Proteinuria

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

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

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

5.9 Infusion Reactions

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

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

6 ADVERSE REACTIONS

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

- Gastrointestinal Perforations *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.1).]*
- Surgery and Wound Healing Complications *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.2).]*
- Hemorrhage *[See Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.3).]*
- Non-Gastrointestinal Fistula Formation *[See Dosage and Administration (2.4), Warnings and Precautions (5.4).]*
- Arterial Thromboembolic Events *[See Dosage and Administration (2.4), Warnings and Precautions (5.5).]*
- Hypertensive Crisis *[See Dosage and Administration (2.4), Warnings and Precautions (5.6).]*
- Reversible Posterior Leukoencephalopathy Syndrome *[See Dosage and Administration (2.4), Warnings and Precautions (5.7).]*
- Proteinuria *[See Dosage and Administration (2.4), Warnings and Precautions (5.8).]*

The most common adverse reactions observed in Avastin patients at a rate > 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.

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

6.1 Clinical Trial Experience

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

The data below reflect exposure to Avastin in 2661 patients with mCRC, non-squamous NSCLC, MBC, glioblastoma, or mRCC in controlled (Studies 1, 2, 4, 5, 6 and 9) or uncontrolled, single arm (Study 7) trials treated at the recommended dose and schedule for a median of 8 to 16 doses of Avastin. [See *Clinical Studies (14)*.] The population was aged 21-88 years (median 59), 46.0% male and 84.1% white. The population included 1089 first- and second-line mCRC patients who received a median of 11 doses of Avastin, 480 first-line metastatic NSCLC patients who received a median of 8 doses of Avastin, 592 MBC patients who had not received chemotherapy for metastatic disease received a median of 8 doses of Avastin, 163 glioblastoma patients who received a median of 9 doses of Avastin, and 337 mRCC patients who received a median of 16 doses of Avastin.

Surgery and Wound Healing Complications

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

In Study 7, events of post-operative wound healing complications (craniotomy site wound dehiscence and cerebrospinal fluid leak) occurred in patients with previously treated glioblastoma: 3/84 patients in the Avastin alone arm and 1/79 patients in the Avastin plus irinotecan arm. [See *Boxed Warning, Dosage and Administration (2.4), Warnings and Precautions (5.2)*.]

Hemorrhage

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

Venous Thromboembolic Events

The incidence of Grade 3–4 venous thromboembolic events was higher in patients with mCRC or NSCLC receiving Avastin with chemotherapy as compared to those receiving chemotherapy alone. The risk of developing a second subsequent thromboembolic event in mCRC patients receiving Avastin and chemotherapy was increased compared to patients receiving chemotherapy alone. In Study 1, 53 patients (14%) on the bolus-IFL plus Avastin arm and 30 patients (8%) on the bolus-IFL plus placebo arm received full dose warfarin following a venous thromboembolic event. Among these patients, an additional thromboembolic event occurred in 21% (11/53) of patients receiving bolus-IFL plus Avastin and 3% (1/30) of patients receiving bolus-IFL alone.

The overall incidence of Grade 3–4 venous thromboembolic events in Study 1 was 15.1% in patients receiving bolus-IFL plus Avastin and 13.6% in patients receiving bolus-IFL plus placebo. In Study 1, the incidence of the following Grade 3–4 venous thromboembolic events was higher in patients receiving bolus-IFL plus Avastin as compared to patients receiving bolus-IFL plus placebo: deep venous thrombosis (34 vs. 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

Neutropenia and Infection

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

In Study 7, one fatal event of neutropenic infection occurred in a patient with previously treated glioblastoma receiving Avastin alone. The incidence of any grade of infection in patients receiving Avastin alone was 55% and the incidence of Grade 3-5 infection was 10%.

