AVASTIN IN NSCLC:
Clinical Summary

Indication

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.

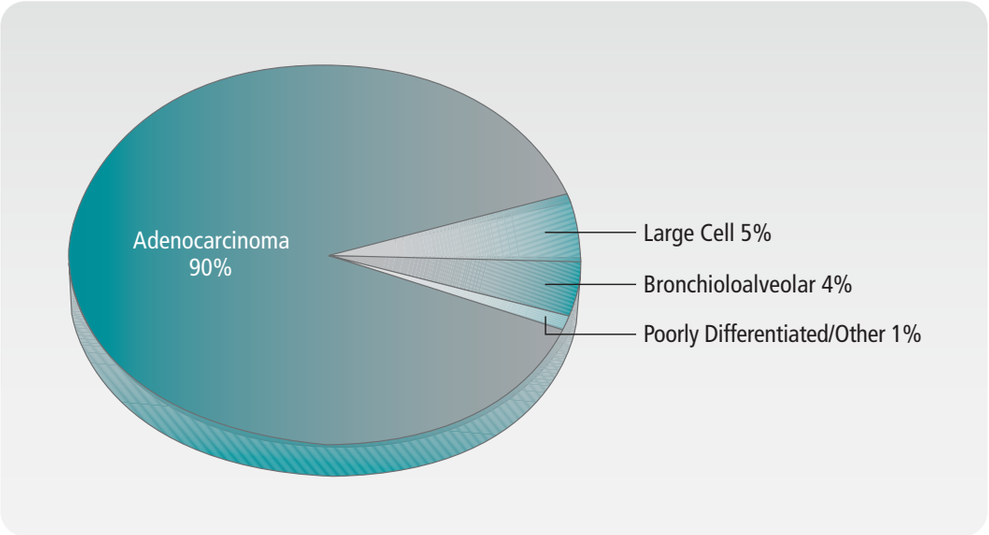
Please see accompanying full Prescribing Information, including **Boxed WARNINGS**, and pages 16–19 for additional important safety information.

AVASTIN®
bevacizumab

Non-small cell lung cancer (NSCLC)
The leading cause of cancer death in men and women[1]

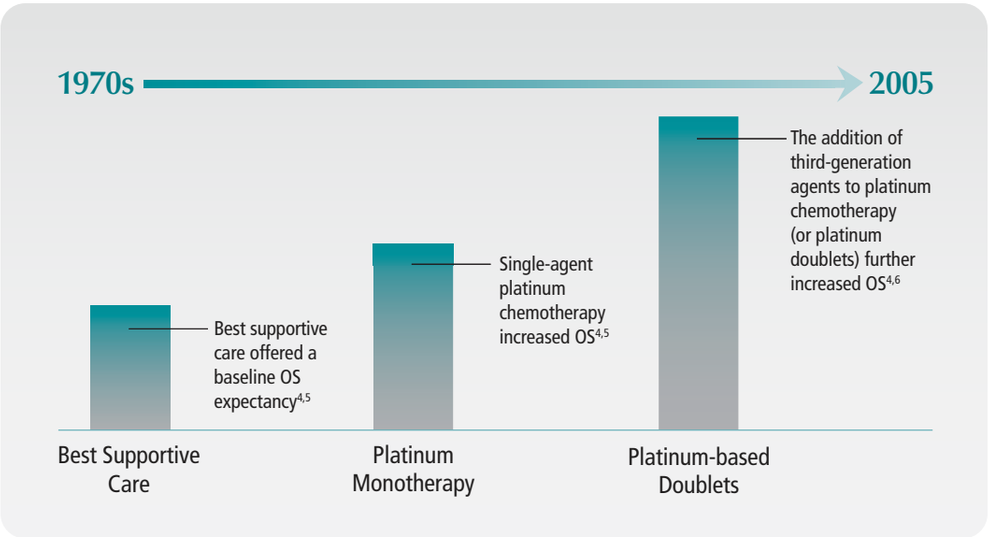
NSCLC comprises approximately 90% of lung cancers[2]

Most common non-squamous NSCLC histologic subtypes[3]



Key milestones in the treatment of metastatic non-squamous NSCLC

Progress over 4 decades with chemotherapy alone



OS=overall survival.

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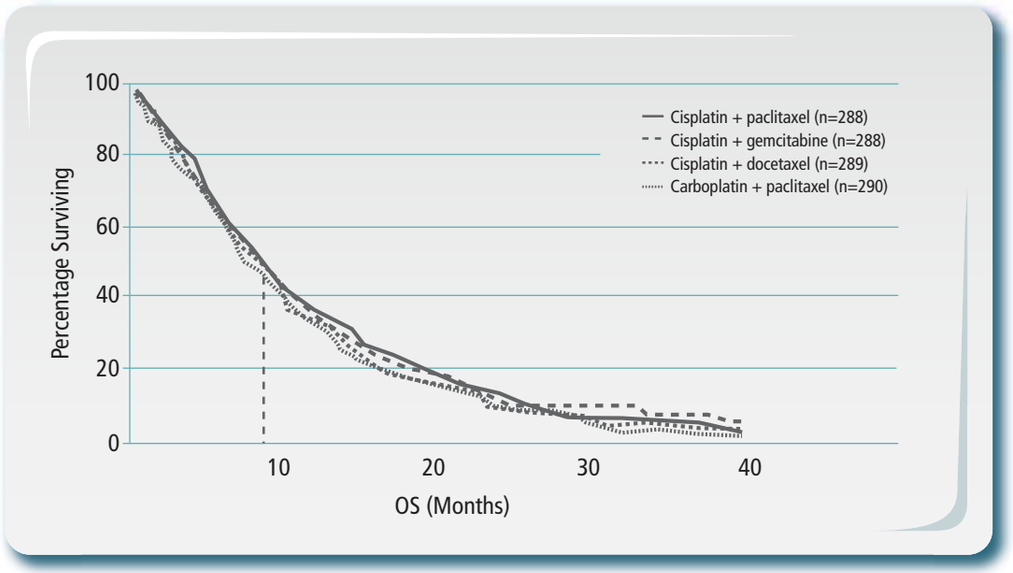
AVASTIN® bevacizumab

2002: The emergence of a chemotherapy reference standard

Study E1594 compared the efficacy of 4 commonly used platinum-based chemotherapy doublets

- Results demonstrated a median OS of approximately 8 months with each combination[6]
  - Paclitaxel/carboplatin (PC) had a lower rate of toxic effects than other regimens[6]
- PC was chosen as the chemotherapy reference standard for future Eastern Cooperative Oncology Group (ECOG) trials based on safety[6]

OS in ECOG Study E1594[6]

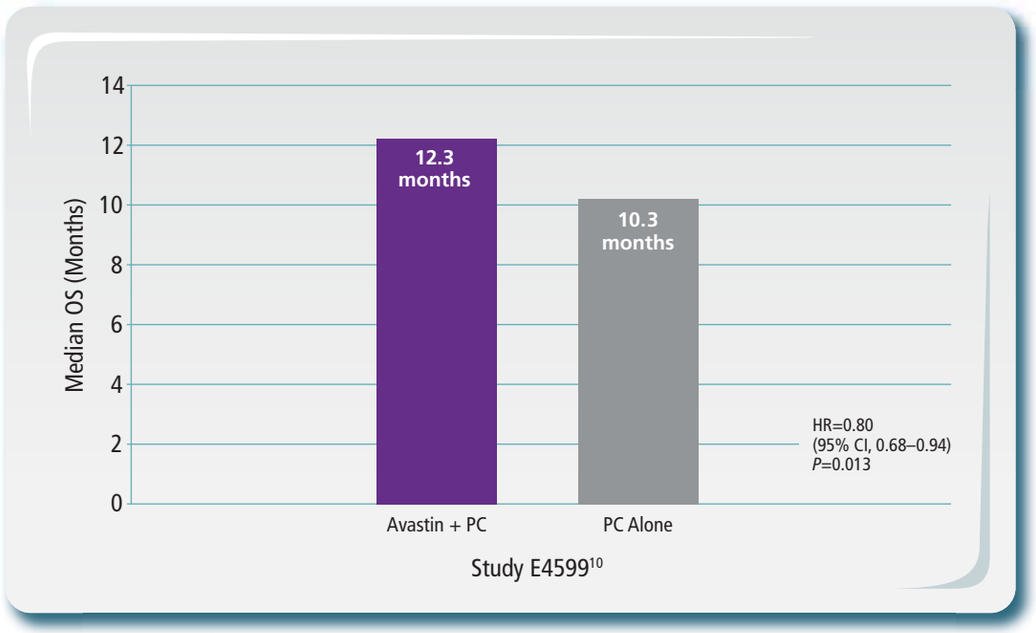


Boxed WARNINGS

- **Gastrointestinal (GI) perforation**
  - Serious and sometimes fatal GI perforation occurs at a higher incidence (up to 2.4%) in Avastin-treated patients compared to controls. Discontinue Avastin for GI perforation
- **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 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
- **Hemorrhage**
  - Severe or fatal hemorrhage, hemoptysis, GI bleeding, CNS hemorrhage, and vaginal bleeding are increased in Avastin-treated patients. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis

Avastin plus PC
A standard in the treatment of first-line metastatic non-squamous NSCLC

Avastin plus PC is recognized as a standard of care in the first-line treatment of metastatic non-squamous NSCLC[7-9]



HR=hazard ratio; CI=confidence interval.

"Avastin plus paclitaxel/carboplatin is [a] standard of care for all eligible first-line NSCLC patients. It should be offered to all patients who meet the eligibility criteria, which are important to keep in mind, because Avastin plus paclitaxel/carboplatin may give patients an improved survival outcome."

—Ronald B. Natale, MD
Cedars-Sinai Outpatient Cancer Center

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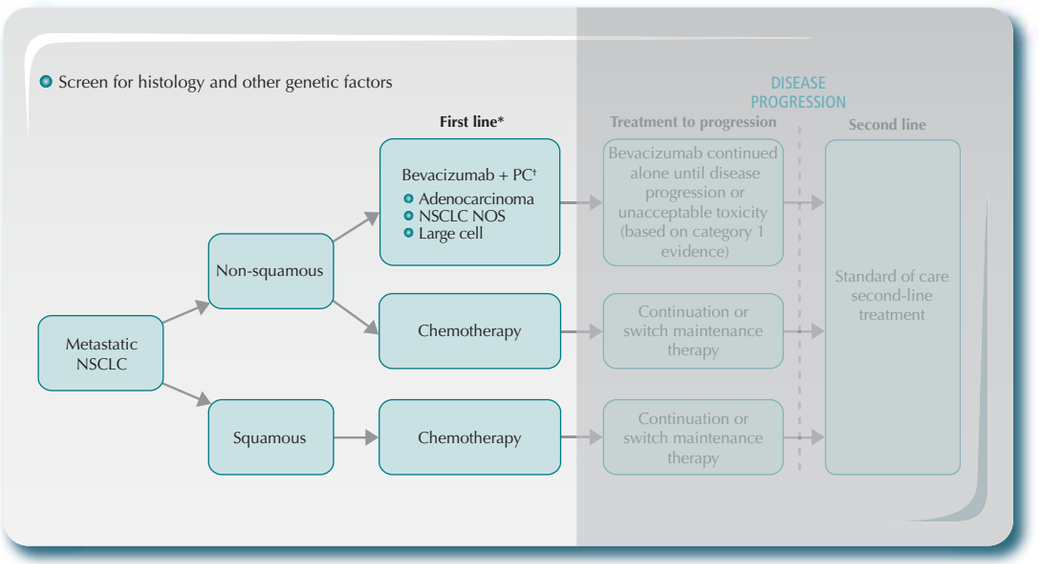
AVASTIN® bevacizumab

2011: The first-line treatment decision

Bevacizumab plus chemotherapy [PC] remains a recognized standard of care for first-line non-squamous NSCLC

Evidence-based treatment for metastatic NSCLC[8-10]



NOS=not otherwise specified.
*Chemotherapy given for up to 6 cycles.
†No history of hemoptysis; ECOG performance status (PS) 0–1.

"As therapeutic options in NSCLC have expanded, oncologists have more flexibility of using certain agents in different lines of therapy (based on data and FDA approval). Therefore, ensuring that active agents can be appropriately incorporated at various points of therapy must be a treatment goal for patients with advanced NSCLC."

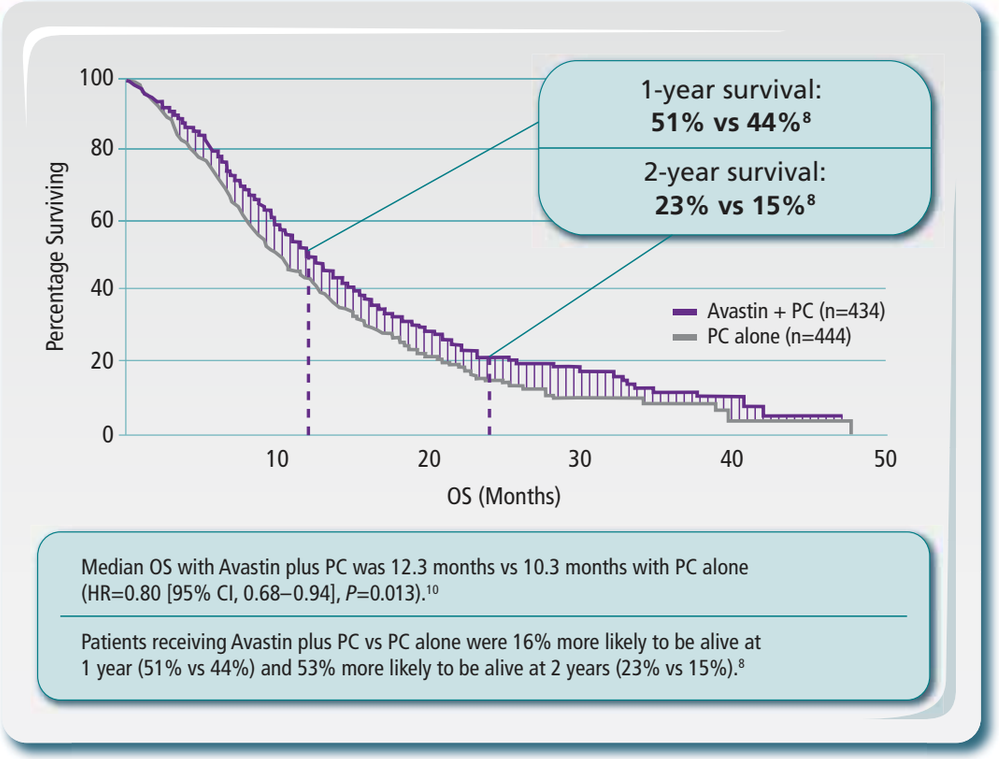
—Mark A. Socinski, MD
University of North Carolina, Chapel Hill

Additional serious adverse events

- Additional serious and sometimes fatal adverse events with increased incidence in the Avastin-treated arm vs control included
  - — Non-GI fistula formation (≤0.3%)
  - — Arterial thromboembolic events (grade ≥3, 2.4%)
  - — Proteinuria including nephrotic syndrome (<1%)
- Additional serious adverse events with increased incidence in the Avastin-treated arm vs control included
  - — Hypertension (grade 3–4, 5%–18%)
  - — Reversible posterior leukoencephalopathy syndrome (RPLS) (<0.1%)
- Infusion reactions with the first dose of Avastin were uncommon (<3%), and severe reactions occurred in 0.2% of patients
- Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin

Avastin plus PC significantly increased median OS by 19% (12.3 vs 10.3 months with PC alone) in Study E4599[10]

In Study E4599, Avastin plus PC demonstrated clinically meaningful 1- and 2-year survival rates in first-line metastatic non-squamous NSCLC (51% and 23%, respectively, vs 44% and 15% with PC alone)[8]



- Avastin plus PC demonstrated a median progression-free survival (PFS) of 6.2 months (vs 4.5 months with PC alone, HR=0.66 [95% CI, 0.57–0.77], $P<0.001$) in Study E4599, based on investigator assessment (not independently verified)[8,10]
- Avastin plus PC had a response rate of 35% vs 15% with PC alone ($P<0.001$), based on investigator assessment (not independently verified)[8]
- In the absence of disease progression, 60% of patients receiving Avastin plus PC in Study E4599 completed 6 cycles of therapy (vs 44% in the PC alone arm), thereby making those patients eligible to continue Avastin alone until disease progression or unacceptable toxicity[11]

"Please remember [Study E4599] is one of the rare trials of lung cancer...where we had the trifecta of benefits for all [eligible] patients (ie, improved rates of response,‡ improved rates of progression-free survival,‡ and improved overall survival)....We had all 3 when we added bevacizumab to the combination of carboplatin and paclitaxel."

—Mark Kris, MD
Memorial Sloan-Kettering Cancer Center

‡Response rate and PFS were based on investigator assessment (not independently verified).[8]

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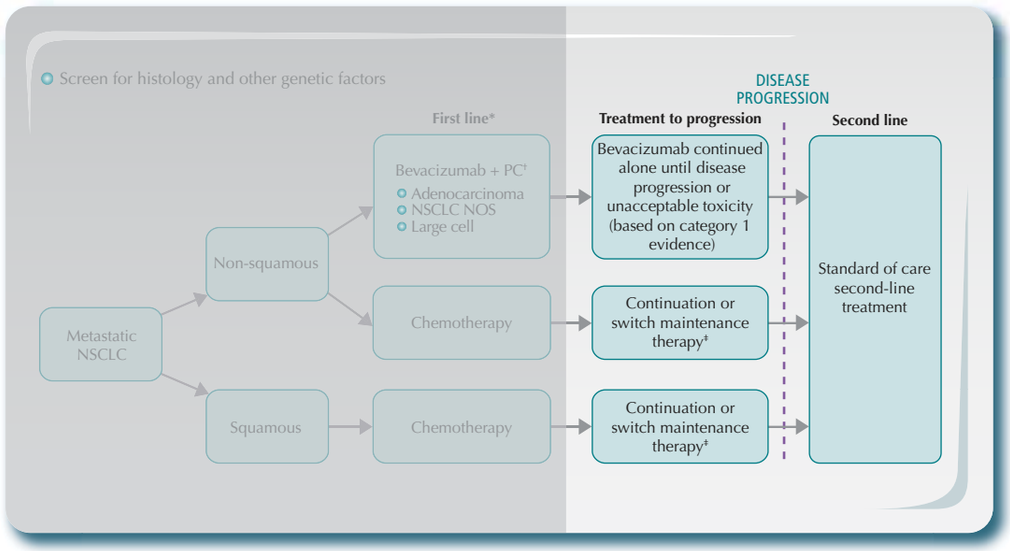
AVASTIN® bevacizumab

2011: The treatment duration decision

Evidence-based treatment for metastatic NSCLC[8-10]



*Chemotherapy given for up to 6 cycles.
†No history of hemoptysis; ECOG PS 0–1.

Bevacizumab is the only FDA-approved agent for first-line metastatic non-squamous NSCLC that has an NCCN category 1 recommendation for continuation maintenance (based on high-level evidence and uniform consensus)[9]

NCCN Guidelines	Bevacizumab should be given until progression.[9] Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.[9]

NCCN=National Comprehensive Cancer Network.

