Table 6
Grade 1−5 Adverse Events in Study 11
(Occurring at Higher Incidence [≥ 5%] in Chemo + Avastin vs. Chemo + Placebo)

System Organ Class Preferred Term	Carboplatin + Gemcitabine + Placebo (n=233)	Carboplatin + Gemcitabine + Bevacizumab (n=247)
Blood and Lymphatic System Disorders		
Thrombocytopenia	51%	58%
Gastrointestinal Disorders		
Diarrhea	29%	38%
Gingival Bleeding	0%	7%
Hemorrhoids	3%	8%
Nausea	66%	72%
Stomatitis	7%	15%
General Disorders and Administration Site Conditions		
Fatigue	75%	82%
Mucosal Inflammation	10%	15%
Infections and Infestations		
Sinusitis	9%	15%
Injury, Poisoning and Procedural Complications		
Contusion	9%	17%
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	19%	28%
Back Pain	13%	21%
Nervous System Disorders		
Dizziness	17%	23%
Headache	30%	49%
Psychiatric Disorders		
Insomnia	15%	21%
Renal and Urinary Disorders		
Proteinuria	3%	20%
Respiratory, Thoracic and Mediastinal Disorders		
Cough	18%	26%
Dysphonia	3%	13%
Dyspnea	24%	30%
Epistaxis	14%	55%
Oropharyngeal Pain	10%	16%
Rhinorrhea	4%	10%
Sinus Congestion	2%	8%
Vascular Disorders		
Hypertension	9%	42%

Grade 3 or 4 adverse events occurring at a higher incidence (≥ 2%) in 247 patients treated with Avastin plus chemotherapy compared to 233 patients treated with placebo plus chemotherapy were

thrombocytopenia (40.1% vs. 33.9%), nausea (4.5% vs. 1.3%), fatigue (6.5% vs. 4.3%), headache (3.6% vs. 0.9%), proteinuria (9.7% vs. 0.4%), dyspnea (4.5% vs. 1.7%), epistaxis (4.9% vs. 0.4%), and hypertension (17.0% vs. 0.9%). Grade ≥ 3 Anemia (16.2% vs. 18.9%) and decreased white blood cell count (1.6% vs. 4.3%) occurred with a ≥ 2% higher frequency in the chemotherapy alone arm compared to the Avastin plus chemotherapy arm. There were no Grade 5 adverse events occurring at a higher incidence (≥ 2%) for the Avastin plus chemotherapy arm compared to the placebo plus chemotherapy arm.

Platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with carboplatin and paclitaxel, followed by Avastin as a single agent

Adverse events occurring in a randomized, open-label study, Study 12, of chemotherapy compared to Avastin plus chemotherapy, are presented in Table 7.

Table 7
Grade 1−5 Adverse Events in Study 12
(Occurring at Higher Incidence [≥ 5%] in Chemo + Avastin vs. Chemo Alone)

System Organ Class Preferred Term	Carboplatin + Paclitaxel (n=332)	Carboplatin + Paclitaxel + Bevacizumab (n=325)
Gastrointestinal disorders		
Diarrhea	32%	39%
Abdominal pain	28%	33%
Vomiting	25%	33%
Stomatitis	16%	33%
Metabolism and nutrition disorders		
Decreased appetite	25%	35%
Hyperglycemia	24%	31%
Hypomagnesemia	17%	27%
Hyponatremia	6%	17%
Hypoalbuminaemia	6%	11%
Hypocalcemia	5%	12%
Hyperkalemia	3%	9%
Musculoskeletal and connective tissue disorders		
Arthralgia	30%	45%
Myalgia	18%	29%
Pain in extremity	14%	25%
Back pain	10%	17%
Muscular weakness	8%	13%
Neck pain	0%	9%
Respiratory, thoracic and Mediastinal disorders		
Dyspnea	25%	30%
Cough	17%	30%
Epistaxis	2%	33%
Rhinitis allergic	4%	17%
Nasal mucosal disorder	3%	14%
Nervous system disorders		