Proteinuria

Grade 3-4 proteinuria ranged from 0.7 to 7.4% in Studies 1, 2, 4 and 9. The overall incidence of proteinuria (all grades) was only adequately assessed in Study 9, in which the incidence was 20%. Median onset of proteinuria was 5.6 months (range 15 days to 37 months) after initiation of Avastin. Median time to resolution was 6.1 months (95% CI 2.8 months, 11.3 months). Proteinuria did not resolve in 40% of patients after median follow up of 11.2 months and required permanent discontinuation of Avastin in 30% of the patients who developed proteinuria (Study 9). [See *Warnings and Precautions (5.8).*]

Congestive Heart Failure

The incidence of Grade ≥ 3 left ventricular dysfunction was 1.0% in patients receiving Avastin compared to 0.6% in the control arm across indications. In patients with MBC, the incidence of Grade 3-4 congestive heart failure (CHF) was increased in patients in the Avastin plus paclitaxel arm (2.2%) as compared to the control arm (0.3%). Among patients receiving prior anthracyclines for MBC, the rate of CHF was 3.8% for patients receiving Avastin as compared to 0.6% for patients receiving paclitaxel alone. The safety of continuation or resumption of Avastin in patients with cardiac dysfunction has not been studied.

Metastatic Colorectal Cancer (mCRC)

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

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

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.

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/LY+ Avastin (n=109)
<u>Special Senses</u>			
Taste Disorder	9%	14%	21%
<u>Urogenital</u>			
Proteinuria	24%	36%	36%

Avastin in Combination with FOLFOX4 in Second-line mCRC

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

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

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

Metastatic Breast Cancer (MBC)

Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected in Study 5. Grade 3-4 adverse events occurring at a higher incidence ($\geq 2\%$) in 363 patients receiving paclitaxel plus Avastin compared with 348 patients receiving paclitaxel alone were sensory neuropathy (24% vs. 18%), hypertension (16% vs. 1%), fatigue (11% vs. 5%), infection without neutropenia (9% vs. 5%), neutrophils (6% vs. 3%), vomiting (6% vs. 2%), diarrhea (5% vs. 1%), bone pain (4% vs. 2%), headache (4% vs. 1%), nausea (4% vs. 1%), cerebrovascular ischemia (3% vs. 0%), dehydration (3% vs. 1%), infection with unknown ANC (3% vs. 0.3%), rash/desquamation (3% vs. 0.3%) and proteinuria (3% vs. 0%).

Sensory neuropathy, hypertension, and fatigue were reported at a $\geq 5\%$ higher absolute incidence in the paclitaxel plus Avastin arm compared with the paclitaxel alone arm.

Fatal adverse reactions occurred in 6/363 (1.7%) of patients who received paclitaxel plus Avastin. Causes of death were gastrointestinal perforation (2), myocardial infarction (2), diarrhea/abdominal, and pain/weakness/hypotension (2).

Avastin is not approved for use in combination with capecitabine or for use in second or third line treatment of MBC. The data below are presented to provide information on the overall safety profile of Avastin in women with breast cancer since Study 6 is the only randomized, controlled study in which all adverse events were collected for all patients. All patients in Study 6 received prior anthracycline and taxane therapy in the adjuvant setting or for metastatic disease. Grade 1–4 events which occurred at a higher incidence ($\geq 5\%$) in patients receiving capecitabine plus Avastin compared to the capecitabine alone arm are presented in Table 3.

Table 3
 NCI-CTC Grade 1–4 Adverse Events in Study 6 (Occurring at Higher Incidence [$\geq 5\%$] in Capecitabine + Avastin vs. Capecitabine Alone)

	Capecitabine (n=215)	Capecitabine+Avastin (n=229)
<u>Body as a Whole</u>		
Asthenia	47%	57%
Headache	13%	33%
Pain	25%	31%
<u>Cardiovascular</u>		
Hypertension	2%	24%
<u>Digestive</u>		
Stomatitis	19%	25%
<u>Metabolic/Nutrition</u>		
Weight loss	4%	9%
<u>Musculoskeletal</u>		
Myalgia	8%	14%
<u>Respiratory</u>		
Dyspnea	18%	27%
Epistaxis	1%	16%
<u>Skin/Appendages</u>		
Exfoliative dermatitis	75%	84%
<u>Urogenital</u>		
Albuminuria	7%	22%

Glioblastoma

All adverse events were collected in 163 patients enrolled in Study 7 who either received Avastin alone or Avastin plus irinotecan. All patients received prior radiotherapy and temozolomide. Avastin was administered at 10 mg/kg every 2 weeks alone or in combination with irinotecan. Avastin was discontinued due to adverse events in 4.8% of patients treated with Avastin alone.