‡Maintenance therapy as defined by the NCCN®

Continuation maintenance	Use of at least 1 of the agents given in first line, beyond 4–6 cycles, in the absence of disease progression[9]
Switch maintenance	Initiation of a different agent, not included as part of the first-line regimen, in the absence of disease progression, after 4–6 cycles of initial therapy[9]

Avastin Prescribing Information includes duration of Avastin treatment[10]

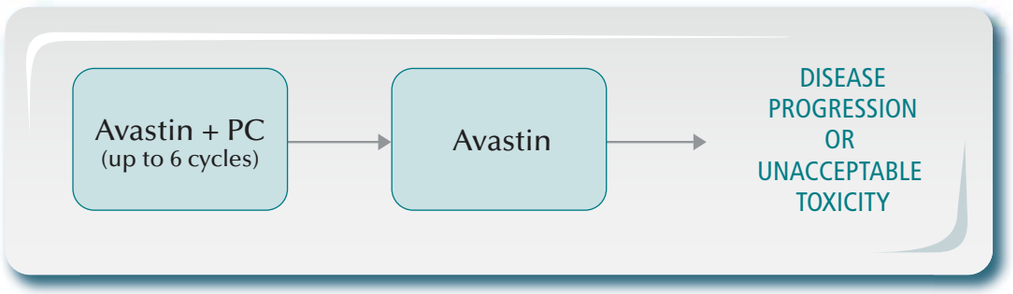
FDA-approved prescribing information for the duration of Avastin treatment[10]

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

Important safety information—Study E4599

- Grade 3–5 (nonhematologic) and grade 4–5 (hematologic) adverse events in Study E4599 occurring at a ≥2% higher incidence in Avastin-treated patients vs controls 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%)

Avastin plus PC demonstrated an increase in OS with Avastin given until disease progression or unacceptable toxicity[10]

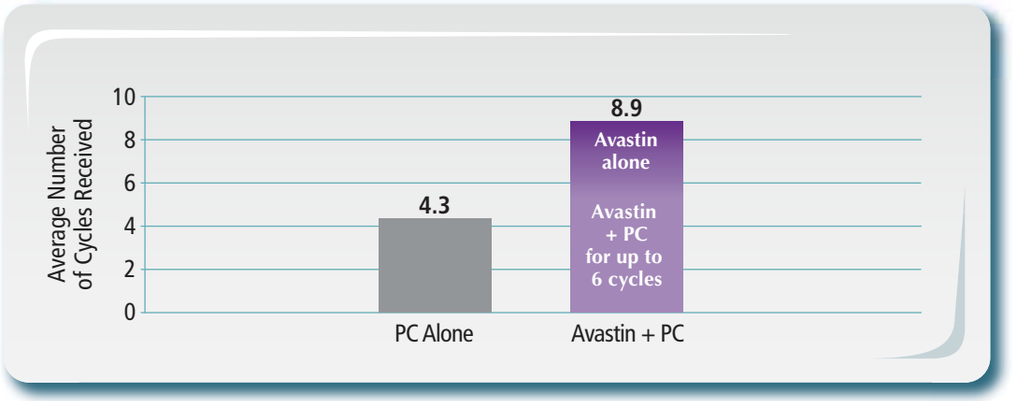


- In Study E4599, 53% of patients in the Avastin plus PC arm continued with Avastin alone, and 50% of these patients received more than 5 cycles of Avastin alone[8]

"Among the 215 patients receiving bevacizumab monotherapy, the most common grade 3 or 4 toxic effects were hypertension (in 12 patients [5.6%]), proteinuria (in 9 patients [4.2%]), fatigue (in 11 patients [5.1%]), and dyspnea (in 12 patients [5.6%])."

—Sandler A, Gray R, Perry MC, et al. *N Engl J Med*. 2006;355:2542-2550.

In Study E4599, patients who were responding or had stable disease after up to 6 cycles of Avastin plus PC were eligible to continue on Avastin alone until disease progression or unacceptable toxicity[10,12]



Important treatment considerations—Dose modifications

- There are no recommended dose reductions
- Discontinue Avastin in patients with
  - **Gastrointestinal (GI) perforations (GI perforations, fistula formation in the GI tract, intra-abdominal abscess)**
  - Fistula formation involving an internal organ
  - **Wound dehiscence and wound healing complications requiring medical intervention**
  - **Serious hemorrhage (ie, requiring medical intervention)**
  - Severe arterial thromboembolic event (ATE)
  - Hypertensive crisis or hypertensive encephalopathy
  - Reversible posterior leukoencephalopathy syndrome (RPLS) (symptoms usually resolve or improve within days, although some patients have experienced ongoing neurologic sequelae)
  - Nephrotic syndrome
- Temporarily suspend Avastin for at least 4 weeks prior to elective surgery, severe hypertension not controlled with medical management, moderate to severe proteinuria pending further evaluation, and severe infusion reactions
- The safety of resumption of Avastin therapy in patients that experienced RPLS, ATE, and moderate to severe proteinuria is unknown

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AVASTIN® bevacizumab

ECOG Study E4599 included a broad range of patients[8,10,13,14]

Patients studied in ECOG Study E4599 included:

- First-line, locally advanced, metastatic or recurrent NSCLC
- All predominantly non-squamous histologies
  - — Adenocarcinoma
  - — Large cell tumors
  - — Bronchioloalveolar carcinoma (BAC)
  - — Undifferentiated NSCLC, not otherwise specified (NOS)
- Centrally located tumors
- ECOG PS 0–1

Bevacizumab plus chemotherapy [PC] remains a recognized standard of care for first-line non-squamous NSCLC

NCCN includes bevacizumab plus chemotherapy [PC] as a treatment option for first-line non-squamous NSCLC patients using the following criteria[9]

- No history of hemoptysis
- ECOG PS 0–1

Updates to the **WARNINGS AND PRECAUTIONS** section of the Avastin full Prescribing Information state:

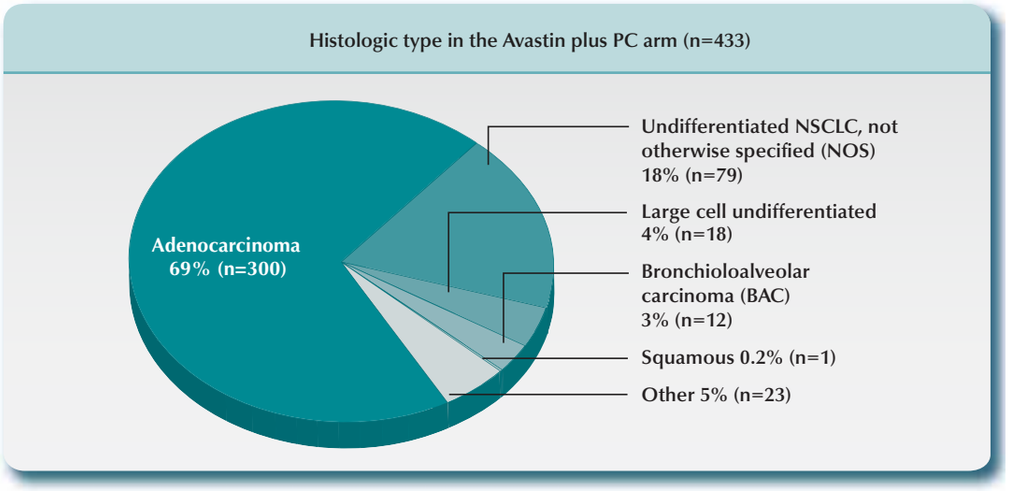
In clinical studies in NSCLC where patients with CNS metastases who completed radiation and surgery more than 4 weeks prior to the start of Avastin were evaluated with serial CNS imaging, symptomatic grade 2 CNS hemorrhage was documented in 1 of 83 Avastin-treated patients (rate 1.2%, 95% CI, 0.06%–5.93%).[10]

CNS=central nervous system.

Most common adverse events

- Most common adverse reactions observed in Avastin patients at a rate >10% and at least twice the control arm rate were
  - — Epistaxis
  - — Headache
  - — Hypertension
  - — Rhinitis
  - — Proteinuria
  - — Taste alteration
  - — Dry skin
  - — Rectal hemorrhage
  - — Lacrimation disorder
  - — Back pain
  - — Exfoliative dermatitis
- Across all studies, Avastin was discontinued in 8.4% to 21% of patients because of adverse reactions

Avastin plus PC demonstrated a significant improvement in OS (12.3 vs 10.3 months, HR=0.80 [95% CI, 0.68–0.94], *P*=0.013) in Study E4599 across the full range of non-squamous NSCLC histologies[8,10,14]



- The majority (69%) of patients in Study E4599 had adenocarcinoma histology[14]
- Patients with centrally located tumors were included in Study E4599[13]
- Study E4599 included only patients with more advanced staging (wet stage IIIB and stage IV)[13]

Please see accompanying full Prescribing Information, including **Boxed WARNINGS**, and pages 16–19 for additional important safety information.

AVASTIN® bevacizumab

Study AVF0757g (Phase II)

Evidence-based dosing of Avastin plus PC in first-line metastatic non-squamous NSCLC

Results from Study AVF0757g* determined 15 mg/kg as a solution for intravenous (IV) infusion every 3 weeks (q3w) until disease progression or unacceptable toxicity as the Avastin dose in Study E4599[8,15]

		Avastin 15 mg/kg IV q3w + PC (n=34)	Avastin 7.5 mg/kg IV q3w + PC (n=32)	PC alone (n=32)†
Primary endpoints	Median time to progression (months)	7.4 (*P*=0.023‡)	4.3	4.2
	Tumor response rate (%)	31.5	28.1	18.8
Secondary endpoint	Median OS (months)	17.7 (*P*=NS‡)	11.6	14.9

NS=not significant.
*Study AVF0757g was not powered to make any definitive conclusions regarding a relationship between different Avastin doses and treatment effect.
†Patients in the PC alone arm could cross over to the 15 mg/kg q3w arm upon progression.
‡Vs control arm.

Important safety information—Study AVF0757g

- The most common events of any severity (≥10% incidence) in the Avastin plus PC group in Study AVF0757g were nausea, leukopenia, neuropathy, peripheral neuritis, infection, paresthesia, vomiting, diarrhea, thrombocytopenia, and fever. In this trial, the incidence of serious or fatal pulmonary hemorrhage was 31% (4 of 13) in Avastin-treated patients with squamous cell histology and 4% (2 of 53) in Avastin-treated patients with histology other than squamous cell. As a result, patients with squamous cell histology were excluded from Study E4599

ECOG Study E4599 (Phase III)

15 mg/kg IV q3w is the only dose of Avastin demonstrated to significantly increase OS in first-line metastatic non-squamous NSCLC

ECOG Study E4599 was a large, multicenter, randomized Phase III trial[8,10]

		Avastin + PC (n=434)	PC alone (n=444)	HR (95% CI)	*P* value
Primary endpoint	Median OS (months)	12.3	10.3	0.80 (0.68–0.94)	0.013

- Avastin plus PC demonstrated a median PFS of 6.2 months (vs 4.5 months with PC alone, HR=0.66 [95% CI, 0.57–0.77], $P<0.001$) in Study E4599, based on investigator assessment (not independently verified)[8,10]
- Avastin plus PC had a response rate of 35% vs 15% with PC alone ($P<0.001$), based on investigator assessment (not independently verified)[8]

Important safety information—Study E4599

- Grade 3–5 (nonhematologic) and grade 4–5 (hematologic) adverse events in Study E4599 occurring at a ≥2% higher incidence in Avastin-treated patients vs controls 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%)

Important treatment considerations—Women of childbearing potential

- Avastin increases the risk of ovarian failure and may impair fertility
- Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin
- Long-term effects of Avastin exposure on fertility are unknown
- Prior to initiation of therapy, advise patients of the potential risk of Avastin to the developing fetus
- Counsel patients who become pregnant about the possible risks, including hazard to the fetus and/or loss of pregnancy, of both continued treatment and prolonged exposure following discontinuation, keeping in mind the approximate half-life of Avastin (20 days; range 11–50 days). Patients should also be counseled to continue adequate contraception for at least 6 months following the last dose of Avastin
- Nursing mothers should be advised to discontinue nursing or Avastin, taking into account the half-life of the product and the importance of Avastin to the mother

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AVASTIN® bevacizumab

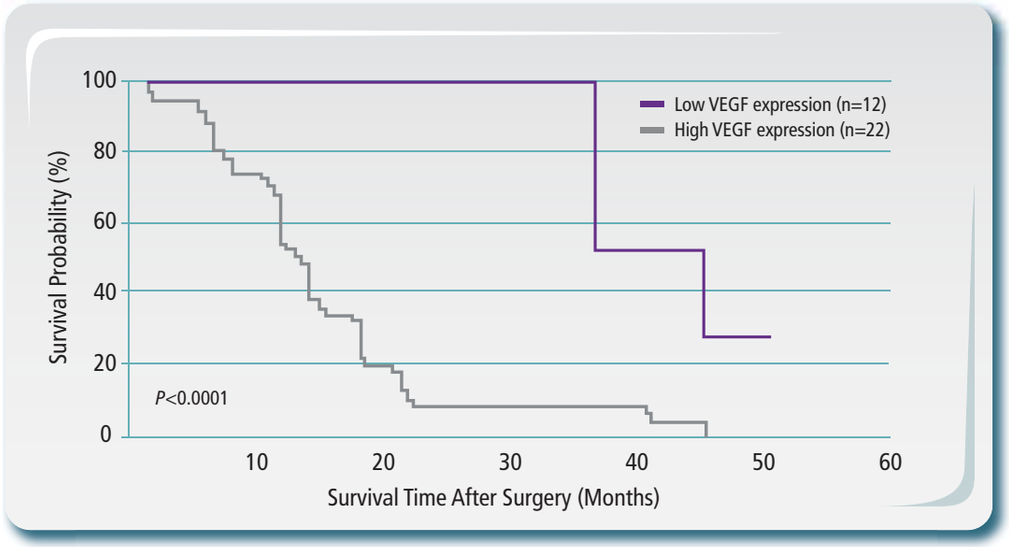
As demonstrated in preclinical models

The VEGF ligand is one of the first pro-angiogenic factors and is present throughout the tumor life cycle[16-19]

- While expressed in normal tissues, vascular endothelial growth factor (VEGF) also is present at physiologically relevant levels in the majority of tumors[20,21]
- High VEGF expression may be associated with
  - — Reduced overall survival[22-26]
  - — Disease progression[22]
  - — Risk of relapse[24,27]
  - — Lymph node involvement[28-30]
  - — Malignant pleural effusion[31]

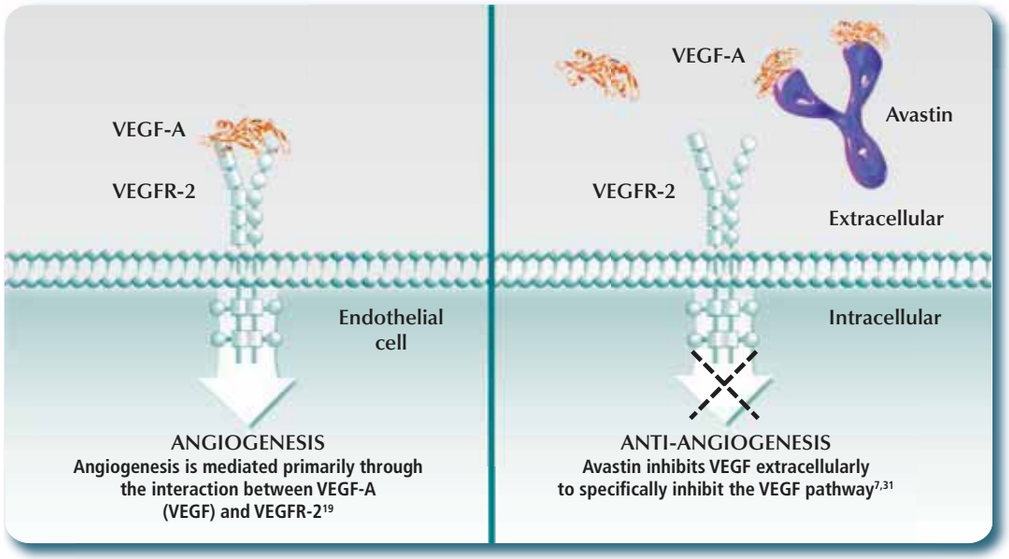
In a retrospective analysis

High VEGF expression was implicated in poorer prognosis in NSCLC[27]



As demonstrated in preclinical models

Avastin directly binds VEGF to inhibit angiogenesis[10,20]



- Avastin is designed to directly bind to VEGF extracellularly to prevent interaction with VEGF receptors (VEGFR) on the surface of endothelial cells, thereby inhibiting its biologic activity[10]
  - — VEGFR is the family of receptors primarily responsible for pro-angiogenic VEGF signaling[20,33,34]
- Extracellular VEGF binding may provide specific inhibition of the VEGF pathway[10,32]

The mechanism of action of Avastin has been elucidated primarily in preclinical models. Its clinical significance is unknown.

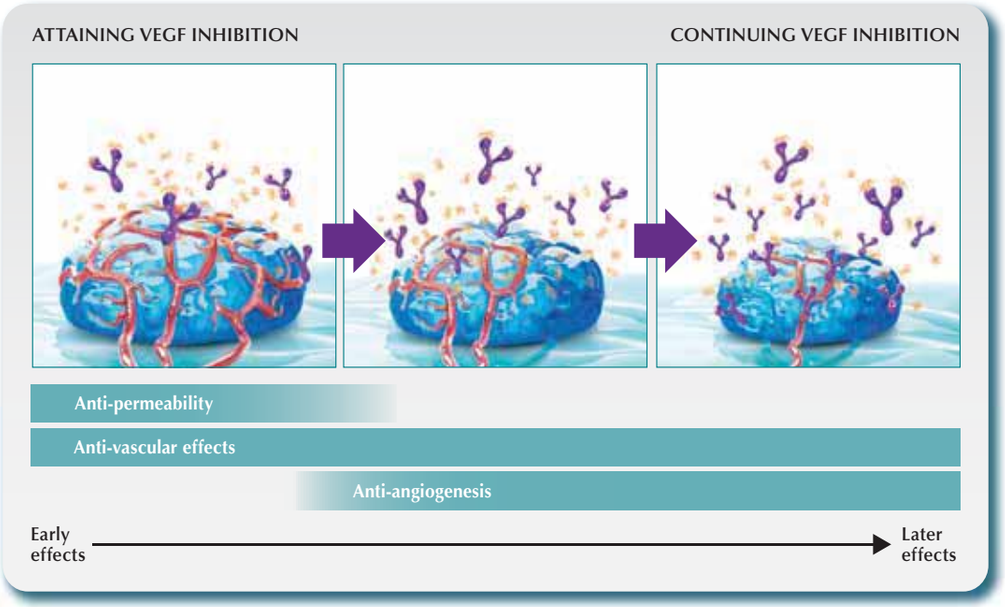
As demonstrated in preclinical models

Over the course of therapy, Avastin may exert multiple effects to inhibit tumor growth and development[35-50]

Proposed effects	Potential effect on vessels	Potential impact on tumor
Anti-vascular	Regression of existing tumor vasculature[35-40]	Reduction of tumor size[36,41]
Anti-angiogenesis	Inhibition of new and recurrent tumor vessel growth[36,42,43]	Inhibition of tumor growth[44-46]
Anti-permeability	Reduction in tumor vessel permeability[35,47-50]	Minimizes the accumulation of fluid/edema within the tumor environment[47-50]

Proposed early and later effects of Avastin[35-41,44,46,51-53]

- The impact of the individual effects of VEGF inhibition may vary over time[36,53]
- Early effects of inhibiting VEGF with Avastin may lead to a reduction in tumor size[35-41]
- Continuation of Avastin may be a critical strategy for maintaining antitumor effects[44,46,51-53]

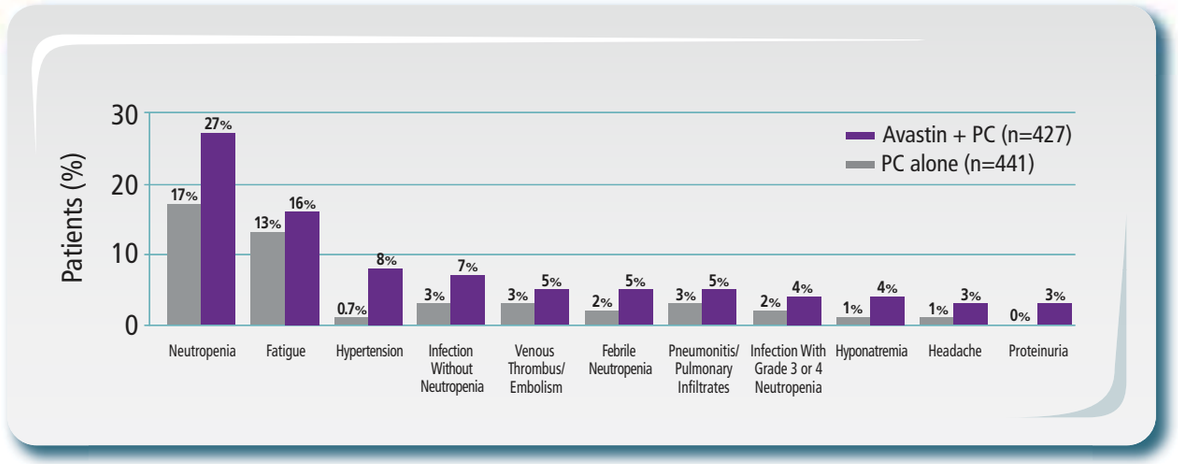


Avastin clinical trials are designed for continuous VEGF suppression[8,54,55]