Headache	20%	38%
Dizziness	8%	13%
Dysarthria	2%	14%
Investigations		
Aspartate aminotransferase increased	9%	15%
Weight decreased	4%	15%
Blood creatinine increased	5%	13%
Skin and subcutaneous tissue Disorders		
Exfoliative rash	16%	23%
Nail disorder	2%	10%
Dry skin	2%	7%
Vascular disorders		
Hypertension	3%	42%
Renal and urinary disorders		
Proteinuria	1%	17%
General disorders and administration Site conditions		
Chest pain	2%	8%
Infections and infestations		
Sinusitis	2%	7%

Grade 3 or 4 adverse events occurring at a higher incidence (≥ 2%) in 325 patients treated with Avastin plus chemotherapy compared to 332 patients treated with chemotherapy alone were hypertension (11.1% vs. 0.6%), fatigue (7.7% vs. 2.7%), febrile neutropenia (6.2% vs. 2.7%), proteinuria (8% vs. 0%), abdominal pain (5.8% vs. 0.9%), hyponatremia (3.7% vs. 0.9%), headache (3.1% vs. 0.9%), and pain in extremity (3.4% vs. 0%). No Grade ≥ 3 adverse events occurred with a ≥ 2% higher frequency in the chemotherapy alone arm compared to the Avastin plus chemotherapy arm. There were no Grade 5 adverse events occurring at a higher incidence (≥ 2%) in the Avastin plus chemotherapy arm compared to the chemotherapy alone arm.

6.2 Immunogenicity

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

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

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the test method and 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, PRES, Mesenteric venous occlusion

Eye disorders (from unapproved intravitreal use for treatment of various ocular disorders): Permanent loss of vision; Endophthalmitis (infectious and sterile); Intraocular inflammation; Retinal detachment; Increased intraocular pressure; Hemorrhage including conjunctival, vitreous hemorrhage or retinal hemorrhage; Vitreous floaters; Ocular hyperemia; Ocular pain or discomfort
Gastrointestinal: Gastrointestinal ulcer, Intestinal necrosis, Anastomotic ulceration
Hemic and lymphatic: Pancytopenia
Hepatobiliary disorders: Gallbladder perforation
Infections and infestations: Necrotizing fasciitis, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation
Musculoskeletal and Connective Tissue Disorders: Osteonecrosis of the jaw; Non-mandibular osteonecrosis (cases have been observed in pediatric patients who have received Avastin)
Neurological: Posterior Reversible Encephalopathy Syndrome (PRES)
Renal: Renal thrombotic microangiopathy (manifested as severe proteinuria)
Respiratory: Nasal septum perforation, dysphonia
Systemic Events (from unapproved intravitreal use for treatment of various ocular disorders): Arterial thromboembolic events, Hypertension, Gastrointestinal perforation, Hemorrhage

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 8, 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

Risk Summary

Avastin may cause fetal harm based on findings from animal studies and the drug's mechanism of action. [*See Clinical Pharmacology (12.1).*] Limited postmarketing reports describe cases of fetal malformations with use of Avastin in pregnancy; however, these reports are insufficient to determine drug associated risks. In animal reproduction studies, intravenous administration of bevacizumab to pregnant rabbits every 3 days during organogenesis at doses approximately 1 to 10 times the clinical dose of 10 mg/kg produced fetal resorptions, decreased maternal and fetal weight gain and multiple congenital malformations including corneal opacities and abnormal ossification of the skull and skeleton including limb and phalangeal defects [*see Data*]. Furthermore, animal models link angiogenesis and VEGF and VEGF Receptor 2 (VEGFR2) to critical aspects of female reproduction, embryofetal development, and postnatal development. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Pregnant rabbits dosed with 10 to 100 mg/kg bevacizumab (approximately 1 to 10 times the clinical dose of 10 mg/kg) every three days during the period of organogenesis (gestation day 6–18) exhibited decreases in maternal and fetal body weights and increased number of fetal resorptions. There were dose-related increases in the number of litters containing fetuses with any type of malformation (42.1% for the 0 mg/kg dose, 76.5% for the 30 mg/kg dose, and 95% for the 100 mg/kg dose) or fetal alterations (9.1% for the 0 mg/kg dose, 14.8% for the 30 mg/kg dose, and 61.2% for the 100 mg/kg dose). Skeletal deformities were observed at all dose levels, with some abnormalities including meningocele observed only at the 100 mg/kg dose level. Teratogenic effects included: reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws; fontanel, rib and hindlimb deformities; corneal opacity; and absent hindlimb phalanges.