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

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

Metastatic Renal Cell Carcinoma (mRCC)

All grade adverse events were collected in Study 9. Grade 3–5 adverse events occurring at a higher incidence ($\geq 2\%$) in 337 patients receiving interferon alfa (IFN- α) plus Avastin compared to 304 patients receiving IFN- α plus placebo arm were fatigue (13% vs. 8%), asthenia (10% vs. 7%), proteinuria (7% vs. 0%), hypertension (6% vs. 1%; including hypertension and hypertensive crisis), and hemorrhage (3% vs. 0.3%; including epistaxis, small intestinal hemorrhage, aneurysm ruptured, gastric ulcer hemorrhage, gingival bleeding, haemoptysis, hemorrhage intracranial, large intestinal hemorrhage, respiratory tract hemorrhage, and traumatic hematoma).

Grade 1–5 adverse events occurring at a higher incidence ($\geq 5\%$) in patients receiving IFN- α plus Avastin compared to the IFN- α plus placebo arm are presented in Table 4.

Table 4
 NCI-CTC Grades 1–5 Adverse Events in Study 9 (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.

The following adverse events were reported at a 5-fold greater incidence in the IFN- α plus Avastin arm compared to IFN- α alone and not represented in Table 4: gingival bleeding (13 patients vs. 1 patient); rhinitis (9 vs. 0); blurred vision (8 vs. 0); gingivitis (8 vs. 1); gastroesophageal reflux disease (8 vs. 1); tinnitus (7 vs. 1); tooth abscess (7 vs. 0); mouth ulceration (6 vs. 0); acne (5 vs. 0); deafness (5 vs. 0); gastritis (5 vs. 0); gingival pain (5 vs. 0) and pulmonary embolism (5 vs. 1).

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving Avastin has not been adequately determined because the assay sensitivity was inadequate to reliably detect lower titers. Enzyme-linked immunosorbent assays (ELISAs) were performed on sera from approximately 500 patients treated with Avastin, primarily in combination with chemotherapy. High titer human anti-Avastin antibodies were not detected.

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and

underlying disease. For these reasons, comparison of the incidence of antibodies to Avastin with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

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

Body as a Whole: Polyserositis

Cardiovascular: Pulmonary hypertension, RPLS, Mesenteric venous occlusion

Eye disorders (reported from unapproved use for treatment of various ocular disorders):

Endophthalmitis; Intraocular inflammation such as iritis and vitritis; Retinal detachment; Other retinal disorders; Increased intraocular pressure; Hemorrhage following intraocular injection including conjunctival, vitreous hemorrhage or retinal hemorrhage; Vitreous floaters; Visual disturbances; Ocular hyperemia; Ocular pain and/or discomfort

Gastrointestinal: Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration

Hemic and lymphatic: Pancytopenia

Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)

Respiratory: Nasal septum perforation, dysphonia

7 DRUG INTERACTIONS

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

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

In Study 9, there was no difference in the mean exposure of interferon alfa administered in combination with Avastin when compared to interferon alfa alone.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no studies of bevacizumab in pregnant women. Reproduction studies in rabbits treated with approximately 1 to 12 times the recommended human dose of bevacizumab resulted in teratogenicity, including an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all doses tested. Other observed effects included decreases in maternal and fetal body weights and an increased number of fetal resorptions. [See *Nonclinical Toxicology (13.3).*]

Human IgG is known to cross the placental barrier; therefore, bevacizumab may be transmitted from the mother to the developing fetus, and has the potential to cause fetal harm when administered to pregnant women. Because of the observed teratogenic effects of known inhibitors of angiogenesis in humans, bevacizumab should be used during pregnancy only if the potential benefit to the pregnant woman justifies the potential risk to the fetus.