- Due to continuous VEGF expression in tumor cells, there is the potential for vessel regrowth if anti-VEGF treatment is removed[44]
- Pivotal clinical trials with Avastin have been designed to maintain VEGF inhibition until disease progression or unacceptable toxicity[8,54,55]
  - This strategy includes instances in which the accompanying combination therapy is modified and/or discontinued[8,54,55]

Avastin plus PC has an acceptable safety profile in appropriate patients

Most common grade 3–5 adverse events in first-line metastatic non-squamous NSCLC patients (≥2% higher incidence in the Avastin arm)[10]



Important safety information—Hemorrhage

- Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin. Across indications, the incidence of grade ≥3 hemorrhagic events among patients receiving Avastin ranged from 1.2% to 4.6%
- Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis (≥1/2 tsp of red blood)
- Discontinue Avastin in patients with serious hemorrhage (ie, requiring medical intervention)

Avastin safety profile[10]

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

Gastrointestinal (GI) perforation (see **Boxed WARNINGS** in full Prescribing Information)

- Serious, and sometimes fatal, GI perforation occurs at a higher incidence in Avastin-treated patients compared to controls. The incidences of GI perforation, some fatal, in Avastin-treated patients range from 0.3% to 2.4% across clinical trials
- 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 GI perforations (GI perforation, fistula formation in the GI tract, intra-abdominal abscess)

Surgery and wound healing complications (see **Boxed WARNINGS** in full Prescribing Information)

- The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients
  - — In a controlled clinical trial in MCRC patients who underwent surgery, the incidence of wound healing complications, including serious and fatal complications, was 15% vs 4% in patients who did not receive Avastin
- Avastin therapy should not be initiated for at least 28 days following major surgery. The surgical incision should be fully healed prior to initiation of Avastin
- The appropriate interval between discontinuation of Avastin and subsequent elective surgery required to reduce the risk of impaired wound healing/wound dehiscence has not been determined. The calculated half-life of Avastin (~20 days; range 11–50 days) should be taken into consideration. Suspend Avastin for at least 28 days prior to elective surgery
- Discontinue Avastin in patients with wound dehiscence and wound healing complications requiring medical intervention

Hemorrhage (see **Boxed WARNINGS** in full Prescribing Information)

- Avastin can result in 2 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, GI bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-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%
- Serious or fatal pulmonary hemorrhage occurred in 4 of 13 (31%) patients with squamous cell histology and 2 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 1 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; 2 patients had grade 3–4 hemorrhage

Avastin safety profile[10] (cont'd)

- Do not administer Avastin to patients with recent hemoptysis (≥1/2 tsp of red blood)
- Discontinue Avastin in patients with serious hemorrhage (ie, requiring medical intervention)

Non-gastrointestinal (non-GI) fistula formation (Warnings and Precautions)

- Serious, and sometimes fatal, non-GI fistula formation involving tracheo-esophageal, bronchopleural, biliary, vaginal, renal, and bladder sites occurs at higher incidence in Avastin-treated patients compared to controls
- The incidence of non-GI perforation was ≤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

Arterial thromboembolic events (ATEs) (Warnings and Precautions)

- Serious, and sometimes fatal, ATEs, including cerebral infarction, transient ischemic attacks, myocardial infarction, angina, and a variety of other ATEs, occurred at a higher incidence in patients receiving Avastin compared to the control arms
- Across indications, the incidence of grade ≥3 ATEs 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 an ATE during therapy was increased in patients with a history of ATE or age greater than 65 years
- Permanently discontinue Avastin in patients who experience a severe ATE. The safety of resumption of Avastin therapy after resolution of an ATE has not been studied

Hypertension (Warnings and Precautions)

- 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% to 18%
- Blood pressure monitoring should be conducted every 2 to 3 weeks during treatment. Treat with antihypertensive therapy and monitor blood pressure regularly
- Patients with Avastin-induced or -exacerbated hypertension who discontinue Avastin should continue to have their blood pressure monitored at regular intervals
- Discontinue Avastin in patients with hypertensive crisis or hypertensive encephalopathy. Temporarily suspend Avastin in patients with severe hypertension that is not controlled with medical management

Reversible posterior leukoencephalopathy syndrome (RPLS) (Warnings and Precautions)

- RPLS has been reported in clinical trials at an incidence of <0.1%
- RPLS is a neurologic disorder that 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 for diagnosis of RPLS
- The onset of symptoms has been reported to occur from 16 hours to 1 year after initiation of Avastin
- 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 in patients previously experiencing RPLS is unknown

Proteinuria (Warnings and Precautions)

- The incidence and severity of proteinuria are increased in patients receiving Avastin compared to controls
- Grade 3 and 4 proteinuria ranged from 0.7% to 7.4% across clinical trials
  - — The overall incidence of proteinuria (all grades) was only adequately assessed in Study 9 (mRCC), in which the incidence was 20%
  - — In Study 9, median onset of proteinuria was 5.6 months (range 15 days to 37 months) and 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
- Nephrotic syndrome occurred in <1% of patients receiving Avastin in clinical trials, in some instances with fatal outcome
- In a published case series, kidney biopsy of 6 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 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 g/24 hours
- Discontinue Avastin in patients with nephrotic syndrome. The safety of continued Avastin treatment in patients with moderate to severe proteinuria is unknown

Infusion reactions (Warnings and Precautions)

- In clinical studies, infusion reactions with the first dose of Avastin were uncommon (<3%), and severe reactions occurred in 0.2% of patients
- Infusion reactions in clinical trials and in postmarketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis
- Avastin infusion should be interrupted in all patients with severe infusion reactions and appropriate medical therapy administered

Ovarian failure/fertility (Warnings and Precautions, Use in Specific Populations)

- Avastin increases the risk of ovarian failure and may impair fertility. Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin. Long-term effects of Avastin exposure on fertility are unknown
- The incidence of ovarian failure was higher (34% vs 2%) in premenopausal women receiving Avastin in combination with mFOLFOX chemotherapy as compared to those receiving mFOLFOX chemotherapy alone as adjuvant treatment for colorectal cancer, a use for which Avastin is not approved

Pregnancy Category C (Use in Specific Populations)

- Prior to initiation of therapy, advise patients of the potential risk of Avastin to the developing fetus. Counsel patients who become pregnant about the possible risks, including hazard to the fetus and/or loss of pregnancy, of both continued treatment and prolonged exposure following discontinuation, keeping in mind the approximate half-life of Avastin (20 days; range 11–50 days). Patients should also be counseled to continue adequate contraception for at least 6 months following the last dose of Avastin

Nursing mothers (Use in Specific Populations)

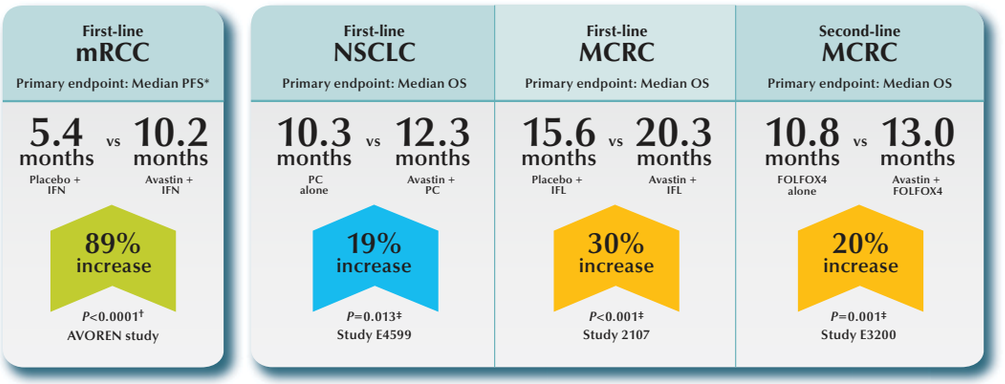
- Women should be advised to discontinue nursing or Avastin, taking into account the half-life of the product, approximately 20 days (range 11–50 days), and the importance of Avastin to the mother

Please see accompanying full Prescribing Information, including **Boxed WARNINGS**, and pages 16–17 for additional important safety information.

AVASTIN® bevacizumab

Avastin-based therapy: Established efficacy in 3 distinct tumor types[8,10,54-56]

Results from pivotal Phase III trials



mRCC=metastatic renal cell carcinoma; IFN=interferon alfa; MCRC=metastatic colorectal cancer; IFL=5-fluorouracil (5-FU)/leucovorin (LV)/irinotecan; FOLFOX4=5-FU/LV/oxaliplatin.

*The initial primary endpoint was OS with secondary endpoints including PFS and safety. Based on the approval of new active therapies during the conduct of the trial, which could have confounded OS analyses, it was agreed with regulatory agencies that PFS would become the main outcome measure.[55]

†Difference statistically significant. HR for PFS in AVOREN: HR=0.60 (95% CI, 0.49–0.72).

‡Difference statistically significant. HRs for survival: Study E4599, HR=0.80 (95% CI, 0.68–0.94); Study 2107, HR=0.66 (95% CI, 0.54–0.81); Study E3200, HR=0.75 (95% CI, 0.63–0.89).[10,12]

Bevacizumab is recognized as a first-line treatment with multiple regimens across 3 distinct tumor types

NCCN guidelines for bevacizumab[9,10,57,58]

First-line **MCRC**	First-line **NSCLC**	First-line **mRCC**
Bevacizumab plus: • FOLFOX • FOLFIRI • IV 5-FU/LV	Bevacizumab plus: • Chemotherapy [PC]	Bevacizumab plus: • IFN

FOLFIRI=5-FU/LV/irinotecan.

Indications

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

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.

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.

Important safety information

- In mRCC, the most common grade 3–5 adverse events in AVOREN, occurring at a ≥2% higher incidence in Avastin-treated patients vs controls, were fatigue (13% vs 8%), asthenia (10% vs 7%), proteinuria (7% vs 0%), hypertension (6% vs 1%), and hemorrhage (3% vs 0.3%)
- In NSCLC, grade 3–5 (nonhematologic) and grade 4–5 (hematologic) adverse events in Study E4599 occurring at a ≥2% higher incidence in Avastin-treated patients vs controls 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%)
- In first-line MCRC, the most common grade 3–4 events in Study 2107, which occurred at a ≥2% higher incidence in the Avastin plus IFL vs IFL groups, were asthenia (10% vs 7%), abdominal pain (8% vs 5%), pain (8% vs 5%), hypertension (12% vs 2%), deep vein thrombosis (9% vs 5%), intra-abdominal thrombosis (3% vs 1%), syncope (3% vs 1%), diarrhea (34% vs 25%), constipation (4% vs 2%), leukopenia (37% vs 31%), and neutropenia (21% vs 14%)
- In second-line MCRC, the most common grade 3–5 (nonhematologic) and 4–5 (hematologic) events in Study E3200, which occurred at a higher incidence (≥2%) in the Avastin plus FOLFOX4 vs FOLFOX4 groups, were diarrhea (18% vs 13%), nausea (12% vs 5%), vomiting (11% vs 4%), dehydration (10% vs 5%), ileus (4% vs 1%), neuropathy–sensory (17% vs 9%), neurologic–other (5% vs 3%), fatigue (19% vs 13%), abdominal pain (8% vs 5%), headache (3% vs 0%), hypertension (9% vs 2%), and hemorrhage (5% vs 1%)

Please see accompanying full Prescribing Information, including **Boxed WARNINGS**, and pages 16–19 for additional important safety information.

AVASTIN® bevacizumab

Dosing per pivotal Phase III trial protocols

Avastin dosing in approved indications[10]

- Avastin is administered as a solution for IV infusion at the following doses

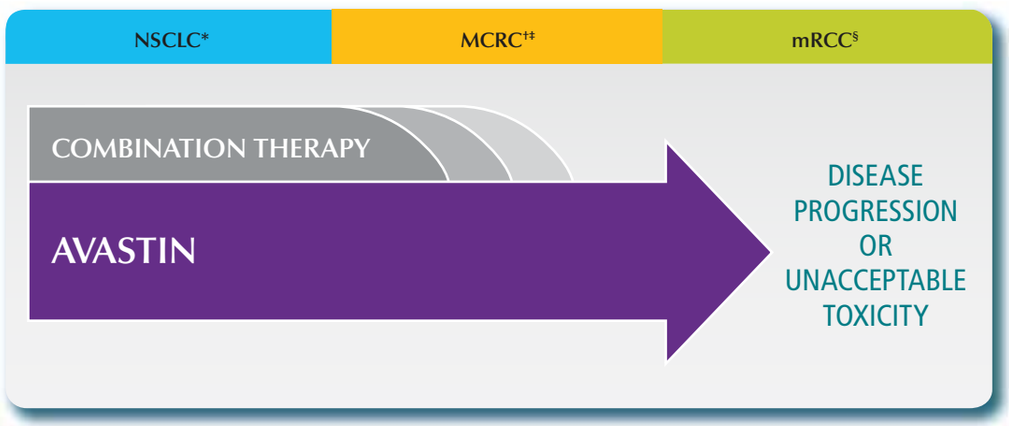
Tumor Type	Dose/Schedule
NSCLC*	15 mg/kg IV q3w
MCRC—IFL† (Study 2107)	5 mg/kg IV q2w
MCRC—FOLFOX4‡ (Study E3200)	10 mg/kg IV q2w
mRCC§	10 mg/kg IV q2w

q2w=every 2 weeks.
*15 mg/kg IV dose evaluated in first-line locally advanced or metastatic non-squamous NSCLC in combination with PC. Avastin plus PC was given for up to 6 cycles, after which Avastin was continued alone until disease progression or unacceptable toxicity.[10]
†5 mg/kg IV dose evaluated in first-line MCRC in combination with IFL.
‡10 mg/kg IV dose evaluated in second-line MCRC in combination with FOLFOX4.
§10 mg/kg IV dose evaluated in first-line mRCC in combination with IFN. AVOREN protocol allowed for IFN dose escalation (attaining a dose of 9 MIU within the first 2 weeks), reduction, or discontinuation. IFN was discontinued after 52 weeks or earlier.[10,55]

- In the majority of approved indications (mRCC, NSCLC, and second-line MCRC), Avastin is consistently dosed at the weekly equivalent of 5 mg/kg[10]
  - — In first-line MCRC, Avastin is dosed at the weekly equivalent of 2.5 mg/kg in combination with IFL[10]

Study results were achieved with Avastin continued until disease progression or unacceptable toxicity

Avastin duration in approved indications[10]



FDA-approved prescribing information for the duration of Avastin treatment[10]

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

Indications

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

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.

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- In second-line MCRC, the most common grade 3–5 (nonhematologic) and 4–5 (hematologic) events in Study E3200, which occurred at a higher incidence (≥2%) in the Avastin plus FOLFOX4 vs FOLFOX4 groups, were diarrhea (18% vs 13%), nausea (12% vs 5%), vomiting (11% vs 4%), dehydration (10% vs 5%), ileus (4% vs 1%), neuropathy–sensory (17% vs 9%), neurologic–other (5% vs 3%), fatigue (19% vs 13%), abdominal pain (8% vs 5%), headache (3% vs 0%), hypertension (9% vs 2%), and hemorrhage (5% vs 1%)

Important treatment considerations—Women of childbearing potential

- Avastin increases the risk of ovarian failure and may impair fertility
- Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin
- Long-term effects of Avastin exposure on fertility are unknown
- Prior to initiation of therapy, advise patients of the potential risk of Avastin to the developing fetus
- Counsel patients who become pregnant about the possible risks, including hazard to the fetus and/or loss of pregnancy, of both continued treatment and prolonged exposure following discontinuation, keeping in mind the approximate half-life of Avastin (20 days; range 11–50 days). Patients should also be counseled to continue adequate contraception for at least 6 months following the last dose of Avastin
- Nursing mothers should be advised to discontinue nursing or Avastin, taking into account the half-life of the product and the importance of Avastin to the mother

Important treatment considerations—Dose modifications

- There are no recommended dose reductions
- Discontinue Avastin in patients with
  - **Gastrointestinal (GI) perforations (GI perforations, fistula formation in the GI tract, intra-abdominal abscess)**
  - Fistula formation involving an internal organ
  - **Wound dehiscence and wound healing complications requiring medical intervention**
  - **Serious hemorrhage (ie, requiring medical intervention)**
  - Severe arterial thromboembolic event (ATE)
  - Hypertensive crisis or hypertensive encephalopathy
  - Reversible posterior leukoencephalopathy syndrome (RPLS) (symptoms usually resolve or improve within days, although some patients have experienced ongoing neurologic sequelae)
  - Nephrotic syndrome
- Temporarily suspend Avastin for at least 4 weeks prior to elective surgery, severe hypertension not controlled with medical management, moderate to severe proteinuria pending further evaluation, and severe infusion reactions
- The safety of resumption of Avastin therapy in patients that experienced RPLS, ATE, and moderate to severe proteinuria is unknown

Please see accompanying full Prescribing Information, including **Boxed WARNINGS**, and pages 16–19 for additional important safety information.

AVASTIN® bevacizumab

Genentech is committed to providing practices and eligible patients with reimbursement and coverage support

Helping patients access our therapies

We want your patients to get the Avastin you prescribe, regardless of their ability to pay. The Specialists at Avastin Access Solutions can provide expertise regarding access and reimbursement issues for the Avastin your patients need.