8.2 Lactation

No data are available regarding the presence of bevacizumab in human milk, the effects on the breast fed infant, or the effects on milk production. Human IgG is present in human milk, but published data suggest that breast milk antibodies do not enter the neonatal and infant circulation in substantial amounts. Because of the potential for serious adverse reactions in breastfed infants from bevacizumab, advise a nursing woman that breastfeeding is not recommended during treatment with Avastin.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Avastin may cause fetal harm when administered to a pregnant woman. Advise female patients of reproductive potential to use effective contraception during treatment with Avastin and for 6 months following the last dose of Avastin. [*See Use in Specific Populations (8.1).*]

Infertility

Females

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 (5.12), Adverse Reactions (6.1*).]

8.4 Pediatric Use

The safety, effectiveness and pharmacokinetic profile of Avastin in pediatric patients have not been established. In published literature reports, cases of non-mandibular osteonecrosis have been observed in patients under the age of 18 years who have received Avastin. Avastin is not approved for use in patients under the age of 18 years.

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.

Animal Data

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

8.5 Geriatric Use

In Study 1, severe adverse events that occurred at a higher incidence ($\geq$2%) in patients aged $\geq$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 5, 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 (5.9)*.]

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

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

10 OVERDOSAGE

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

11 DESCRIPTION

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity studies of bevacizumab have been conducted.

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

13.2 Animal Toxicology and/or Pharmacology

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.

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 8 and Figure 1.

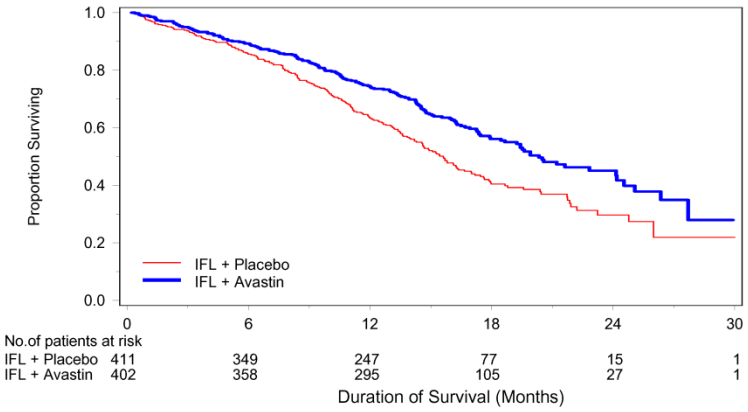
Table 8
Study 1 Efficacy Results

	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%).

Study 4

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

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

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

The addition of Avastin to fluoropyrimidine-based chemotherapy resulted in a statistically significant prolongation of survival and PFS; there was no significant difference in overall response rate, a key secondary outcome measure. Results are presented in Table 9 and Figure 2.