8.3 Nursing Mothers

It is not known whether Avastin is secreted in human milk, but human IgG is excreted in human milk. Published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because many drugs are secreted in human milk and because of

the potential for serious adverse reactions in nursing infants from bevacizumab, a decision should be made whether to discontinue nursing or discontinue drug, taking into account the half-life of the bevacizumab (approximately 20 days [range 11–50 days]) and the importance of the drug to the mother. [See *Clinical Pharmacology* (12.3).]

8.4 Pediatric Use

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

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

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

8.5 Geriatric Use

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

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

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

In Study 5, there were insufficient numbers of patients ≥ 65 years old to determine whether the overall adverse events profile was different in the elderly as compared with younger patients.

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

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

10 OVERDOSAGE

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

11 DESCRIPTION

Avastin (bevacizumab) is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human vascular endothelial growth factor (VEGF) in *in vitro* and *in vivo* assay systems. Bevacizumab contains human framework regions and the complementarity-determining regions of a murine antibody that binds to VEGF. Avastin has an approximate molecular weight of 149 kD. Bevacizumab is produced in a mammalian cell (Chinese

Hamster Ovary) expression system in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity studies of bevacizumab have been conducted.

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

13.2 Animal Toxicology and/or Pharmacology

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

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

13.3 Reproductive and Developmental Toxicology

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

14 CLINICAL STUDIES

14.1 Metastatic Colorectal Cancer (mCRC)

Study 1

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

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

The addition of Avastin resulted in an improvement in survival across subgroups defined by age (< 65 yrs, ≥ 65 yrs) and gender. Results are presented in Table 5 and Figure 1.

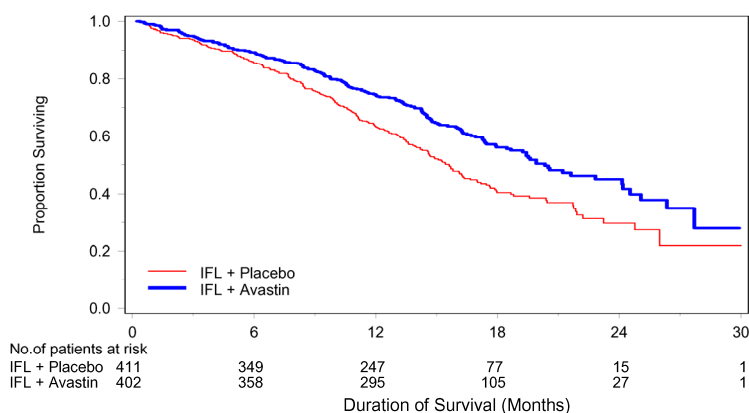
Table 5
Study 1 Efficacy Results

	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.

Figure 1
Duration of Survival in Study 1



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

Study 2

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

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

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

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

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

Study 3

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

14.2 Unresectable Non–Squamous Non–Small Cell Lung Cancer (NSCLC)

Study 4

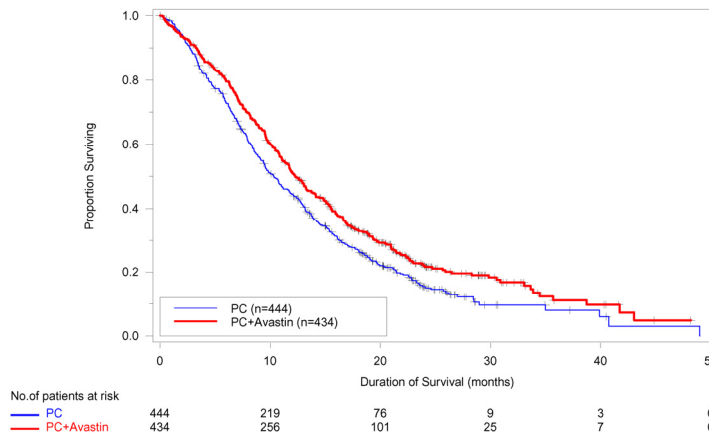
The safety and efficacy of Avastin as first-line treatment of patients with locally advanced, metastatic, or recurrent non–squamous NSCLC was studied in a single, large, randomized, active-controlled, open-label, multicenter study.