AVASTIN® bevacizumab Access Solutions®

Coverage and Reimbursement

- Help with benefits and coverage issues
  - — Benefits investigation
  - — Prior authorization
  - — Recertification
- Help with reimbursement issues
  - — Denials and appeals
  - — Billing and coding information

Patient Assistance

- Genentech® Access to Care Foundation (GATCF) support for qualifying uninsured and rendered uninsured patients
- Referrals to independent, non-profit organizations for co-pay assistance
- Genentech BioOncology Co-pay Card
- Avastin Patient Assistance Program
- Cancer*Care*

Informational Resources

- My Patient Solutions, our online patient management tool
- Communication assistance services
  - — Translation services
  - — Telephone to telephone typewriter (TTY) services
- Product spoilage and replacement information
- Medicare/Medicaid search tool
- Glossary of access and reimbursement terms

Committed to helping patients

- Since 1985, when its first product was approved, Genentech has donated approximately $2.3 billion in free medicine to uninsured patients through the Genentech® Access to Care Foundation (GATCF)
- Since 2005, Genentech has donated more than $550 million to independent non-profit organizations that provide co-pay assistance
- In 2010, Genentech Access Solutions helped more than 107,000 patients with coverage and reimbursement issues

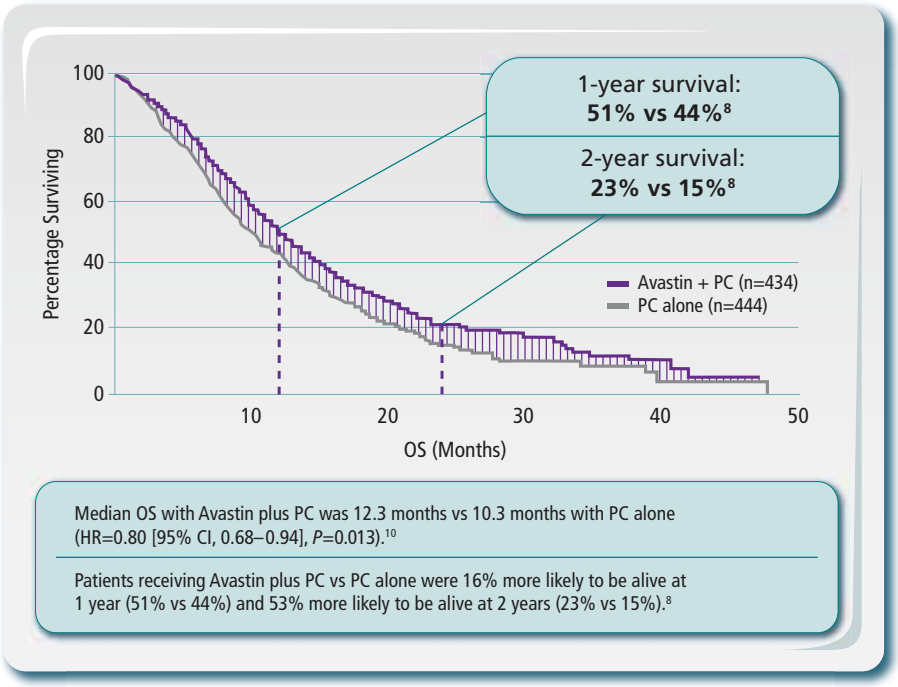
To speak live with one of our Specialists, call **(888) 249-4918** from 6 AM-5 PM PT, Monday to Friday, or visit AvastinAccessSolutions.com

Notes

References: 1. American Cancer Society. What are the key statistics about lung cancer? http://www.cancer.org/docroot/CRI/content/CRI_2_4_1x_What_Are_the_Key_Statistics_About_Lung_Cancer_15.asp?sitearea=. Accessed March 25, 2011. **2.** American Cancer Society. What is non-small cell lung cancer? http://www.cancer.org/docroot/CRI/content/CRI_2_4_1x_What_Is_Non-Small_Cell_Lung_Cancer.asp?sitearea=. Accessed March 25, 2011. **3.** Synovate's Tandem Cancer Audits Program. 2009. **4.** Breathnach OS, Freidlin B, Conley B, et al. *J Clin Oncol*. 2001;19:1734-1742. **5.** Non-small Cell Lung Cancer Collaborative Group. *BMJ*. 1995;311:899-909. **6.** Schiller JH, Harrington D, Belani CP, et al. *N Engl J Med*. 2002;346:92-98. **7.** Sandler AB, Gray R, Brahmer J, et al. Slides presented at: American Society of Clinical Oncology; May 13-17, 2005; Orlando, FL. **8.** Sandler A, Gray R, Perry MC, et al. *N Engl J Med*. 2006;355:2542-2550. **9.** The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (Version 2.2012). ©2011 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed November 15, 2011. To view the most recent and complete version of the guidelines, go online to www.nccn.org. **10.** Avastin Prescribing Information. Genentech, Inc. September 2011. **11.** Sandler A, Leon L, Fages S, et al. Poster presented at: World Conference on Lung Cancer; July 3-7, 2011; Amsterdam, The Netherlands. **12.** Data on file. Genentech, Inc. **13.** Sandler AB, Schiller JH, Gray R, et al. *J Clin Oncol*. 2009;27:1405-1412. **14.** Cohen MH, Gootenberg J, Keegan P, Pazdur R. *Oncologist*. 2007;12:713-718. **15.** Johnson DH, Fehrenbacher L, Novotny WF, et al. *J Clin Oncol*. 2004;22:2184-2191. **16.** Folkman J. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology*. Vol 2. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:2865-2882. **17.** Hanrahan V, Currie MJ, Gunningham SP, et al. *J Pathol*. 2003;200:183-194. **18.** Fontanini G, Vignati S, Boldrini L, et al. *Clin Cancer Res*. 1997;3:861-865. **19.** Rini BI, Small EJ. *J Clin Oncol*. 2005;23:1028-1043. **20.** Hicklin DJ, Ellis LM. *J Clin Oncol*. 2005;23:1011-1027. **21.** Bergers G, Benjamin LE. *Nat Rev Cancer*. 2003;3:401-410. **22.** Imoto H, Osaki T, Taga S, et al. *J Thorac Cardiovasc Surg*. 1998;115:1007-1014. **23.** Kaya A, Ciledag A, Gulbay BE, et al. *Respir Med*. 2004;98:632-636. **24.** Des Guetz G, Uzzan B, Nicolas P, et al. *Br J Cancer*. 2006;94:1823-1832. **25.** O'Byrne KJ, Koukourakis MI, Giatromanolaki A, et al. *Br J Cancer*. 2000;82:1427-1432. **26.** Jacobsen J, Grankvist K, Rasmuson T, et al. *BJU Int*. 2004;93:297-302. **27.** Yuan A, Yu CJ, Chen WJ, et al. *Int J Cancer (Pred Oncol)*. 2000;89:475-483. **28.** Saad RS, Kordunsky L, Liu YL, et al. *Mod Pathol*. 2006;19:1317-1323. **29.** Ottaiano A, Franco R, Talamanca AA, et al. *Clin Cancer Res*. 2006;12:2795-2803. **30.** Ishigami SI, Arii S, Furutani M, et al. *Br J Cancer*. 1998;78:1379-1384. **31.** Yeh HH, Lai WW, Chen HHW, et al. *Oncogene*. 2006;25:4300-4309. **32.** Presta LG, Chen H, O'Connor SJ, et al. *Cancer Res*. 1997;57:4593-4599. **33.** Ferrara N. *Endocr Rev*. 2004;25:581-611. **34.** Ferrara N, Hillan KJ, Gerber HP, et al. *Nat Rev Drug Discov*. 2004;3:391-400. **35.** O'Connor JPB, Carano RAD, Clamp AR, et al. *Clin Cancer Res*. 2009;15:6674-6682. **36.** Tobelem G. *Targ Oncol*. 2007;2:153-164. **37.** Yuan F, Chen Y, Dellian M, et al. *Proc Natl Acad Sci U S A*. 1996;93:14765-14770. **38.** Willett CG, Boucher Y, di Tomaso E, et al. *Nat Med*. 2004;10:145-147. **39.** Lee CG, Heijn M, di Tomaso E, et al. *Cancer Res*. 2000;60:5565-5570. **40.** Gerber HP, Ferrara N. *Cancer Res*. 2005;65:671-680. **41.** Yanagisawa M, Yorozu K, Kurasawa M, et al. *Anti-Cancer Drugs*. 2010;21:687-694. **42.** Borgström P, Hillan KJ, Sriramarao P, et al. *Cancer Res*. 1996;56:4032-4039. **43.** Borgström P, Bourdon MA, Hillan KJ, et al. *Prostate*. 1998;35:1-10. **44.** Bagri A, Berry L, Gunter B, et al. *Clin Cancer Res*. 2010;16:3887-3900 [and supplemental appendix]. **45.** Warren RS, Yuan H, Matli MR, et al. *J Clin Invest*. 1995;95:1789-1797. **46.** Mabuchi S, Terai Y, Morishige K, et al. *Clin Cancer Res*. 2008;14:7781-7789. **47.** Ribeiro SCC, Vargas FS, Antonangelo L, et al. *Respirology*. 2009;14:1188-1193. **48.** Watanabe M, Boyer JL, Crystal RG. *Hum Gene Ther*. 2009;20:598-610. **49.** Mesiano S, Ferrara N, Jaffe RB. *Am J Pathol*. 1998;153:1249-1256. **50.** Gerstner ER, Duda DG, di Tomaso E, et al. *Nat Rev Clin Oncol*. 2009;6:229-236. **51.** Galizia G, Lieto E, Ferraraccio F, et al. *Clin Cancer Res*. 2004;10:3490-3499. **52.** Vosseler S, Mirancea N, Bohlen P, et al. *Cancer Res*. 2005;65:1294-1305. **53.** Nagy JA, Dvorak AM, Dvorak HF. *Annu Rev Pathol*. 2007;2:251-275. **54.** Hurwitz H, Fehrenbacher L, Novotny W, et al. *N Engl J Med*. 2004;350:2335-2342. **55.** Escudier B, Pluzanska A, Koralewski P, et al. *Lancet*. 2007;370:2103-2111. **56.** Giantonio BJ, Catalano PJ, Meropol NJ, et al. *J Clin Oncol*. 2007;25:1539-1544. **57.** The NCCN Kidney Cancer Clinical Practice Guidelines in Oncology (Version 1.2012). ©2011 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed November 15, 2011. **58.** The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Version 2.2012). ©2011 National Comprehensive Cancer Network, Inc. http://www.nccn.org. Accessed November 15, 2011. To view the most recent and complete version of the guidelines, go online to www.nccn.org.

Avastin plus PC significantly increased median OS by 19% (12.3 vs 10.3 months with PC alone) in Study E4599[10]

In Study E4599, Avastin plus PC demonstrated clinically meaningful 1- and 2-year survival rates in first-line metastatic non-squamous NSCLC (51% and 23%, respectively, vs 44% and 15% with PC alone)[8]



Median OS with Avastin plus PC was 12.3 months vs 10.3 months with PC alone (HR=0.80 [95% CI, 0.68–0.94], *P*=0.013).[10]

Patients receiving Avastin plus PC vs PC alone were 16% more likely to be alive at 1 year (51% vs 44%) and 53% more likely to be alive at 2 years (23% vs 15%).[8]

Boxed WARNINGS

- **Gastrointestinal (GI) perforation**
  - — Serious and sometimes fatal GI perforation occurs at a higher incidence in Avastin-treated patients compared to controls
  - — The incidences of GI perforation ranged from 0.3% to 2.4% across clinical studies
  - — Discontinue Avastin in patients with GI perforation
- **Surgery and wound healing complications**
  - — The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients
  - — Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. 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 Avastin at least 28 days prior to elective surgery and in patients with wound healing complications requiring medical intervention
- **Hemorrhage**
  - — Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin. Across indications, the incidence of grade ≥3 hemorrhagic events among patients receiving Avastin ranged from 1.2% to 4.6%
  - — Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis (≥1/2 tsp of red blood)
  - — Discontinue Avastin in patients with serious hemorrhage (ie, requiring medical intervention)

Please see accompanying full Prescribing Information, including **Boxed WARNINGS**, and pages 16–19 for additional important safety information.

Genentech
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www.avastin.com

AVASTIN® bevacizumab

This reprint contains data from a Genentech-sponsored phase III clinical trial that led to the approval of Genentech's product Avastin (bevacizumab). The FDA has approved Avastin 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.

This reprint contains information and conclusions that are not contained in the approved product labeling, including certain data regarding: endpoints other than Overall Survival (objective response rate), efficacy among patient subgroups, proposed mechanism of action, and safety. Please see accompanying full prescribing information for Avastin.

The following authors of the attached publication are or have acted as paid consultants or advisors to Genentech: A. Sandler, J. Brahmer, J.H. Schiller, A. Dowlati, and D.H. Johnson.

Important Safety Information for Avastin

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  - *Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis (≥1/2 tsp of red blood)*
  - *Discontinue Avastin in patients with serious hemorrhage (ie, requiring medical intervention)*

Additional serious adverse events

- *Additional serious and sometimes fatal adverse events with increased incidence in the Avastin-treated arm vs control included*
  - *Non-GI fistula formation (≤0.3%)*
  - *Arterial thromboembolic events (grade ≥3, 2.4%)*
  - *Proteinuria including nephrotic syndrome (<1%)*
- *Additional serious adverse events with increased incidence in the Avastin-treated arm vs control included*
  - *Hypertension (grade 3–4, 5%–18%)*
  - *Reversible posterior leukoencephalopathy syndrome (RPLS) (<0.1%)*
- *Infusion reactions with the first dose of Avastin were uncommon (<3%), and severe reactions occurred in 0.2% of patients*
- *Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin*

Most common adverse events

- *Most common adverse reactions observed in Avastin patients at a rate >10% and at least twice the control arm rate were*
- *Epistaxis*
- *Headache*
- *Hypertension*
- *Rhinitis*
- *Proteinuria*
- *Taste alteration*
- *Dry skin*
- *Rectal hemorrhage*
- *Lacrimation disorder*
- *Back pain*
- *Exfoliative dermatitis*
- *Across all studies, Avastin was discontinued in 8.4% to 21% of patients because of adverse reactions*

Pregnancy warning

- *Avastin may impair fertility*
- *Based on animal data, Avastin may cause fetal harm*
- *Advise patients of the potential risk to the fetus during and following Avastin and the need to continue adequate contraception for at least 6 months following the last dose of Avastin*
- *For nursing mothers, discontinue nursing or Avastin, taking into account the importance of Avastin to the mother*

Important safety information—Study E4599

- *Grade 3–5 (nonhematologic) and grade 4–5 (hematologic) adverse events in Study E4599 occurring at a ≥2% higher incidence in Avastin-treated patients vs controls 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%)*

For additional safety and other information, please see accompanying full prescribing information.

ORIGINAL ARTICLE

Paclitaxel–Carboplatin Alone or with Bevacizumab for Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

Bevacizumab, a monoclonal antibody against vascular endothelial growth factor, has been shown to benefit patients with a variety of cancers.

METHODS

Between July 2001 and April 2004, the Eastern Cooperative Oncology Group (ECOG) conducted a randomized study in which 878 patients with recurrent or advanced non–small-cell lung cancer (stage IIIB or IV) were assigned to chemotherapy with paclitaxel and carboplatin alone (444) or paclitaxel and carboplatin plus bevacizumab (434). Chemotherapy was administered every 3 weeks for six cycles, and bevacizumab was administered every 3 weeks until disease progression was evident or toxic effects were intolerable. Patients with squamous-cell tumors, brain metastases, clinically significant hemoptysis, or inadequate organ function or performance status (ECOG performance status, >1) were excluded. The primary end point was overall survival.

RESULTS

The median survival was 12.3 months in the group assigned to chemotherapy plus bevacizumab, as compared with 10.3 months in the chemotherapy-alone group (hazard ratio for death, 0.79; P=0.003). The median progression-free survival in the two groups was 6.2 and 4.5 months, respectively (hazard ratio for disease progression, 0.66; P<0.001), with corresponding response rates of 35% and 15% (P<0.001). Rates of clinically significant bleeding were 4.4% and 0.7%, respectively (P<0.001). There were 15 treatment-related deaths in the chemotherapy-plus-bevacizumab group, including 5 from pulmonary hemorrhage.

CONCLUSIONS

The addition of bevacizumab to paclitaxel plus carboplatin in the treatment of selected patients with non–small-cell lung cancer has a significant survival benefit with the risk of increased treatment-related deaths. (ClinicalTrials.gov number, NCT00021060.)

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In the United States, lung cancer affects approximately 171,000 people annually and is the leading cause of cancer-related deaths.[1] Approximately 85% of these patients have non–small-cell lung cancer. The Eastern Cooperative Oncology Group (ECOG) conducted a randomized clinical trial comparing four platin-based, two-drug chemotherapy regimens in more than 1100 patients.[2] The median survival was 8 months, with no significant differences in overall survival among the groups. Although modest progress has been made with the use of chemotherapy in patients with metastatic non–small-cell lung cancer, additional treatment options are needed.

Angiogenesis is one of the hallmarks of cancer.[3] Vascular endothelial growth factor (VEGF), an endothelial-cell–specific mitogen, is the major regulator of angiogenesis in normal and malignant tissue.[4,5] Increased expression of VEGF has been found in most tumors in humans, including non–small-cell lung cancers, and in many instances, it is associated with increased risks of recurrence, metastasis, and death.[6-9] Preclinical studies have shown that a murine monoclonal antibody against VEGF can inhibit the growth of human tumor xenografts when given alone or with chemotherapy.[10-13] A humanized variant of this antibody (bevacizumab [Avastin, Genentech]) has clinical activity in human cancer and increases survival when added to standard chemotherapy in metastatic colon cancer.[14]

A randomized phase 2 study, involving patients with advanced non–small-cell lung cancer who had not previously received chemotherapy, compared paclitaxel and carboplatin alone with paclitaxel and carboplatin plus bevacizumab, with bevacizumab at a dose of 7.5 mg or 15 mg per kilogram of body weight intravenously every 3 weeks.[15] In the group receiving the higher dose of bevacizumab, as compared with the two other groups, the median time to disease progression was significantly longer. However, of the 66 patients who received bevacizumab, life-threatening pulmonary hemorrhage occurred in 6, including four fatal events. Serious hemorrhagic events appeared to be more common among patients with predominantly squamous-cell carcinomas. These preliminary results prompted the present phase 3 study, which was designed to investigate whether the addition of bevacizumab to paclitaxel and carboplatin improves survival in patients with metastatic nonsquamous-cell, non–small-cell lung cancer.

METHODS

PATIENTS

Between July 2001 and April 2004, we conducted a randomized study in which 878 patients with recurrent or advanced non–small-cell lung cancer (stage IIIB or IV) were assigned to paclitaxel and carboplatin chemotherapy alone (paclitaxel–carboplatin group) (444 patients) or paclitaxel and carboplatin plus bevacizumab (paclitaxel–carboplatin–bevacizumab group) (434 patients). Eligible patients were required to have histologically or cytologically confirmed, newly diagnosed stage IIIB (malignant pleural effusion) or stage IV cancer or recurrent non–small-cell lung cancer for which they had not received chemotherapy. Other inclusion criteria were measurable or nonmeasurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST),[16] an ECOG performance status of 0 or 1, and adequate hematologic, hepatic, and renal function (including urinary excretion of ≤500 mg of protein per day).

Exclusion criteria were histologic evidence of predominantly squamous-cell cancer; hemoptysis (½ tsp or more per event — a criterion added after a grade 5 pulmonary hemorrhage occurred in a patient with pretreatment hemoptysis); central nervous system (CNS) metastases (to reduce concern about possible CNS hemorrhage); pregnancy or lactation; a history of documented hemorrhagic diathesis or coagulopathy; therapeutic anticoagulation; regular use of aspirin (>325 mg per day), nonsteroidal antiinflammatory agents, or other agents known to inhibit platelet function; radiation therapy within 21 days before enrollment or major surgery within 28 days before enrollment; clinically significant cardiovascular disease; and medically uncontrolled hypertension.

LABORATORY CORRELATES

Plasma VEGF levels were measured at baseline in the initial 166 consecutive patients (79 in the paclitaxel–carboplatin group and 87 in the paclitaxel–carboplatin–bevacizumab group) by means of an enzyme-linked immunosorbent assay. Each sample was assayed in duplicate.

STUDY DESIGN

Treatment assignments were designed to achieve a balance between the two study groups in permuted blocks with stratification according to measurable versus nonmeasurable disease, prior radiation

therapy versus no prior radiation therapy, prior weight loss of less than 5% versus 5% or more, and non–small-cell lung cancer, stage IIIB, with pleural effusion versus stage IV or recurrent disease. The primary end point was overall survival. Prespecified stopping rules were based on toxic effects.

Patients were randomly assigned to receive paclitaxel at a dose of 200 mg per square meter of body-surface area and carboplatin at a dose calculated to produce an area under the concentration–time curve of 6.0 mg per milliliter per minute, administered intravenously on day 1, or paclitaxel and carboplatin plus bevacizumab at a dose of 15 mg per kilogram given intravenously on day 1.[15] Chemotherapy was repeated every 21 days for a total of six cycles unless there was evidence of disease progression or intolerance of the study treatment. Patients in the paclitaxel–carboplatin–bevacizumab group continued to receive bevacizumab monotherapy every 3 weeks until evidence of disease progression or unacceptable toxic effects developed.

The protocol was approved by the institutional review boards of all participating institutions and was carried out in accordance with the Declaration of Helsinki, current Food and Drug Administration Good Clinical Practices, and local ethical and legal requirements. ECOG designed and coordinated the study and was responsible for all aspects of the data collection and analysis; the authors made the decision to publish the data. The authors assume responsibility for the overall content and integrity of the manuscript and vouch for the accuracy and completeness of the reported data; their views do not necessarily represent the official views of the National Cancer Institute (NCI). Bevacizumab (Cancer Chemotherapy National Service Center code 704865) was provided by Genentech and distributed by the NCI.

ASSESSMENTS

After the baseline evaluation, tumor status was assessed every 6 weeks for 24 weeks, then every 9 weeks for the remainder of the treatment period, and then every 12 weeks after the completion of treatment. Responses were assessed using RECIST and required confirmation at least 4 weeks after initial documentation.