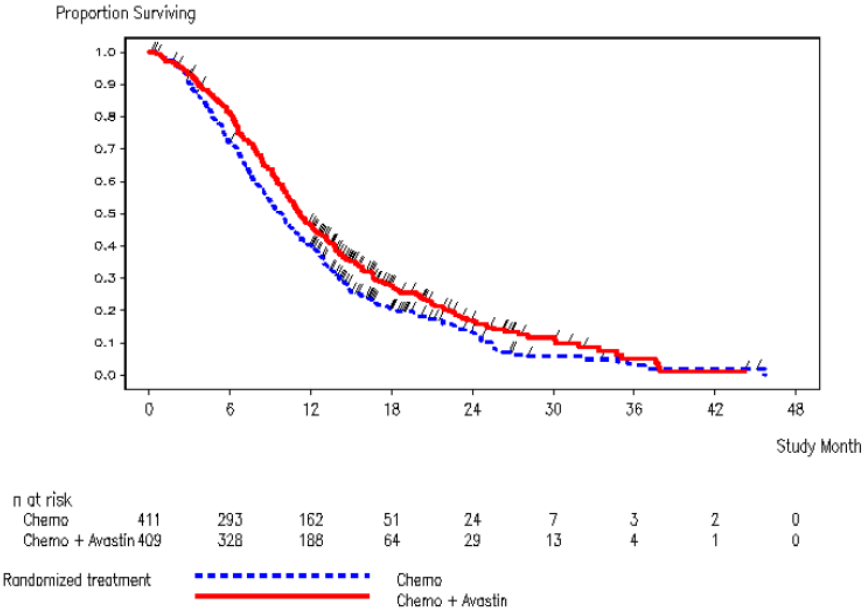
Table 9
Study 4 Efficacy Results

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

[a] p = 0.0057 by unstratified log rank test.

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

Figure 2
Duration of Survival in Study 4



14.2 Lack of Efficacy in Adjuvant Treatment of Colon Cancer

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

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

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

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

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

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

Study 5

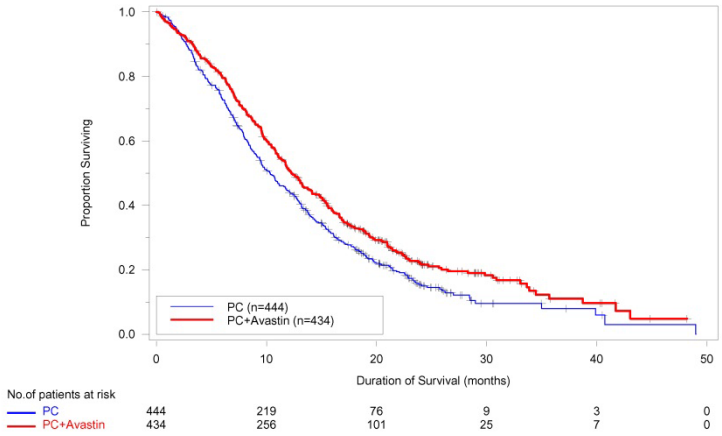
The safety and efficacy of Avastin as first-line treatment of patients with locally advanced, metastatic, or recurrent non–squamous NSCLC was studied in a single, large, randomized, active-controlled, open-label, multicenter study.

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 ($\geq$ 1/2 tsp of red blood), unstable angina, or receiving therapeutic anticoagulation were excluded. The main outcome measure was duration of survival.

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

The results are presented in Figure 3. 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 3
Duration of Survival in Study 5



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].

14.4 Glioblastoma

Study 6

The efficacy and safety of Avastin was evaluated in Study 6, 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 7

Study 7, 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 6. Median duration of response was 3.9 months (95% CI 2.4, 17.4).

14.5 Metastatic Renal Cell Carcinoma (mRCC)

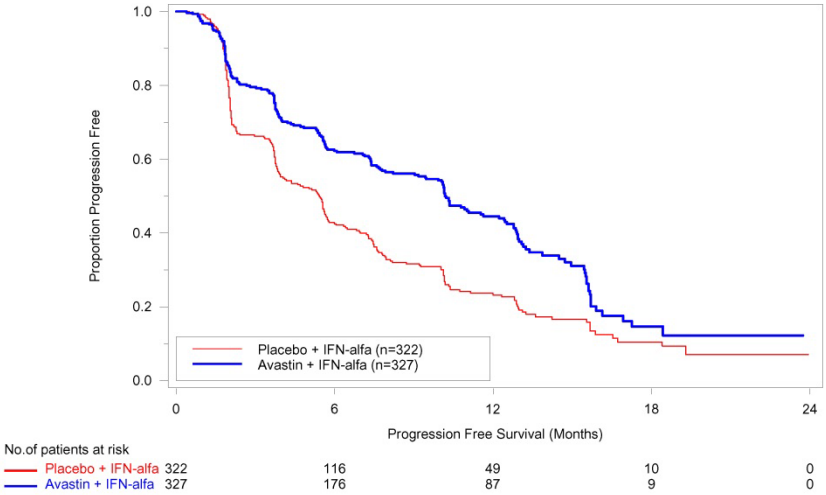
Study 8

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 4. 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 4
Progression-Free Survival in Study 8