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

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

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

Figure 2
Duration of Survival in Study 4



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

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

14.3 Metastatic Breast Cancer (MBC)

Study 5

The efficacy and safety of Avastin as first-line treatment of patients with MBC was studied in a single, open-label, randomized, multicenter study. Patients who had not received chemotherapy for locally recurrent or MBC were randomized (1:1) to receive paclitaxel (90 mg/m² IV once weekly for 3 out of 4 weeks) alone or in combination with Avastin (10 mg/kg IV infusion every 2 weeks). Patients were treated until disease progression or unacceptable toxicity. In situations where paclitaxel was discontinued or held, treatment with Avastin alone could be continued until disease progression. Patients with breast cancer overexpressing HER2 were not eligible unless they had received prior therapy with trastuzumab.

Prior hormonal therapy for the treatment of metastatic disease was allowed, as was prior adjuvant chemotherapy or hormonal therapy. Adjuvant taxane therapy, if received, must have been completed 12 or more months prior to study entry. Patients with central nervous system metastasis were excluded. The main outcome measure of the study was PFS as assessed by independent radiographic review. Secondary outcome measures were OS and ORR.

Of the 722 patients randomized, the median age was 55 years, 76% were white, 55% were postmenopausal, and 64% were ER and/or PR positive. Patient characteristics were similar across treatment arms. Thirty-six percent had received prior hormonal therapy for advanced disease, and 66% had received adjuvant chemotherapy, including 20% with prior taxane use and 50% with prior anthracycline use. Efficacy results are summarized in Table 6.

Table 6
Avastin Efficacy Results from Study 5

Efficacy Parameter	Avastin + Paclitaxel (n=368)	Paclitaxel Alone (n=354)	p-value	HR (95% CI)
<u>Progression-free Survival</u>	11.3	5.8		0.48
[median, months (95% CI)]	(10.5, 13.3)	(5.4, 8.2)	<0.0001	(0.39, 0.61)
<u>Overall Survival</u>	26.5	24.8		0.87
[median, months (95% CI)]	(23.7, 29.2)	(21.4, 27.4)	0.14	(0.72, 1.05)
Partial Response Rate ^a (PR)	48.9% ^b	22.2%	<0.001	—

^a Includes only patients with measurable disease.

^b The difference in partial response rates is 26.7% with a 95% CI (18.4%, 35.0%).

The addition of Avastin to paclitaxel resulted in an improvement in PFS with no significant improvement in OS. Partial response rates in patients with measurable disease were higher with Avastin plus paclitaxel. No complete responses were observed.

Thirty-four percent of the patients had incomplete follow-up for disease progression; therefore an exploratory analysis using similar imputation between arms was performed, which yielded a hazard ratio of 0.57.

Study 6

The efficacy and safety of Avastin as second- and third-line treatment of patients with MBC was studied in a single open-label randomized study. Patients who had received prior anthracycline and taxane therapy in the adjuvant setting or for their MBC were randomized (1:1) to receive capecitabine alone or in combination with Avastin. Of the 462 enrolled patients, the median age was 51 years, 81% were white, and 50% were ER positive. Patient characteristics were similar across the treatment arms.

The study failed to demonstrate a statistically significant effect on PFS or OS. The median PFS was 4.2 months in the capecitabine arm and 4.9 months in the capecitabine plus Avastin arm (log-rank p-value = 0.86, hazard ratio 0.98). The median OS was 14.5 months in the capecitabine arm and 15.1 months in the capecitabine plus Avastin arm (hazard ratio of 1.08).

14.4 Glioblastoma

Study 7

The efficacy and safety of Avastin was evaluated in Study 7, an open-label, multicenter, randomized, non-comparative study of patients with previously treated glioblastoma. Patients received Avastin (10 mg/kg IV) alone or Avastin plus irinotecan every 2 weeks until disease progression or until unacceptable toxicity. All patients received prior radiotherapy (completed at least 8 weeks prior to receiving Avastin) and temozolomide. Patients with active brain hemorrhage were excluded.

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

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

Study 8

Study 8, was a single-arm, single institution trial with 56 patients with glioblastoma. All patients had documented disease progression after receiving temozolomide and radiation therapy. Patients received Avastin 10 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity.