Assessments of toxic effects were made according to the common toxicity criteria (version 2) of the NCI. Because of concern about pulmonary hemorrhage, any serious bleeding event (grade 3 or higher) was reported to ECOG and the study chairman within 24 hours after its occurrence.

STATISTICAL ANALYSIS

The original study design called for the enrollment of a total of 640 patients, with the final analyses to be performed after 500 deaths had occurred. The design included two planned suspensions of recruitment for the safety analysis after a total of 112 patients had been enrolled and then after a total of 336 patients had been enrolled and planned interim analyses of survival after 218 and 350 deaths had occurred. The plan to suspend recruitment after enrollment of 336 patients was eliminated in August 2003, on the basis of the recommendation by the data monitoring committee; in January 2004, the planned enrollment was increased to 842 patients, with a planned final analysis after 650 deaths had occurred, to target a smaller treatment effect than that in the original study design. The increase in accrual was based on a recommendation by the ECOG Lung Committee, which was unaware of the results of the efficacy analysis. The revised design yielded an 80.5% power of the study to detect a hazard ratio for death of 0.80 in the group treated with chemotherapy plus bevacizumab, with the use of a one-sided test and an overall type I error of 2.5%.

The design specified interim analyses after 286 deaths had occurred (44%) and after 455 deaths had occurred (70%), with stopping rules both for a demonstrated difference between the study groups and for a demonstrated lack of benefit on the basis of the confidence intervals (CIs) for the hazard ratio,[17] estimated by means of a stratified partial-likelihood test with the use of an O'Brien–Fleming boundary. The study was continuously monitored for rates of grades 4 and 5 bleeding events, with early stopping if the rate among the first 336 patients enrolled was significantly higher in the paclitaxel–carboplatin–bevacizumab group than in the paclitaxel–carboplatin group, as calculated with the use of Fisher's exact test.

All efficacy analyses were based on a comparison of the assigned treatments. The primary analysis excluded patients deemed to be ineligible on central review of the submitted data. However, an intention-to-treat analysis of all patients showed similar results ($P=0.005$ for survival). Survival was defined as the time from randomization to death

from any cause, and progression-free survival as the time from randomization to documented disease progression (according to RECIST) or death. Event–time distributions were estimated by the Kaplan–Meier method. Cox proportional-hazards models, stratified according to the measurability of disease, disease stage, presence or absence of prior radiation therapy, and amount of prior weight loss, were used to estimate the hazard ratios and to test for significance of the timing of events. All reported P values are two-sided, and CIs are at the 95% level. Adverse events were compared with the use of Fisher's exact test.

RESULTS

After the second planned interim analysis, the independent data monitoring committee recommended the release of the study results in March 2005, since the criteria for significance prespecified in the protocol had been met (Wald statistic, 2.67; O'Brien–Fleming boundary, at 72.2% information, 2.41). The results reported here include follow-up through October 2005 (median, 19 months; minimum time from study entry to the cutoff point for the primary analysis, 18 months).

BASELINE CHARACTERISTICS OF THE PATIENTS

Between July 19, 2001, and April 27, 2004, including a prespecified suspension between February and August 2002, a total of 878 patients were enrolled, of whom 444 were assigned to treatment with paclitaxel and carboplatin alone and 434 to paclitaxel and carboplatin plus bevacizumab. Twenty-eight patients were excluded from the primary analysis because of eligibility violations or inadequate data (nine patients because of incorrect disease stage, six because of receipt of radiation therapy within three weeks before entry into the study, four because of histologic findings of squamous-cell cancer, and nine for other reasons) (Fig. 1). Table 1 shows the baseline characteristics of eligible patients. The two groups were well balanced, except for a difference in distribution according to sex (men accounted for 58% of patients in the paclitaxel–carboplatin group and 50% of those in the paclitaxel–carboplatin–bevacizumab group; P=0.03, with Fisher's exact test).

TREATMENT

The median number of cycles of therapy was five in the paclitaxel–carboplatin group and seven in the paclitaxel–carboplatin–bevacizumab group (including the cycles of bevacizumab monotherapy). Of the 407 patients starting treatment with paclitaxel and carboplatin plus bevacizumab for whom we had adequate information on the duration of treatment, 215 (53%) continued with bevacizumab monotherapy, and of these, 107 (50%) received more than five cycles of monotherapy. Information on treatment at the time of disease progression was available for 528 of the 850 patients included in the primary analysis. Chemo-

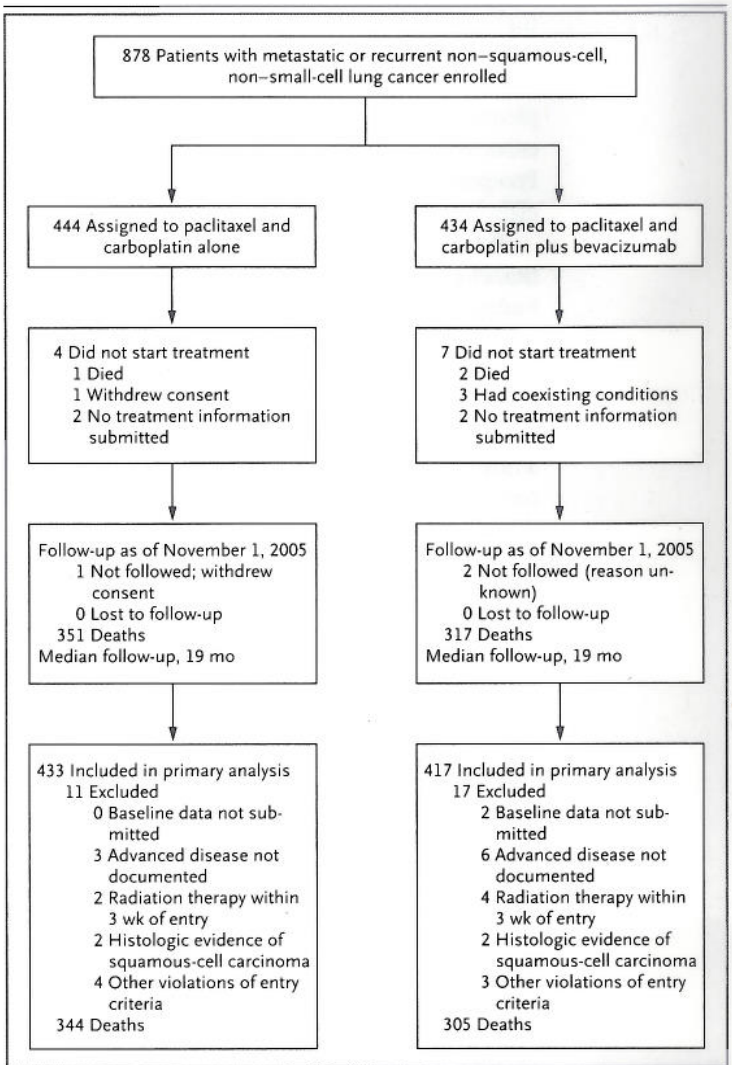

Figure 1. Enrollment, Randomization, and Follow-up of Patients in the Study.
Among the 850 patients included in the primary analysis, there were 344 deaths in the paclitaxel–carboplatin group and 305 in the paclitaxel–carboplatin–bevacizumab group. The total number of deaths among all 878 patients enrolled in the study was 351 in the paclitaxel–carboplatin group and 317 in the paclitaxel–carboplatin–bevacizumab group.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Paclitaxel–Carboplatin Group (N=433)	Paclitaxel–Carboplatin–Bevacizumab Group (N=417)
	no. (%)	
Sex†		
Male	253 (58)	210 (50)
Female	180 (42)	207 (50)
Age ≥65 yr	189 (44)	177 (42)
Race‡		
White	378 (91)	352 (90)
Black	23 (6)	22 (6)
Other	14 (3)	17 (4)
ECOG performance status§		
0	170 (40)	167 (40)
1	260 (60)	247 (60)
Measurable disease	392 (91)	381 (91)
Prior weight loss (≥5%)	121 (28)	117 (28)
Stage IIIB	55 (13)	50 (12)
Stage IV	337 (78)	310 (74)
Recurrent disease	40 (9)	57 (14)
Prior radiation therapy	37 (9)	33 (8)
Adenocarcinoma or not otherwise specified	380 (88)	366 (88)
Large-cell cancer	29 (7)	17 (4)
Bronchioloalveolar carcinoma	11 (3)	12 (3)
Other histologic findings	11 (3)	22 (5)
>2 Sites involved	229 (53)	216 (52)
Pleura involved	111 (26)	112 (27)
Liver involved	73 (17)	90 (22)
Bone involved	149 (34)	118 (28)
Adrenal glands involved	72 (17)	53 (13)

* Because of rounding, percentages may not total 100.
† P=0.03 by Fisher's exact test.
‡ Data on race were not available for 44 patients: 18 in the paclitaxel–carboplatin group and 26 in the paclitaxel–carboplatin–bevacizumab group. Race was determined on the basis of data in hospital records.
§ ECOG performance status was not available for six patients: three in the paclitaxel–carboplatin group and three in the paclitaxel–carboplatin–bevacizumab group.

therapy was given to 200 patients in the paclitaxel–carboplatin group (including 87 of 180 women [48%]) at the time of disease progression, as compared with 180 patients in the paclitaxel–carboplatin–bevacizumab group (82 of 207 women [40%]). In addition, more women in the paclitaxel–carboplatin group received second-line chemotherapy: 48% (87 of 180) as compared with 40% (82 of 207) in the paclitaxel–carboplatin–bevacizumab group. However, there was no significant difference in the number of women who subsequently received epidermal growth factor–tyrosine kinase inhibitors (32 of 180 in the paclitaxel–carboplatin group and 34 of 207 in the paclitaxel–carboplatin–bevacizumab group).

EFFICACY ANALYSIS

The median overall survival was 12.3 months in the paclitaxel–carboplatin–bevacizumab group, as compared with 10.3 months in the paclitaxel–carboplatin group (hazard ratio for death, 0.79; 95% CI, 0.67 to 0.92; P=0.003) (Fig. 2A). Survival rates were 51% in the paclitaxel–carboplatin–bevacizumab group, as compared with 44% in the paclitaxel–carboplatin group, at 1 year and 23%, as compared with 15%, respectively, at 2 years. The median progression-free survival was also significantly improved in the paclitaxel–carboplatin–bevacizumab group (6.2 months, as compared with 4.5 in the paclitaxel–carboplatin group), for a hazard ratio for disease progression of 0.66 (95% CI, 0.57 to 0.77; P<0.001) (Fig. 2B). Among 773 patients with measurable disease, the addition of bevacizumab to paclitaxel and carboplatin improved the response rate; 59 of 392 patients (15%) in the paclitaxel–carboplatin group had a response, as compared with 133 of 381 patients (35%) in the paclitaxel–carboplatin–bevacizumab group (P<0.001).

The effects of bevacizumab on survival and progression-free survival were consistent among the four subgroups, stratified according to whether patients had measurable or nonmeasurable disease, prior radiation therapy or no prior radiation therapy, a weight loss of 5% or more or a loss of less than 5%, and stage IIIb disease (pleural effusion) or stage IV disease, or recurrent disease (Fig. 3).

VEGF LEVELS

Baseline VEGF levels in 166 patients did not differ significantly according to treatment (P=0.13, calculated by the Wilcoxon rank-sum test) or sex (P=0.67) (median VEGF level, 38.7 ng per milliliter in the paclitaxel–carboplatin group and 33.7 ng per milliliter in the paclitaxel–carboplatin–bevacizumab group; 36.7 ng per milliliter in men and 33.7 ng per milliliter in women; range, 12.5 to 445 in all subgroups). VEGF levels before treatment did not correlate with overall survival (P=0.15).

SAFETY

All patients known to have received the study treatment (440 patients in the paclitaxel–carboplatin group and 427 in the paclitaxel–carboplatin–bevacizumab group) were included in the analysis of toxic effects. Reporting was limited to hematologic events of grade 4 or higher and all nonhematologic adverse events of grade 3 or higher. Table 2 lists rates of adverse events in each treatment group. The treating physician's attribution of the adverse event to the treatment or to another cause was not considered in this analysis. The rates of hypertension, proteinuria, bleeding, neutropenia, febrile neutropenia, thrombocytopenia, hyponatremia, rash, and headache were significantly higher in the paclitaxel–carboplatin–bevacizumab group than in the paclitaxel–carboplatin group ($P<0.05$). The difference between the groups appeared during the third cycle; during the first three cycles, events occurred in 57 of the 440 patients in the paclitaxel–carboplatin group (13%) and in 76 of the 427 patients in the paclitaxel–carboplatin–bevacizumab group (18%).

Table 3 lists all causes of death. There were 17 deaths related to toxic effects of the treatment. Two deaths (from gastrointestinal hemorrhage and febrile neutropenia) occurred in patients in the paclitaxel–carboplatin group and 15 occurred in the paclitaxel–carboplatin–bevacizumab group; the difference between the groups was significant ($P=0.001$). Of the 15 deaths in the paclitaxel–carboplatin–bevacizumab group, 5 were attributed to pulmonary hemorrhage, 5 to complications of febrile neutropenia, 2 each to a cerebrovascular event or gastrointestinal hemorrhage, and 1 to a probable pulmonary embolus. Most of the deaths occurred during the first two cycles of therapy. Three patients in the paclitaxel–carboplatin–bevacizumab group died of cardiac events that were not considered to be related to the treatment: a myocardial infarction 40 days after the last dose of bevacizumab, a sudden death (no autopsy) during the 18th cycle of treatment, and cardiac arrest with bradycardia after the third cycle (no autopsy). Among the 215 patients receiving bevacizumab monotherapy, the most common grade 3 or 4 toxic effects were hypertension (in 12 patients [5.6%]), proteinuria (in 9 patients [4.2%]), fatigue (in 11 patients [5.1%]), and dyspnea (in 12 patients [5.6%]).

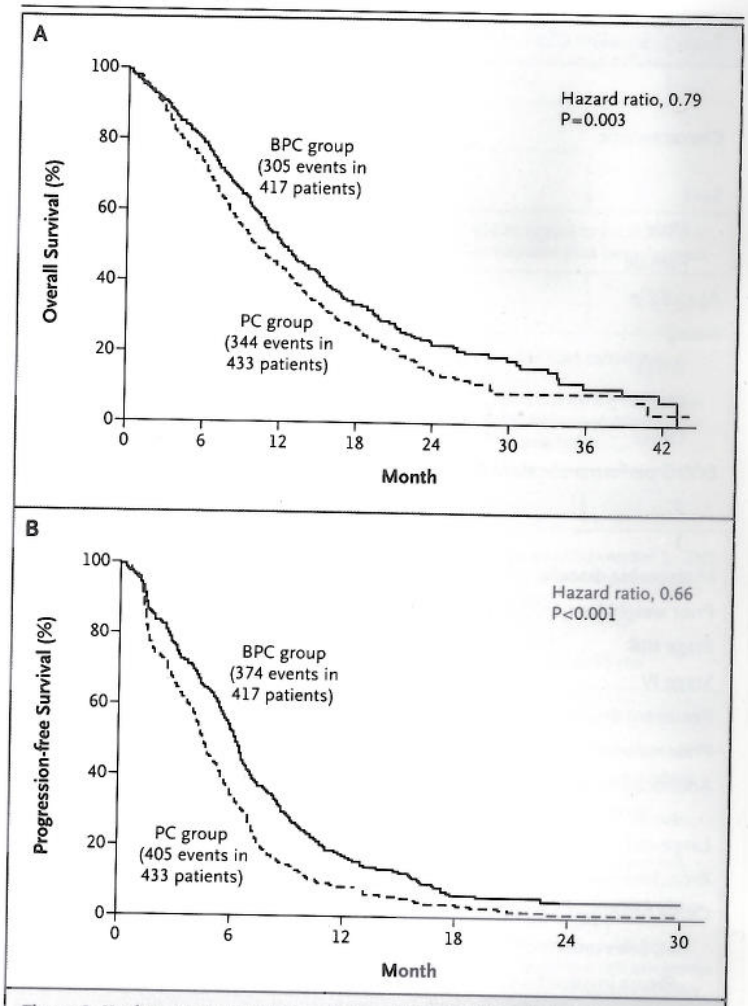

Figure 2. Kaplan–Meier Estimates of Overall Survival (Panel A) and Progression-free Survival (Panel B).

BPC denotes paclitaxel and carboplatin plus bevacizumab, and PC paclitaxel and carboplatin alone.

DISCUSSION

We found that the addition of bevacizumab to a standard, platin-based chemotherapy regimen improved overall survival in patients with advanced non–squamous-cell, non–small-cell lung cancer and a good ECOG performance status. In addition, bevacizumab prolonged progression-free survival and improved the response rate.

The improvement in the response rate was not anticipated a priori, since antiangiogenic drugs were not considered to have a cytotoxic effect.[3] Initially, it was thought that the predominant ef-

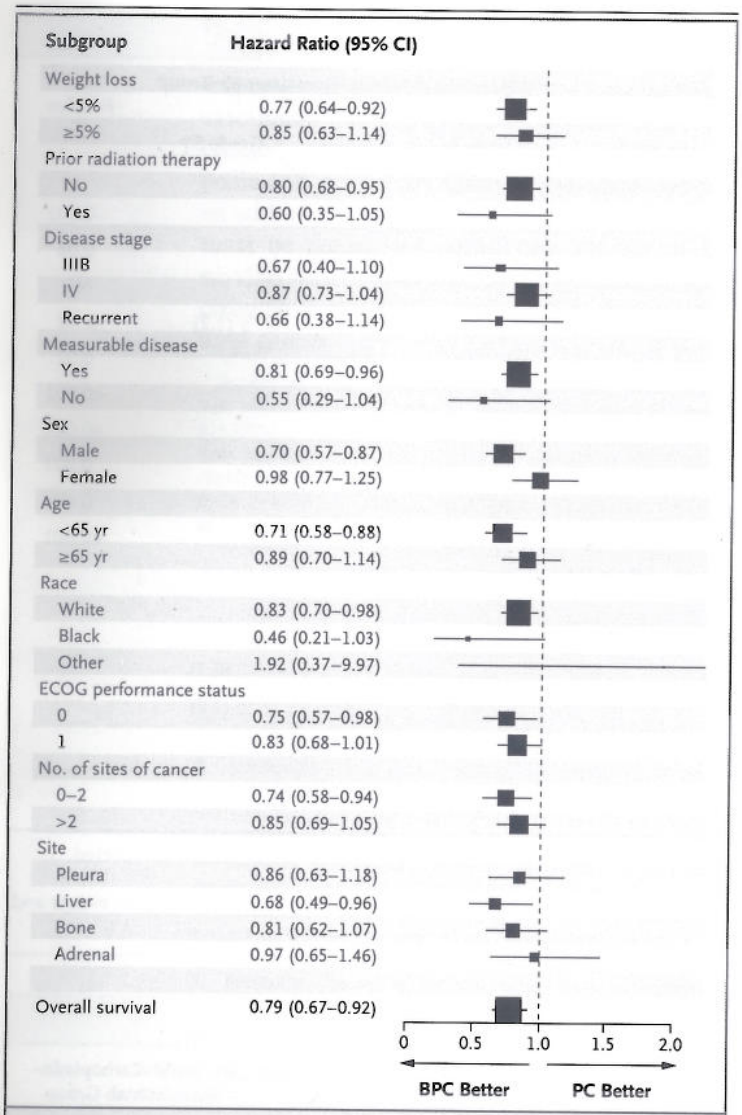

Figure 3. Hazard Ratios for Death, According to the Subgroup Analysis.