14.6 Persistent, Recurrent, or Metastatic Carcinoma of the Cervix

Study 9

Patients with persistent, recurrent, or metastatic carcinoma of the cervix were evaluated in a randomized, four-arm, multi-center trial comparing Avastin plus chemotherapy versus chemotherapy alone (Study 9; GOG-0240). A total of 452 patients were randomized (1:1:1:1) to receive paclitaxel and Cisplatin with or without Avastin, or paclitaxel and topotecan with or without Avastin.

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

- Day 1: Paclitaxel 135 mg/m^2 IV over 24 hours, Day 2: cisplatin 50 mg/m^2 IV plus Avastin; or Day 1: paclitaxel 175 mg/m^2 IV over 3 hours, Day 2: cisplatin 50 mg/m^2 IV plus Avastin ; or Day 1: paclitaxel 175 mg/m^2 IV over 3 hours plus cisplatin 50 mg/m^2 IV plus Avastin
- Day 1: Paclitaxel 175 mg/m^2 over 3 hours plus Avastin, Days 1-3: topotecan 0.75 mg/m^2 over 30 minutes

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

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

The study results for OS in patients who received chemotherapy plus Avastin as compared to chemotherapy alone are presented in Table 10 and Figure 5.

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

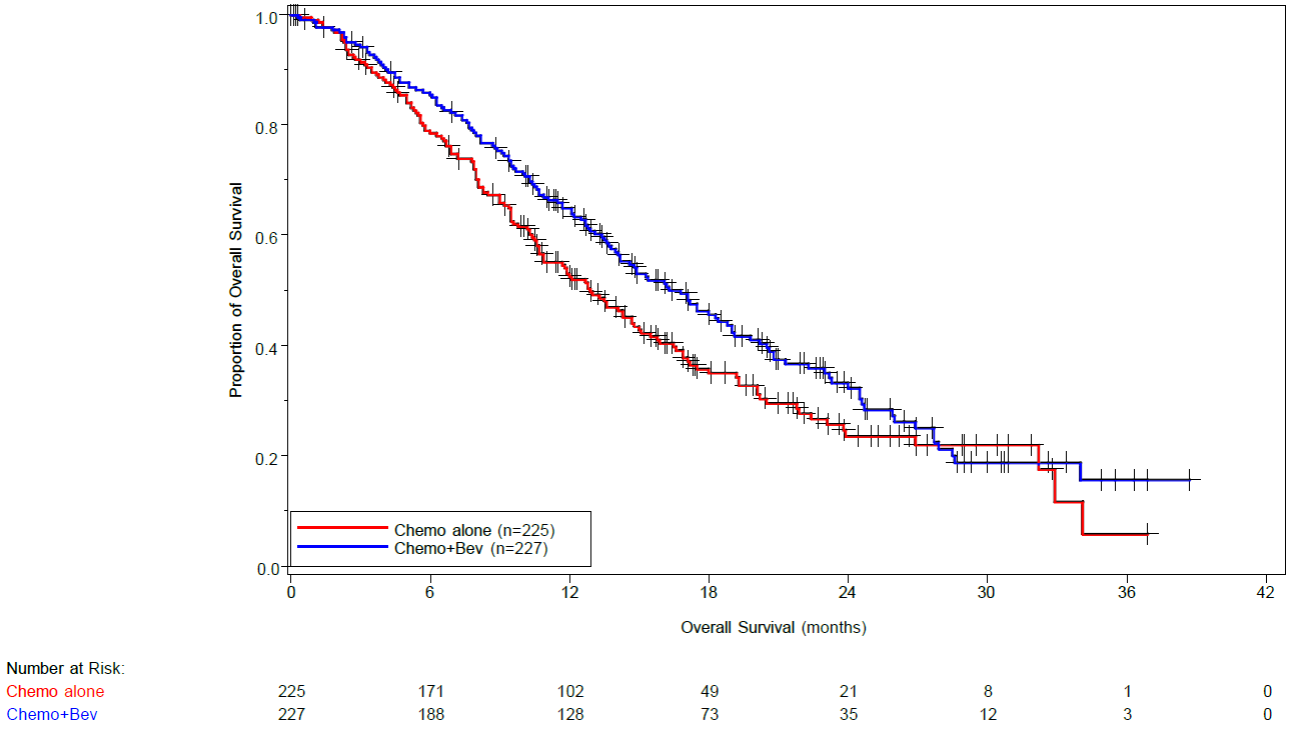


Table 10
Study 9 Efficacy Results: Chemotherapy versus Chemotherapy + Avastin

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