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

The efficacy of Avastin was supported by an objective response rate of 19.6% (95% CI 10.9%, 31.3%) using the same response criteria as in Study 7. Median duration of response was 3.9 months (95% CI 2.4, 17.4).

14.5 Metastatic Renal Cell Carcinoma (mRCC)

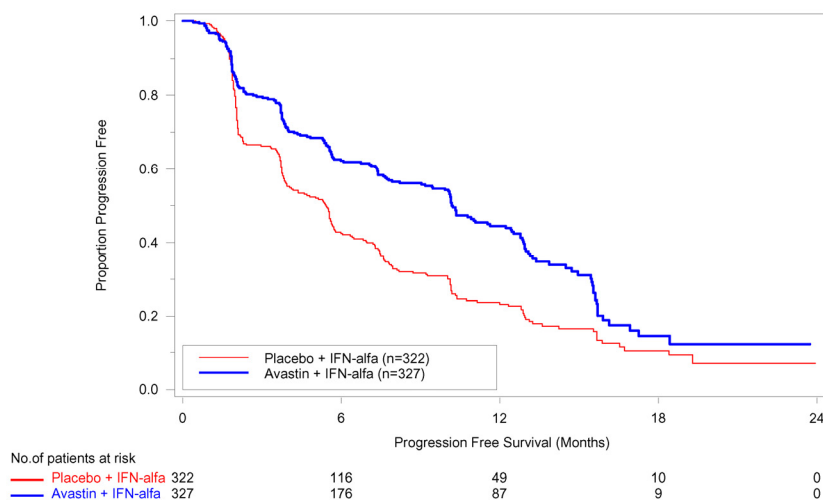
Study 9

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

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

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

Figure 3
Progression-Free Survival in Study 9



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.

Avastin® (bevacizumab)

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

10127309
Initial U.S. Approval: February 2004
Code Revision Date: February 2011
Avastin® is a registered trademark of Genentech, Inc.
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ATTACHMENT 2

Study Arm	Median PFS (months)	Median OS* (months)	ORR
E2100			
Paclitaxel + Avastin	11.3	26.5	48.9%
Paclitaxel	5.8	24.8	22.2%
Between-Arm Difference	5.5	1.7	26.7%
Hazard Ratio (95% CI)	0.48 (0.39, 0.61)	0.87 (0.72, 1.05)	(18.4%, 35%)
	p < 0.0001	p = 0.137	p < 0.0001
AVADO			
Docetaxel + Avastin 15 mg/kg	8.8	30.2	63.1%
Docetaxel + Placebo	7.9	31.9	44.4%
Between-Arm Difference	0.9	-1.7	18.7%
Hazard Ratio (95% CI)	0.62 (0.48, 0.79)	1.00 (0.76, 1.32)	(9.0%, 28.4%)
	p = 0.0003	p = 0.98	p = 0.0001
Docetaxel + Avastin 7.5 mg/kg	8.7	30.8	55.2%
Docetaxel + Placebo	7.9	31.9	44.4%
Between-Arm Difference	0.8	-1.1	10.8%
Hazard Ratio (95% CI)	0.70 (0.55, 0.90)	1.10 (0.84, 1.45)	(0.9%, 20.7%)
	p = 0.0054	p = 0.48	p = 0.0295
RIBBON1			
Taxane/Anthracycline + Avastin	9.2	27.5	51.3%
Taxane/Anthracycline + Placebo	8.0	NR	37.9%
Between-Arm Difference	1.2	NR	13.5%
Hazard Ratio (95% CI)	0.64 (0.52, 0.80)	1.11 (0.86, 1.43)	(4.6%, 22.3%)
	p < 0.0001	p = 0.44	p = 0.0054
Capecitabine + Avastin	8.6	25.7	35.4%
Capecitabine + Placebo	5.7	22.8	23.6%
Between-Arm Difference	2.9	2.9	11.8%
Hazard Ratio (95% CI)	0.69 (0.56, 0.84)	0.88 (0.69, 1.13)	(3.4%, 20.2%)
	p = 0.0002	p = 0.33	p = 0.0097

* Updated OS analysis where available. CI = confidence interval; NR = not reached.