The size of each square represents the number of patients, with larger squares indicating a greater number. Horizontal lines represent confidence intervals. BPC denotes paclitaxel and carboplatin plus bevacizumab, and PC paclitaxel and carboplatin alone.

fect of antiangiogenic agents was the prevention of the development of new blood vessels, and that in this way these agents inhibit tumor growth. Jain reported that elevated VEGF levels cause a disorganized and "leaky" vasculature within the tumor; this effect elevates interstitial pressure and thus decreases delivery of chemotherapy to the tumor.[18] Subsequently, Willett et al. found that bevacizumab increases drug delivery to the tumor.[19] The significant improvement in the response rate in our study and in previous randomized studies of chemotherapy with or without bevacizumab supports the hypothesis that bevacizumab improves drug delivery to the tumor.[14,20,21]

In the phase 2 study that served as the impetus for our trial, an unexpectedly high rate of life-threatening and fatal pulmonary hemorrhages was associated with bevacizumab treatment, particularly in patients with squamous-cell lung cancer.[15] These results led us to exclude patients with predominantly squamous-cell carcinoma, hemoptysis, or both. With these exclusions, the incidence of life-threatening pulmonary hemorrhage was 1.9% (fatal hemorrhage, 1.2%), whereas in the phase 2 study, in which hemoptysis and predominantly squamous-cell carcinoma were not exclusion criteria, the incidence of this complication was 9.1%. Among the five patients who died from pulmonary hemorrhage in our study, one had hemoptysis before entry into the study (before the amendment to exclude patients with hemoptysis of ½ tsp or more at baseline), and hemoptysis developed in another patient during the first cycle of therapy. This second patient continued in the study and had a fatal event during the second cycle of treatment. Clearly, in retrospect, this patient should not have continued to receive bevacizumab. Among the 10 other deaths considered to be related to treatment, 5 were due to complications of febrile neutropenia, 2 to cerebrovascular events, and 2 to gastrointestinal hemorrhage; 1 was thought to be due to a pulmonary embolus.

Neutropenia has not been associated with bevacizumab, yet five patients in the paclitaxel–carboplatin–bevacizumab group had grade 5 febrile neutropenia. Other investigators have reported increased rates of neutropenia when bevacizumab was combined with chemotherapy.[22] The hypertension, proteinuria, and headache observed in this study are adverse events that had previously been associated with bevacizumab. They were generally manageable and did not require permanent discontinuation of bevacizumab.

The benefits of bevacizumab were consistent among all prespecified stratification groups. Exploratory analyses of the treatment groups according to baseline characteristics showed that bevacizumab was beneficial in all the subgroups assessed, with the possible exception of survival among women. The median overall survival in the paclitaxel–carboplatin group and the paclitaxel–carboplatin–bevacizumab group was 8.7 and 11.7

Table 2. Adverse Events, According to Treatment.*

Adverse Event	Paclitaxel–Carboplatin Group (N=440)			Paclitaxel–Carboplatin–Bevacizumab Group (N=427)			P Value
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5†	
	number of patients (percent)						
Neutropenia		74 (16.8)			109 (25.5)		0.002
Thrombocytopenia		1 (0.2)			7 (1.6)		0.04
Anemia		4 (0.9)			0		NS
Febrile neutropenia	8 (1.8)		1 (0.2)	17 (4.0)		5 (1.2)	0.02
Hyponatremia	4 (0.9)	1 (0.2)		11 (2.6)	4 (0.9)		0.02
Hypertension	2 (0.5)	1 (0.2)		29 (6.8)	1 (0.2)		<0.001
Proteinuria				11 (2.6)	2 (0.5)		<0.001
Headache	2 (0.5)			13 (3.0)			0.003
Rash or desquamation	2 (0.5)			10 (2.3)			0.02
Bleeding events (all)	3 (0.7)			19 (4.4)			<0.001
Central nervous system hemorrhage					3 (0.7)		
Epistaxis	1 (0.2)			3 (0.7)			
Hematemesis						2 (0.5)	
Hemoptysis	1 (0.2)			2 (0.5)	1 (0.2)	5 (1.2)	
Melena or gastrointestinal bleeding	1 (0.2)		1 (0.2)	3 (0.7)	1 (0.2)		
Other hemorrhage				1 (0.2)	1 (0.2)		

* Values are unadjusted between-group differences. For hematologic adverse events, only data on grades 4 and 5 events were reported. NS denotes not significant (P>0.05).

† Three other grade 5 adverse events occurred in the paclitaxel–carboplatin–bevacizumab group: two patients had cerebrovascular events and one had a pulmonary embolus.

months, respectively, among men and 13.1 and 13.3 months, respectively, among women. Possible explanations for this finding include imbalances between the two groups with respect to known or unknown baseline prognostic factors, imbalances in the use of second- and third-line therapies, statistical chance, or a true sex-based difference. More women in the paclitaxel–carboplatin group received second-line chemotherapy than in the paclitaxel–carboplatin–bevacizumab group. However, there was no significant difference between the two groups in the number of women who subsequently received epidermal growth factor–tyrosine kinase inhibitors.

Although it has been postulated that baseline VEGF levels correlate with the clinical outcome with bevacizumab treatment, in this trial, the baseline plasma VEGF levels did not correlate with survival. The absence of a correlation was also reported in a trial of first-line therapy with irinotecan, fluorouracil, and leucovorin with or without bevacizumab in patients with colorectal cancer.[23]

Table 3. Causes of Death.

Variable	Paclitaxel–Carboplatin Group	Paclitaxel–Carboplatin–Bevacizumab Group
	number of patients	
Total deaths	344	305
Cause		
Lung cancer	309	260
Toxic effects	2	14*
Coexisting conditions	16	16
Unknown cause	17	15

* One patient in the paclitaxel–carboplatin–bevacizumab group who had a grade 5 adverse event was considered to be ineligible because of undocumented advanced disease; data on this patient are not included in the table (but were included in the analysis of adverse events).

In summary, the addition of bevacizumab to a standard, platin-based, two-agent chemothera-

py regimen conferred a significant improvement in overall survival, progression-free survival, and response rate in patients with non–squamous-cell carcinoma and a good performance status. Increased toxic effects, particularly febrile neutropenia and pulmonary hemorrhage, were associated with the addition of bevacizumab. These risks must be considered within the context of the survival benefit conferred by the addition of bevacizumab to standard treatment for non–small-cell lung cancer.

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REFERENCES

1. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. CA Cancer J Clin 2005;55:10-30. [Erratum, CA Cancer J Clin 2005;55:259.]
2. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non–small-cell lung cancer. N Engl J Med 2002;346:92-8.
3. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000;100:57-70.
4. Folkman J. What is the evidence that tumors are angiogenesis dependent? J Natl Cancer Inst 1990;82:4-6.
5. Ferrara N. The role of vascular endothelial growth factor in pathological angiogenesis. Breast Cancer Res Treat 1995;36:127-37.
6. Mattern J, Koomagi R, Volm M. Association of vascular endothelial growth factor expression with intratumoral microvessel density and tumour cell proliferation in human epidermoid lung carcinoma. Br J Cancer 1996;73:931-4.
7. Brown LF, Berse B, Jackman RW, et al. Expression of vascular permeability factor (vascular endothelial growth factor) and its receptors in adenocarcinomas of the gastrointestinal tract. Cancer Res 1993;53:4727-35.
8. Brown LF, Berse B, Jackman RW, et al. Expression of vascular permeability factor (vascular endothelial growth factor) and its receptors in breast cancer. Hum Pathol 1995;26:86-91.
9. Seto T, Higashiyama M, Funai H, et al. Prognostic value of expression of vascular endothelial growth factor and its flt-1 and KDR receptors in stage I non-small-cell lung cancer. Lung Cancer 2006;53:91-6.
10. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med 2003;9:669-76.
11. Kim KJ, Li B, Winer J, et al. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. Nature 1993;362:841-4.
12. Kabbinavar FF, Wong JT, Ayala RE, Wintroub AB, Kim KJ, Ferrara N. The effect of antibody to vascular endothelial growth factor and cisplatin on the growth of lung tumors in nude mice. Proc Am Assoc Cancer Res 1995;36:488.
13. Borgstrom P, Gold DP, Hillan KJ, Ferrara N. Importance of VEGF for breast cancer angiogenesis in vivo: implications from intravital microscopy of combination treatments with an anti-VEGF neutralizing monoclonal antibody and doxorubicin. Anticancer Res 1999;19:4203-14.
14. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.
15. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2004;22:2184-91.
16. James K, Eisenhauer E, Christian M, et al. Measuring response in solid tumors: unidimensional versus bidimensional measurement. J Natl Cancer Inst 1999;91:523-8.
17. Jennison C, Turnbull BW. Interim analyses: the repeated confidence interval approach. J R Stat Soc [B] 1989;51:305-61.
18. Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. Nat Med 2001;7:987-9.
19. Willett CG, Boucher Y, di Tomaso E, et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. Nat Med 2004;10:145-7. [Erratum, Nat Med 2004;10:649.]
20. Giantonio BJ, Catalano PJ, Meropol NJ, et al. High-dose bevacizumab improves survival when combined with FOLFOX4 in previously treated advanced colorectal cancer: results from the Eastern Cooperative Oncology Group (ECOG) study E3200. J Clin Oncol 2005;23:Suppl:16S. abstract.
21. Miller KD, Wang W, Gralow J, al. A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: a trial coordinated by the Eastern Cooperative Oncology Group (E2100). Breast Cancer Res Treat 2005;94:Suppl 1:S6. abstract.
22. Kozloff M, Cohn A, Christiansen N, et al. Safety of bevacizumab among patients receiving first-line chemotherapy for metastatic colorectal cancer: preliminary results from a larger registry in the U.S. J Clin Oncol 2005;23:Suppl:16S. abstract.
23. Jubb AM, Hurwitz HI, Bai W, et al. Impact of vascular endothelial growth factor-A expression, thrombospondin-2 expression, and microvessel density on the treatment effect of bevacizumab in metastatic colorectal cancer. J Clin Oncol 2006;24:217-27.

This reprint contains data from a Genentech-sponsored phase II clinical trial that determined the investigated dose in the phase III clinical trial that led to the approval of Genentech's product Avastin (bevacizumab). The FDA has approved Avastin 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.

This reprint is being provided to you solely for purposes of understanding how dosing was determined for the Phase III pivotal study E4599. This reprint contains information that is not contained in the approved product labeling, including efficacy, patient eligibility, dose, duration, proposed mechanism of action, and safety. Please see accompanying full prescribing information for Avastin.

The following authors of the attached publication are or have acted as paid consultants or advisors to Genentech: D.H. Johnson, W.F. Novotny, J.J. Nemunaitis, J. Gaudreault, E. Holmgren, and F. Kabbinavar.

Important Safety Information for Avastin

Boxed WARNINGS

- ***Gastrointestinal (GI) perforation***
  - *Serious and sometimes fatal GI perforation occurs at a higher incidence in Avastin-treated patients compared to controls*
  - *The incidences of GI perforation ranged from 0.3% to 2.4% across clinical studies*
  - *Discontinue Avastin in patients with GI perforation*
- ***Surgery and wound healing complications***
  - *The incidence of wound healing and surgical complications, including serious and fatal complications, is increased in Avastin-treated patients*
  - *Do not initiate Avastin for at least 28 days after surgery and until the surgical wound is fully healed. 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 Avastin at least 28 days prior to elective surgery and in patients with wound healing complications requiring medical intervention*
- ***Hemorrhage***
  - *Severe or fatal hemorrhage, including hemoptysis, GI bleeding, hematemesis, central nervous system hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving Avastin. Across indications, the incidence of grade ≥3 hemorrhagic events among patients receiving Avastin ranged from 1.2% to 4.6%*
  - *Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis (≥1/2 tsp of red blood)*
  - *Discontinue Avastin in patients with serious hemorrhage (ie, requiring medical intervention)*

Additional serious adverse events

- *Additional serious and sometimes fatal adverse events with increased incidence in the Avastin-treated arm vs control included*
  - *Non-GI fistula formation (≤0.3%)*
  - *Arterial thromboembolic events (grade ≥3, 2.4%)*
  - *Proteinuria including nephrotic syndrome (<1%)*
- *Additional serious adverse events with increased incidence in the Avastin-treated arm vs control included*
  - *Hypertension (grade 3–4, 5%–18%)*
  - *Reversible posterior leukoencephalopathy syndrome (RPLS) (<0.1%)*
- *Infusion reactions with the first dose of Avastin were uncommon (<3%), and severe reactions occurred in 0.2% of patients*
- *Inform females of reproductive potential of the risk of ovarian failure prior to starting treatment with Avastin*

Most common adverse events

- *Most common adverse reactions observed in Avastin patients at a rate >10% and at least twice the control arm rate were*

— *Epistaxis*	— *Proteinuria*	— *Lacrimation disorder*
— *Headache*	— *Taste alteration*	— *Back pain*
— *Hypertension*	— *Dry skin*	— *Exfoliative dermatitis*
— *Rhinitis*	— *Rectal hemorrhage*	

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

Pregnancy warning

- *Avastin may impair fertility*
- *Based on animal data, Avastin may cause fetal harm*
- *Advise patients of the potential risk to the fetus during and following Avastin and the need to continue adequate contraception for at least 6 months following the last dose of Avastin*
- *For nursing mothers, discontinue nursing or Avastin, taking into account the importance of Avastin to the mother*

Important safety information—Study E4599

- *Grade 3–5 (nonhematologic) and grade 4–5 (hematologic) adverse events in Study E4599 occurring at a ≥2% higher incidence in Avastin-treated patients vs controls 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%)*

For additional safety and other information, please see accompanying full prescribing information.

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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ABSTRACT

Purpose
To investigate the efficacy and safety of bevacizumab plus carboplatin and paclitaxel in patients with advanced or recurrent non–small-cell lung cancer.

Patients and Methods
In a phase II trial, 99 patients were randomly assigned to bevacizumab 7.5 (n = 32) or 15 mg/kg (n = 35) plus carboplatin (area under the curve = 6) and paclitaxel (200 mg/m^2) every 3 weeks or carboplatin and paclitaxel alone (n = 32). Primary efficacy end points were time to disease progression and best confirmed response rate. On disease progression, patients in the control arm had the option to receive single-agent bevacizumab 15 mg/kg every 3 weeks.

Results
Compared with the control arm, treatment with carboplatin and paclitaxel plus bevacizumab (15 mg/kg) resulted in a higher response rate (31.5% *v* 18.8%), longer median time to progression (7.4 *v* 4.2 months) and a modest increase in survival (17.7 *v* 14.9 months). Of the 19 control patients that crossed over to single-agent bevacizumab, five experienced stable disease, and 1-year survival was 47%. Bleeding was the most prominent adverse event and was manifested in two distinct clinical patterns; minor mucocutaneous hemorrhage and major hemoptysis. Major hemoptysis was associated with squamous cell histology, tumor necrosis and cavitation, and disease location close to major blood vessels.

Conclusion
Bevacizumab in combination with carboplatin and paclitaxel improved overall response and time to progression in patients with advanced or recurrent non–small-cell lung cancer. Patients with nonsquamous cell histology appear to be a subpopulation with improved outcome and acceptable safety risks.

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INTRODUCTION

Vascular endothelial growth factor (VEGF) was originally discovered in the 1980s.[1-3] It is a highly conserved, homodimeric, heparin-binding glycoprotein that exists in several isoforms and functions as an endothelial cell specific mitogen.[4] VEGF mediates its effects by interacting with VEGF receptor-1 (Flt-1) and VEGF receptor-2 (KDR, flk-1) and is considered essential for normal developmental vasculogenesis and angiogenesis.[4] Transformed cell lines often express VEGF mRNA and secrete VEGF, whereas transfection of Chinese hamster ovary cells with expression vectors encoding VEGF allow these cells to form tumors in nude mice.[5] Further evidence that VEGF plays an important role in tumor angiogenesis comes from the observation that an antibody to VEGF, alone or in combination with chemotherapy, can inhibit tumor growth in vivo.[6-8] Thus, VEGF serves as a major tumor angiogenesis factor during ep-

ithelial carcinogenesis and for this reason it is considered to be a rational therapeutic target.

Bevacizumab (Avastin; Genentech, Inc, South San Francisco, CA) is the recombinant humanized version of the murine antihuman VEGF monoclonal antibody A4.6.1.[9] In phase I trials, bevacizumab was generally well tolerated and was not associated with a dose-limiting toxicity.[10] When combined with classical cytotoxic chemotherapy agents, there was no exacerbation of expected toxicities.[11] Based on these observations, we initiated a randomized phase II trial in patients with advanced non–small-cell lung cancer (NSCLC) in which bevacizumab was combined with carboplatin plus paclitaxel. We opted to use carboplatin and paclitaxel because it is efficacious and generally less toxic than most standard regimens.[12] Furthermore, in preclinical studies, these agents demonstrated enhanced tumor growth inhibition when combined with an antiangiogenic agent.[13]

PATIENTS AND METHODS

Patient Eligibility

Patients with histologically confirmed stage IIIB (with pleural effusion), stage IV, or recurrent NSCLC were eligible. Patients with small-cell or mixed histologies were excluded. Additional eligibility requirements included age $\geq$ 18 years, bi-dimensionally measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leq$ 2, life expectancy $\geq$ 3 months, and availability for regular follow-up. Patients who had received prior chemotherapy or biotherapy, radiotherapy to an area of measurable disease (unless disease progression had been documented following completion of therapy), or radiotherapy within 2 weeks preceding day 0 were excluded from the trial. Additional exclusion criteria included an absolute neutrophil count $\leq$ 1,500/μL, hemoglobin less than 9 gm/dL, platelet count $\leq$ 100,000/μL, bilirubin $>$ 2.0 mg/dL, AST or ALT $\geq$ 5 times upper limit of normal (ULN) for subjects with metastases, $>$ 2.5 $\times$ ULN for those without metastases, and serum creatinine $>$ 1.8 mg/dL. Patients with nonhealing wounds, ulcers, or bone fractures, significant cardiovascular disease (ie, uncontrolled hypertension, myocardial infarction within 6 months, unstable angina, $\geq$ NYHA grade 2 congestive heart failure, or serious cardiac arrhythmia), clinically significant peripheral vascular disease, CNS metastasis, active secondary malignancies (other than basal cell carcinoma of the skin), an active infection, or pregnancy were excluded. In addition, because of the potential for impaired wound healing, major surgery within 4 weeks before day 0, a fine needle biopsy or an open biopsy within 1 week before day 0, a significant recent traumatic injury, or the anticipation of a major surgical procedure were exclusion criteria. Recent or current use of aspirin or oral and/or parenteral anticoagulants (except low-dose coumadin 1 mg) was not allowed. Written informed consent was required. The study was approved by the institutional review boards of all participating centers and conducted in accordance with the United States Food and Drug Administration Good Clinical Practice requirements.

Study Design and Treatments

Eligible patients were randomly assigned to carboplatin/paclitaxel alone or carboplatin/paclitaxel plus low-dose (7.5 mg/kg) or high-dose (15 mg/kg) bevacizumab using an interactive voice response system. In an earlier phase I trial, bevacizumab doses of 0.1, 0.3, 1.0, 3.0, and 10 mg/kg yielded no identifiable dose limiting toxicity.[10] We thus selected the 7.5 and 15 mg/kg doses based on pharmacokinetic modeling that predicted these doses would result in steady-state trough antibody concentrations of approximately 70 to 140 μg/mL respectively. Importantly, inhibition of tumor growth was observed at antibody serum concentrations between 10 and 30 μg/mL in mice. Also, in a separate phase I trial, various combinations of chemotherapy plus bevacizumab were assessed for safety.[11] Bevacizumab in combination with carboplatin plus paclitaxel appeared to be safe and well tolerated in this patient population. Randomization was stratified by ECOG PS (0 or 1 v 2) but not histology or stage. Patients received up to six cycles of carboplatin/paclitaxel. Paclitaxel (200 mg/m^2) was administered over 3 hours every 3 weeks. Carboplatin dosing was based on the Calvert formula[14] with a target area under the curve of 6 mg/mL $\times$ min and glomerular filtration rate (GFR) estimated for males as GFR = (140 – age) $\times$ weight/72 $\times$ (serum creatinine). For females, a correction factor of 0.85 was used. Carboplatin was administered over 15 to 30 minutes, beginning 60 minutes after completion of the paclitaxel. Dose reductions were permitted for febrile neutropenia or absolute neutrophil count less than 1,000/μL for $\geq$ 5 days, any clinically significant bleeding ($\geq$ grade 2), grade 3 nausea/vomiting not controlled by antiemetic medication, evidence of hepatic (AST $>$ 5 $\times$ ULN or bilirubin $>$ 3 $\times$ ULN), cardiovascular (symptomatic arrhythmia, hypotension [$<$ 90/60 mmHg or fluid replacement] or chest pain), neurologic ($\geq$ grade 2) or other grade 3 or 4 toxicity. Bevacizumab was administered by intravenous infusion over 90 minutes, 1 hour after each cycle of chemotherapy. If the initial infusion was well tolerated, subsequent infusion times were shortened to 30 to 60 minutes. The bevacizumab dose was not modified during this study. On completing the planned chemotherapy, nonprogressing patients were allowed to continue on bevacizumab at the same dose and schedule for up to a maximum of 18 doses. Patients in the control arm were permitted to receive bevacizumab (15 mg/kg) on disease progresssion.

All patients received standard supportive care, including blood and platelet transfusions, antibiotics, and antiemetics, as appropriate. Granulocyte colony-stimulating factor was administered only if there was persistent neutropenia despite dose reductions during the previous cycle. Patients were followed for survival information every 2 months until death or loss to follow-up.

Study Parameters

Baseline evaluation included assessment of ECOG PS, standard hematology, chemistry, electrolytes, urinalysis, INR/aPTT, and physical examination. Baseline tumor assessments, with prospective identification of sentinel lesions to be followed over the course of the study, included a chest x-ray, computed tomography scans of head, chest, abdomen, and bone scans. Tumor status was assessed after cycles 3, 6, 10, 14, and 18 using standard ECOG tumor response criteria. Tumor responses required confirmation $\geq$ 4 weeks after initial documentation. Responses were independently determined by the investigator and an independent review facility (IRF) blinded to treatment assignment. Safety evaluations including physical examination, laboratory tests, and vital sign monitoring were performed before, during, and

after bevacizumab infusions (before chemotherapy for patients in the control arm).

Statistical Considerations

The primary efficacy end points were time to progression (TTP) and tumor response rate. Secondary efficacy end points were overall survival and duration of response. Efficacy analyses were based on an intent-to-treat analysis. Standard survival analysis using a Kaplan-Meier approach was performed. The log-rank test was used to provide a formal statistical assessment of the differences between treatment arms. The Cox proportional hazards model was used to estimate the hazard ratio. A two-sided χ^2 test was used to compare tumor response for each bevacizumab arm with the control arm. Exploratory analyses included multivariate adjustments to assess TTP using the Cox model, and for the impact of several baseline factors on the estimates of treatment effect for TTP and survival. The study was designed to have approximately 80% power to detect an increase in the response rate of 25% (ie, from 27% to 52%) in the pooled bevacizumab treated arms. For comparing a single bevacizumab arm with control, the study had 80% power to detect a 30% improvement. The study had 80% power to detect a 100% improvement in the median TTP between the control arm and the pooled bevacizumab-treated arms, or a 150% improvement in TTP between the control arm and any single bevacizumab arm. A single interim analysis was planned for the purpose of assessing safety. Results of significance tests at the interim analyses were not to be considered significant unless *P* values were less than .0001.

RESULTS

Patient Characteristics and Disposition

The study was conducted in 12 centers in North America. Patient characteristics are presented in Table 1. In general, the three arms were reasonably well balanced for usual prognostic features, although there were some imbalances observed. For example, the high-dose bevacizumab arm enrolled a higher percentage of women, whereas squamous histology and stage IV disease were more frequent in the low-dose cohort. One patient assigned to the high-dose bevacizumab arm did not receive protocol therapy because of the discovery of a CNS metastasis just before initiating treatment.

Treatment Status

Patients in the high-dose arm received more doses of bevacizumab compared with those in the low-dose arm (median, 10 *v* 8 respectively; range, 1 to 18 in both groups). However, the mean relative dose-intensity (actual dose received/protocol-assigned dose during treatment period) was similar in the two arms (93% and 95%, respectively). Patients in all three arms received a median of six cycles of carboplatin plus paclitaxel. There were minor imbalances in the number of doses of chemotherapy received but the mean relative dose-intensity was similar among the three arms, and in the range of 80% to 100% of target.

Table 1. Selected Demographic and Baseline Characteristics

Parameter	Control (n = 32)	Bevacizumab 7.5 mg/kg (n = 32)	Bevacizumab 15 mg/kg (n = 35)	Total (N = 99)
Sex				
Female	8	12	19	39
Male	24	20	16	60
ECOG status				
0	15	16	19	50
1	15	15	12	42
2	2	1	4	7
Duration of current cancer				
< 1 year	22	24	28	74
1 year	4	2	4	10
2 years	2	2	1	5
≥ 3 years	4	4	2	10
Prior cancer therapy				
Any	13	10	10	33
Radiation	8	9	7	24
Other*	11	7	9	27
Histology				
Adenocarcinoma	17	20	23	60
Large-cell anaplastic	4	1	5	10
Squamous cell	7	10	3	20
Other	4	1	4	9
Cancer stage				
IIIB	6	2	7	15
IV	26	30	28	84

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*Mainly surgery.

Efficacy Results

The overall response rate showed a trend toward improved response for patients receiving bevacizumab, with the highest response noted in the high-dose group (31.5%) and the lowest in the control group (18.8%; Table 2). Based on the investigator assessment, 85 patients experienced disease progression, 27 of 32 patients (five censored) in the control arm, 29 of 32 patients (three censored) in the low-dose bevacizumab arm, and 29 of 34 patients (five censored) in the high-dose arm. Median TTP was longer in the high-dose bevacizumab arm compared with the control arm (7.4 *v* 4.2 months; $P = .023$; Fig 1). This translates to a 46% reduction in the hazard of progressing (Cox proportional hazard model). The IRF findings affirm the investigator-determined results (TTP, 7.0 *v* 5.9 months; $P = .185$; hazard of progression, 33%). TTP in the low-dose bevacizumab and control arms were similar (Table 3). Survival for the high-dose bevacizumab arm was modestly longer than the control arm (17.7 *v* 14.9 months; $P = .63$; Fig 2).

On disease progression, 19 control patients crossed over to single-agent bevacizumab and five experienced disease stabilization. The median duration of treatment was 12 weeks and five patients received bevacizumab for more than

Table 2. Investigator and IRF Assessments of Outcome

	Control (n = 32)	Bevacizumab 7.5 mg/kg (n = 32)	Bevacizumab 15 mg/kg (n = 34)
Response rate, %			
Investigator	18.8	28.1	31.5
IRF	31.3	21.9	40.0
TTP, months			
Investigator			
Median	4.2	4.3	7.4
Range	0-12.6*	0.2-12.9*	0.7-12.5
IRF			
Median	5.9	4.1	7.0
Range	0.2-12.6*	0.2-13.1*	0.3-13.2*
Survival, months			
Median	14.9	11.6	17.7
Range	0.2-57.0	0.2-56.8*	0.8-57.8*
P		.84	.63

Abbreviations: IRF, independent review facility; TTP, time to progression.
*Indicates censored value.

6 months. One patient had a significantly longer time to disease progression on cross-over therapy compared with control therapy (120 days *v* 60 days). Survival at 12 months was 47.4% following cross-over.

Safety and Toxicity Results

Nine patients died as the result of an adverse event (AE) not directly related to progressive disease; four in each of the bevacizumab arms and one in the control arm. The causes of death for low-dose bevacizumab included hemorrhage of unknown origin (probable hemoptysis), hemoptysis, unknown cause, and liver failure. In the high-dose arm, the deaths were attributed to aspiration pneumonitis, pulmonary hemorrhage, *Aspergillus* lung abscess, and chronic obstructive pulmonary disease. The death in the control arm was as a result of sepsis.

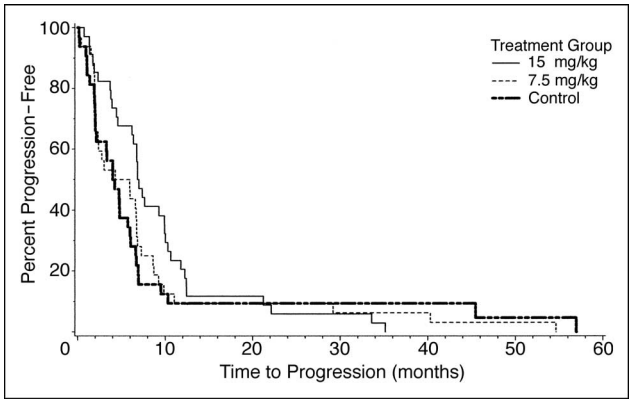


Fig 1. Kaplan-Meier curve showing time to progression according to independent review facility/investigator assessment for carboplatin/paclitaxel (control), bevacizumab 7.5 mg/kg and 15 mg/kg arms, respectively.

Eleven patients discontinued treatment as a result of a nonfatal AE. Discontinuations occurred as a result of: hemorrhagic event (three patients) in the low-dose bevacizumab arm; a hemorrhagic event (one patient); *Aspergillus* lung abscess (one patient); aspiration pneumonia (one patient); thrombotic stroke (one patient); vertebral fracture (one patient); and peripheral neuropathy (paclitaxel-related; one patient) in the high-dose arm. In two cases, bevacizumab was discontinued following initiation of anticoagulant therapy. Bevacizumab was withheld from one patient with subclavian vein thrombosis.

The addition of bevacizumab to carboplatin and paclitaxel resulted in only modest changes to the expected toxicity profile of chemotherapy alone (Table 3). Nausea and/or vomiting, renal toxicity, and peripheral neuropathy did not appear to be increased with bevacizumab. A trend toward slightly greater toxicity was noted in leucopenia, diarrhea, and minor systemic events such as fever, headache, rash, and chills. AEs observed in patients who received bevacizumab following failure of chemotherapy were generally similar in incidence to those observed in patients treated concurrently, with the possible exception of hemoptysis and epistaxis. These AEs both appeared to be less common (11% each) in this patient group, and only one thrombotic event (deep thrombophlebitis) was reported.

Several bevacizumab-associated AEs may be mechanism-based and warrant special emphasis including hypertension, proteinuria, and bleeding. Hypertension was reported for patients in both the low- and high-dose bevacizumab arms (five and six patients, respectively), and rarely in the control arm (one event). Grade 3 hypertension (defined as requiring new or increased antihypertensive medical therapy) was observed in the high-dose arm (two patients). The greatest increases from baseline in systolic blood pressure were also recorded in this dose group (range, +7.46 to 14.29 mmHg on day 42). Of the 12 patients reported to have a hypertensive AE, seven had a history of hypertension and eight required treatment with oral antihypertensive therapy. No patient in the trial discontinued bevacizumab because of hypertension. Asymptomatic proteinuria, as determined by dipstick analysis, was observed in 21 bevacizumab patients (seven low-dose and 14 high-dose patients) and two patients in the control arm. One patient in the low-dose arm developed clinically apparent nephrotic syndrome. A renal biopsy revealed cryoglobulinemic glomerulonephritis.

Two distinct clinical patterns of bleeding were observed during the study; minor mucocutaneous hemorrhage and major hemoptysis. The most common mucocutaneous bleeding was grade 1 or 2 epistaxis, which was reported in 31% of low-dose bevacizumab patients and 44% of high-dose patients compared to 6% of control patients. None required a change in bevacizumab administration. Six patients experienced a major life-threatening

Table 3. Selected Adverse Events by Body System and Preferred Term

	Control			7.5 mg/kg			15 mg/kg		
	All Events			All Events			All Events		
	No. of Patients	%	Grade 3/4	No. of Patients	%	Grade 3/4	No. of Patients	%	Grade 3/4
Chills	3	9.4	0	4	12.5	0	4	11.8	0
Diarrhea	6	18.8	0	9	28.1	3	14	41.2	1
Epistaxis	2	6.3	0	10	31.3	0	15	44.1	0
Fever	4	12.5	0	11	34.4	2	11	32.4	2
Headache	3	9.4	0	10	31.3	1	16	47.1	2
Hemorrhage	0	0	0	4	12.5	2	0	0	0
Hypertension	1	3.1	1	5	15.6	0	6	17.6	2
Hemoptysis	2	6.3	0	9	28.1	3	4	11.8	1
Infection	8	25.0	1	10	31.3	0	12	35.3	2
Leukopenia	10	31.3	7	15	46.9	10	19	55.9	13
Nausea	15	46.9	1	16	50.0	1	17	50.0	2
Neuropathy	9	28.1	0	4	12.5	0	5	14.7	1
Paresthesia	7	21.9	0	9	28.1	0	12	35.3	0
Peripheral neuritis	9	28.1	1	8	25.0	0	13	38.2	2
Rash	3	9.4	0	11	34.4	0	8	23.5	0
Stomatitis	3	9.4	0	5	15.6	0	8	23.5	0
Thrombocytopenia	5	15.6	0	2	6.3	0	7	20.6	1
Thrombotic events	3	9.4	3	4	12.5	2	6	17.6	5
Vomiting	6	18.8	1	6	18.8	1	8	23.5	1

NOTE. Values represent the number of patients (%) experiencing an event. Grade based on National Cancer Institute Common Toxicity Criteria, Version 1.

bleeding described as hemoptysis or hematemesis. Four events were fatal. All six patients had centrally-located tumors close to major blood vessels. Five cases had cavitation or necrosis of tumors, either at baseline or developing during bevacizumab therapy (Fig 3). Four of the severe hemorrhages occurred in patients with squamous carcinomas and five occurred in the low-dose bevacizumab arm. We conducted an exploratory analysis excluding squamous histology patients. This subset analysis suggested that bevacizumab improves response rate (20%; 31.8%; 50%), TTP (4.0 months; 6.3 months; 7.1 months), and survival (12.2 months; 14.0 months; 17.8 months) in nonsquamous carcinomas with only a small increased risk of serious bleeding (~4%; Table 4 and Fig 4).

DISCUSSION

This randomized phase II study was designed to evaluate the safety and efficacy of bevacizumab in combination with carboplatin and paclitaxel in patients with advanced or recurrent NSCLC. Bevacizumab is a humanized variant of a murine anti-VEGF antibody which may exert a direct antiangiogenic effect by binding to and clearing VEGF from the tumor microenvironment.[9] Additional antitumor activity may be obtained via the effects of bevacizumab on tumor vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells.[15] This study sought to exploit these potential antitumor effects by administering bevacizumab concurrently with chemotherapy and through continuation of bevacizumab after the prespecified six cycles of chemotherapy was delivered. NSCLC was felt to be an appropriate target for bevacizumab, as high expression of VEGF is common in this disease and is associated with a poor outcome.[16,17] Furthermore, in preclinical studies, the combination of carboplatin and paclitaxel with antiangiogenesis agents yielded improved antitumor activity.[13]

Our data suggest that the addition of bevacizumab to carboplatin and paclitaxel results in higher response rates, longer time to disease progression, and improved overall survival relative to this chemotherapy regimen without bevacizumab.[12,18] Although numerically these improvements appeared to be greatest in the high-dose bevacizumab arm as compared to the low-dose arm, the study lacks sufficient power to make any definitive conclusions regarding a possible relationship between dose and treatment effect. Recognizing the potential for investigator bias in this open label trial design, we used an IRF to perform a separate, blinded assessment of the response rates and time to progression. Except for the overall response rate in the control arm, the results of the IRF assessment were virtually identical to that recorded by the participating investigators. Notably, patients in all three treatment arms experienced a median survival of approximately 1 year or longer (Fig 1). Patients in the control arm experienced a particularly impressive median survival of 14.9 months. This compares to median

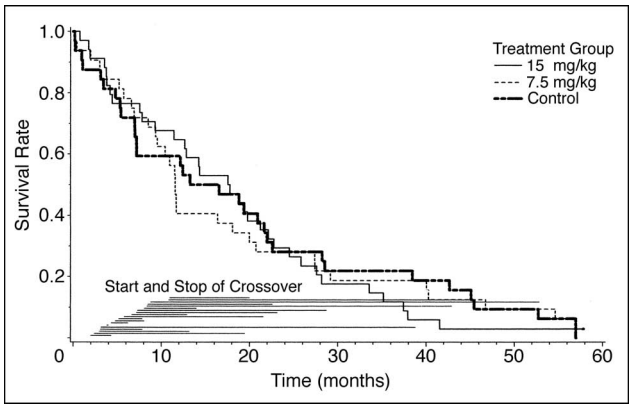


Fig 2. Kaplan-Meier curve showing overall survival for carboplatin/paclitaxel (control), bevacizumab 7.5 mg/kg and 15 mg/kg arms, respectively.

survivals of approximately 8 months in similar patient populations reported in recently completed cooperative group phase III trials.[12,18] The fact that 19 of the 32 control patients crossed over to single agent bevacizumab on disease progression may have impacted on the median survival of this cohort. Although none of the cross-over patients demonstrated an objective response, five maintained stable disease for more than 6 months. The median survival of cross-over patients was 10 months, which compares quite favorably to that observed in patients receiving second line docetaxel therapy.[19,20] This observation also is consistent with the data derived from numerous preclinical models that suggest antiangiogenic therapy is cytostatic rather than cytocidal.[21]

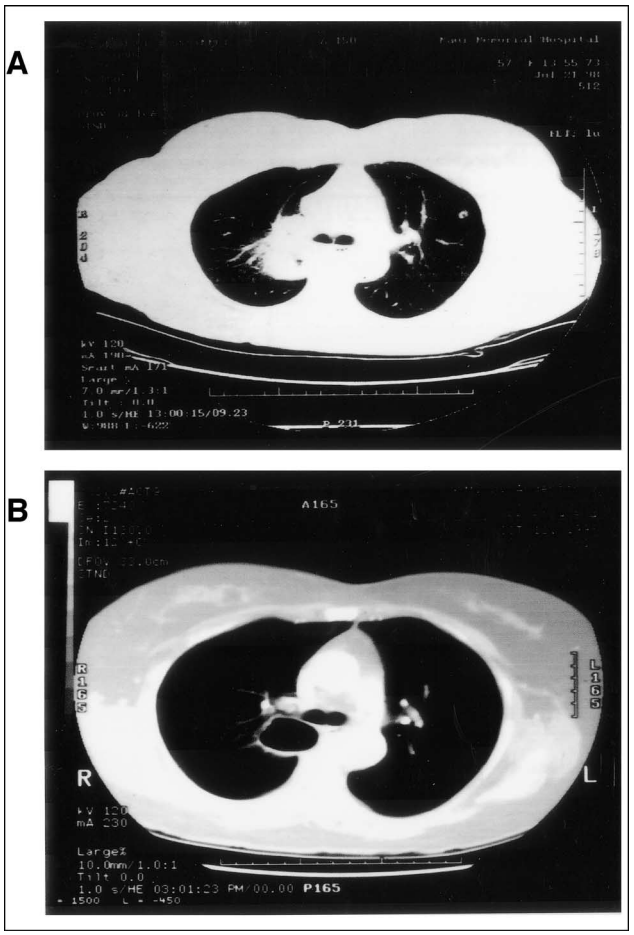


Fig 3. Area of tumor necrosis and cavitation following three cycles of treatment. (A) Tumor before treatment; (B) necrosis and cavitation.

In general, the addition of bevacizumab to carboplatin and paclitaxel was well tolerated. The incidence and severity of nausea and vomiting, renal toxicity, and neuropathy were not increased relative to chemotherapy alone.[12,18] The trends suggesting slightly higher rates of neutropenia and diarrhea will need to be more fully evaluated in larger randomized trials. Minor mucosal bleeding (eg, epistaxis), hypertension, and proteinuria are AEs that have been observed in other clinical trials of bevacizumab.[10,11,22,23] These events were also observed in this trial, but were minor in severity and did not require discontinuation of bevacizumab. Of much greater concern, however, was the occurrence of six life-threatening pulmonary hemorrhages in patients receiving bevacizumab. These events were more common in the low-dose bevacizumab arm (five of six patients), occurred both early ($\leq$ 60 days) and late ($\geq$ 180 days) during treatment and were more frequent with squamous carcinomas (four of 13 patients) compared with adenocarcinomas (two of 54 patients). Pulmonary hemorrhage also appeared to be associated with centrally located tumors, tumors closely adjacent to major blood vessels, and the presence or development of tumor cavitation. Because squamous cell tumors are more frequently centrally located and have a greater tendency to cavitate as compared to adenocarcinoma, it is not clear whether histology alone is the central risk factor for bleeding, or simply a surrogate for other risk factors. An exploratory response and survival analysis in patients with nonsquamous histology revealed

Table 4. Outcomes in Patients With Non-Squamous Cell Histology

Outcome	Control (n = 25)	Bevacizumab 7.5 mg/kg (n = 22)	Bevacizumab 15 mg/kg (n = 32)
Response rate, %	20	31.8	50
TTP, months			
Median	4.0	6.3	7.1
Range	0.2-12.2*	0.4-13.1*	0.6-13.2*
P		.29	.01
Survival, months			
Median	12.2	14.0	17.8
Range	0.2-57.0	2.0-56.8*	0.8-57.8*
P		.32	.57

Abbreviation: TTP, time to progression.
*Indicates censored value.

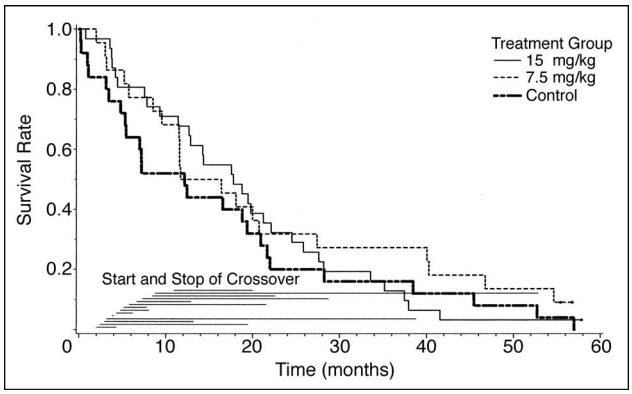


Fig 4. Kaplan-Meier curve showing overall survival in patients with non–small-cell lung cancer of nonsquamous cell histology.

an apparent improvement in response rate, time to progression and median survival in the bevacizumab arms. In this cohort of nonsquamous carcinomas, the overall risk of severe hemorrhage was approximately 4%. Additional investigation of potential risk factors and strategies to further reduce the incidence of this serious AE are underway.

Although the incidence of severe hemorrhage in this trial is problematic, one might also view these events as pyrrhic victories. Indeed, in preclinical models, antiangiogenic agents can induce central tumor necrosis similar to that observed in this trial[24] (Fig 3). One might envision such an event taking place following bevacizumab in a patient harboring a centrally located large squamous carcinoma with pre-existing cavitation. The poorly developed neovessels, lacking a well-formed musculature, might be more prone to hemorrhage into the resulting necrotic tumor cavity. This scenario supports a strategy of combined chemotherapy and an antiangiogenic drug since the former targets the viable rim of tumor that is resistant to the antiangiogenic compound. Somewhat paradoxically perhaps, antiangiogenic agents may also result in normalization of tumor vessels with resultant reduction in intratumoral interstitial pressure, thereby enhancing cytotoxic drug delivery to the malignant cells.[15] Finally, while antiangiogenic drugs are less prone to development of resistance, it should come as no surprise that cancer cells are fully capable of circumventing the growth inhibitory effect of a single agent simply by production of an alternative proangiogenic factor.[15,21] In such a situation, combination antiangiogenic therapy could prove advantageous.[25,26] In summary, these data suggest that bevacizumab in combination with carboplatin and paclitaxel improves response rate, time to progression, and overall survival in patients with advanced NSCLC. To validate these provocative results, a prospective, randomized comparison of carboplatin and paclitaxel ± bevacizumab is underway in patients with nonsquamous carcinomas (E4599). Of note, the recently reported results of a completed phase III trial evaluating bevacizumab in first-line metastatic colorectal cancer validates this general approach to cancer therapy.[27]

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Owns stock (not including shares held through a public mutual fund): William F. Novotny, Genentech; Russell F. DeVore, Genentech; Jacques Gaudreault, Genentech; Eric Homgren, Genentech. Acted as a consultant within the last 2 years: David H. Johnson, Genentech; John J. Nemunaitis, Genentech. Performed contract work within the last 2 years: John J. Nemunaitis, Genentech. Received more than $2,000 a year from a company for either of the last 2 years: David H. Johnson, Genentech; William F. Novotny, Genentech; Jacques Gaudreault, Genentech; Eric Holmgren, Genentech; Fairooz Kabbinavar, Genentech.

REFERENCES

1. Senger DR, Galli SJ, Dvorak AM, et al: Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid. Science 219:983-985, 1983

2. Ferrara N, Henzel WJ: Pituitary follicular cells secrete a novel heparin-binding growth factor specific for vascular endothelial cells. Biochem Biophys Res Commun 161:851-858, 1989

3. Leung DW, Cachianes G, Kuang WJ, et al: Vascular endothelial growth factor is a secreted angiogenic mitogen. Science 246:1306-1309, 1989

4. Ferrara N, Gerber HP, LeCouter J: The biology of VEGF and its receptors. Nat Med 9:669-676, 2003

5. Ferrara N, Winer J, Burton T, et al: Expression of vascular endothelial growth factor does not promote transformation but confers a growth advantage in vivo to Chinese hamster ovary cells. J Clin Invest 91:160-170, 1993

6. Kim KJ, Li B, Winer J, et al: Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. Nature 362:841-844, 1993

7. Kabbinavar F, Wong FF, Ayala JT, et al: The effect of antibody to vascular endothelial growth factor and cisplatin on the growth of lung tumors in nude mice. Proc Am Assoc Cancer Res 36:488, 1995 (abstr 2900)

8. Borgstrom P, Gold DP, Hillan KJ, et al: Importance of VEGF for breast cancer angiogenesis in vivo: Implications from intravital microscopy of combination treatments with an anti-VEGF neutralizing monoclonal antibody and doxorubicin. Anticancer Res 19:4203-4214, 1999

9. Presta LG, Chen H, O'Connor SJ, et al: Humanization of an anti-vascular endothelial growth factor monoclonal antibody for the therapy of solid tumors and other disorders. Cancer Res 57:4593-4599, 1997

10. Gordon MS, Margolin K, Talpaz M, et al: Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. J Clin Oncol 19:843-850, 2001

11. Margolin K, Gordon MS, Holmgren E, et al: Phase Ib trial of intravenous recombinant humanized monoclonal antibody to vascular endothelial growth factor in combination with chemotherapy in patients with advanced cancer: Pharmacologic and long-term safety data. J Clin Oncol 19:851-856, 2001

12. Schiller JH, Harrington D, Belani CP, et al: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92-98, 2002

13. Herbst RS, Takeuchi H, Teicher BA: Paclitaxel/carboplatin administration along with anti-angiogenic therapy in non–small-cell lung and breast carcinoma models. Cancer Chemother Pharmacol 41:497-504, 1998

14. Calvert AH, Newell DR, Gumbrell LA, et al: Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol 7:1748-1756, 1989

15. Jain RK: Normalizing tumor vasculature with anti-angiogenic therapy: A new paradigm for combination therapy. Nat Med 7:987-989, 2001

16. Yuan A, Yu CJ, Kuo SH, et al: Vascular endothelial growth factor 189 mRNA isoform expression specifically correlates with tumor angiogenesis, patient survival, and postoperative relapse in non–small-cell lung cancer. J Clin Oncol 19:432-441, 2001

17. Volm M, Koomagi R, Mattern J: Prognostic value of vascular endothelial growth factor and its receptor Flt-1 in squamous cell lung cancer. Int J Cancer 74:64-68, 1997

18. Kelly K, Crowley J, Bunn PA Jr, et al: Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non–small-cell lung cancer: A Southwest Oncology Group trial. J Clin Oncol 19:3210-3218, 2001

19. Shepherd FA, Dancey J, Ramlau R, et al: Prospective randomized trial of docetaxel versus best supportive care in patients with non–small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 18:2095-2103, 2000

20. Fossella FV, DeVore R, Kerr RN, et al: Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non–small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non–Small Cell Lung Cancer Study Group. J Clin Oncol 18:2354-2362, 2000

21. Kerbel R, Folkman J: Clinical translation of angiogenesis inhibitors. Nat Rev Cancer 2:727-739, 2002

22. Yang JC, Haworth L, Sherry RM, et al: A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. N Engl J Med 349:427-434, 2003

23. Kabbinavar F, Hurwitz HI, Fehrenbacher L, et al: Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 21:60-65, 2003

24. Huang X, Molema G, King S, et al: Tumor infarction in mice by antibody-directed targeting of tissue factor to tumor vasculature. Science 275:547-550, 1997

25. Jung YD, Mansfield PF, Akagi M, et al: Effects of combination anti-vascular endothelial growth factor receptor and anti-epidermal growth factor receptor therapies on the growth of gastric cancer in a nude mouse model. Eur J Cancer 38:1133-1140, 2002

26. Mininberg ED, Herbst RS, Henderson T, et al: Phase I/II study of the recombinant humanized monoclonal anti-VEGF antibody bevacizumab and the EGFR-TK inhibitor erlotinib in patients with recurrent non–small cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 22:627, 2003 (abstr 2521)

27. Hurwitz H, Fehrenbacher L, Cartwright T, et al: Bevacizumab (a monoclonal antibody to vascular endothelial growth factor) prolongs survival in first-line colorectal cancer (CRC): Results of a phase III trial of bevacizumab in combination with bolus IFL (irinotecan, 5-fluorouracil, leucovorin) as first-line therapy in subjects with metastatic CRC. Proc Am Soc Clin Oncol 22: 2003 (abstr 3646)

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----------

Warnings and Precautions: Ovarian Failure (5.10) 09/2011

----------INDICATIONS AND USAGE----------

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

- Metastatic colorectal cancer, with intravenous 5-fluorouracil–based chemotherapy for first- or second-line treatment. (1.1)
- Non-squamous non-small cell lung cancer, with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent or metastatic disease. (1.2)
- 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)
- Ovarian Failure: Inform females of reproductive potential of the risk of ovarian failure with Avastin (5.10)

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

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

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

----------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:September 2011

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the Full Prescribing Information are not listed.

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), 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), 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 ≥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 ≤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)*.]

5.10 Ovarian Failure

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

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)*.]
- Ovarian Failure [See *Warnings and Precautions (5.10), Use in Specific Populations (8.6)*.]

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 4024 patients with CRC, non-squamous NSCLC, MBC, glioblastoma, or mRCC trials including controlled (Studies 1, 2, 4, 5, 6 and 9) or uncontrolled, single arm (Study 7) treated at the recommended dose and schedule for a median of 8 to 23 doses of Avastin. [See *Clinical Studies (14)*.] The population was aged 18-88 years (median 59), 41% male and 85.1% white. The population included 1783 first- and second-line mCRC patients who received a median of 10 doses of Avastin, 669 female adjuvant CRC patients who received a median of 23 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 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, more patients in the Avastin containing arm experienced deep venous thrombosis (34 vs. 19 patients) and intra-abdominal venous thrombosis (10 vs. 5 patients).

The risk of developing a second thromboembolic event while on Avastin and oral anticoagulants was evaluated in two randomized studies. 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 (VTE). 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.

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

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

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.

Ovarian Failure

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

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 (≥ 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 [≥ 2%] Avastin vs. Control)

	Arm 1 IFL + Placebo (n=396)	Arm 2 IFL + Avastin (n=392)
NCI-CTC Grade 3-4 Events	74%	87%
Body as a Whole		
Asthenia	7%	10%
Abdominal Pain	5%	8%
Pain	5%	8%
Cardiovascular		
Hypertension	2%	12%
Deep Vein Thrombosis	5%	9%
Intra-Abdominal Thrombosis	1%	3%
Syncope	1%	3%
Digestive		
Diarrhea	25%	34%
Constipation	2%	4%
Hemic/Lymphatic		
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 (≥ 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 [≥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)
Body as a Whole			
Pain	55%	61%	62%
Abdominal Pain	55%	61%	50%
Headache	19%	26%	26%
Cardiovascular			
Hypertension	14%	23%	34%
Hypotension	7%	15%	7%
Deep Vein Thrombosis	3%	9%	6%
Digestive			
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%
Hemic/Lymphatic			
Thrombocytopenia	0%	5%	5%
Nervous			
Dizziness	20%	26%	19%
Respiratory			
Upper Respiratory Infection	39%	47%	40%
Epistaxis	10%	35%	32%
Dyspnea	15%	26%	25%
Voice Alteration	2%	9%	6%
Skin/Appendages			
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 [≥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)
Special Senses			
Taste Disorder	9%	14%	21%
Urogenital			
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 (≥ 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 (≥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 (≥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 ≥ 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 (≥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 [≥5%] in Capecitabine + Avastin vs. Capecitabine Alone)

	Capecitabine (n=215)	Capecitabine + Avastin (n=229)
Body as a Whole		
Asthenia	47%	57%
Headache	13%	33%
Pain	25%	31%
Cardiovascular		
Hypertension	2%	24%
Digestive		
Stomatitis	19%	25%
Metabolic/Nutrition		
Weight loss	4%	9%
Musculoskeletal		
Myalgia	8%	14%
Respiratory		
Dyspnea	18%	27%
Epistaxis	1%	16%
Skin/Appendages		
Exfoliative dermatitis	75%	84%
Urogenital		
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 (≥ 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 (≥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 [≥ 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)
Gastrointestinal disorders		
Diarrhea	16%	21%
General disorders and administration site conditions		
Fatigue	27%	33%
Investigations		
Weight decreased	15%	20%
Metabolism and nutrition disorders		
Anorexia	31%	36%
Musculoskeletal and connective tissue disorders		
Myalgia	14%	19%
Back pain	6%	12%
Nervous system disorders		
Headache	16%	24%
Renal and urinary disorders		
Proteinuria	3%	20%
Respiratory, thoracic and mediastinal disorders		
Epistaxis	4%	27%
Dysphonia	0%	5%
Vascular disorders		
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
Musculoskeletal: Osteonecrosis of the jaw
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 adequate or well controlled studies of bevacizumab in pregnant women. While it is not known if bevacizumab crosses the placenta, human IgG is known to cross the placenta Reproduction studies in rabbits treated with approximately 1 to 12 times the recommended human dose of bevacizumab demonstrated 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)*.]

Because of the observed teratogenic effects of bevacizumab in animals and of other 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. Human IgG is excreted in human milk, but 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 (≥ 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)*.]

8.6 Females of Reproductive Potential

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

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

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 physeal dysplasia was consistently reported in juvenile monkeys with open growth plates receiving 0.4 to 20 times the human dose. The physeal 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/m^2, 5-FU 500 mg/m^2, and leucovorin (LV) 20 mg/m^2 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.

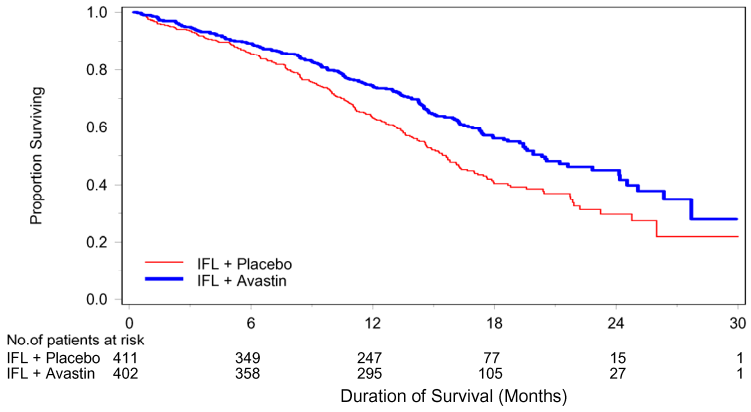
Table 5
Study 1 Efficacy Results

	IFL + Placebo	IFL + Avastin 5 mg/kg q 2 wks
Number of Patients	411	402
Overall Survival[a]		
Median (months)	15.6	20.3
Hazard ratio		0.66
Progression-free Survival[a]		
Median (months)	6.2	10.6
Hazard ratio		0.54
Overall Response Rate[b]		
Rate (percent)	35%	45%
Duration of Response		
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 ± 5-FU for initial therapy for metastatic disease or as adjuvant therapy. Patients were randomized (1:1:1) to IV FOLFOX4 (Day 1: oxaliplatin 85 mg/m^2 and LV 200 mg/m^2 concurrently, then 5-FU 400 mg/m^2 bolus followed by 600 mg/m^2 continuously; Day 2: LV 200 mg/m^2, then 5-FU 400 mg/m^2 bolus followed by 600 mg/m^2 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

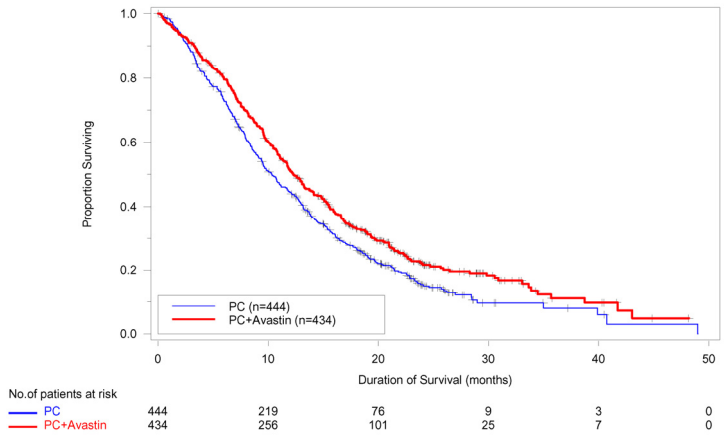
The safety and efficacy of Avastin as first-line treatment of patients with locally advanced, metastatic, or recurrent non–squamous NSCLC was studied in a single, large, randomized, active-controlled, open-label, multicenter study.

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/m^2 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 (≥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 ≥ age 65, and 28% had ≥ 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 ≥ 65 years [HR = 0.91 (95% CI: 0.72, 1.14)] and patients with ≥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 ≥ 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/m^2 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)
Progression-free Survival	11.3	5.8		0.48
[median, months (95% CI)]	(10.5, 13.3)	(5.4, 8.2)	<0.0001	(0.39, 0.61)
Overall Survival	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)

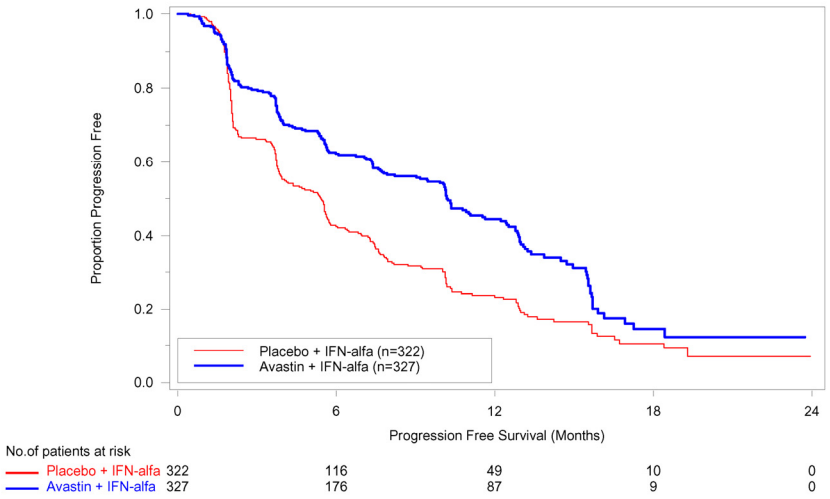
Study 9

Patients with treatment-naïve mRCC were evaluated in a multicenter, randomized, double-blind, international study comparing Avastin plus interferon alfa 2a (IFN- α2a) versus placebo plus IFN-α2a. 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-α2a (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-α2a compared to those receiving IFN-α2a 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 measurable 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-α2a arm and 21 months in the IFN-α2a 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.
- Of the increased risk for ovarian failure following Avastin treatment.

Avastin® (bevacizumab)

Manufactured by:
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A Member of the Roche Group
1 DNA Way
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