[a] Kaplan-Meier estimates.

[b] log-rank test (stratified).

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

Table 11
Study 9 Efficacy Results: Platinum Doublet versus Nonplatinum Doublet

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

[a] Kaplan-Meier estimates.

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

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

Study 10

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

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

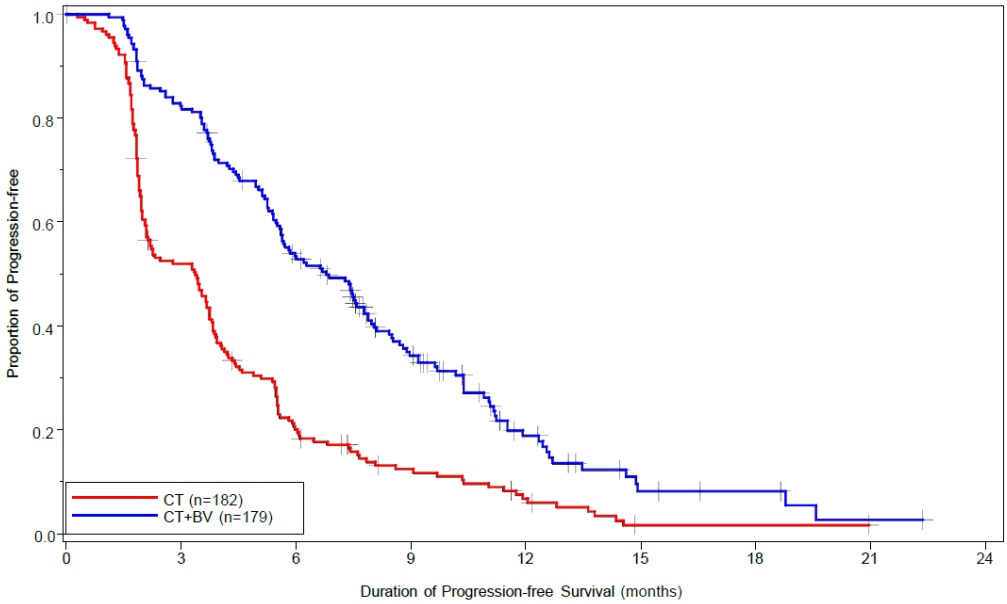
The addition of Avastin to chemotherapy demonstrated a statistically significant improvement in investigator-assessed PFS, which was supported by a retrospective independent review analysis. Study results for the intent to treat (ITT) population are presented in Table 12 and Figure 6. Results for the separate chemotherapy cohorts are presented in Table 13.

Table 12
Efficacy Results in Study 10 ITT Population

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

[a] per stratified Cox proportional hazards model
[b] per stratified logrank test
[c] chemotherapy

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



Number at Risk:

CT	182	92	35	18	9	1	1	0	0
CT+BV	179	144	91	51	19	6	4	1	0

Table 13
Study 10 Efficacy Results in Chemotherapy Cohorts

Efficacy Parameter	Paclitaxel		Topotecan		PLD	
	CT[b] (N=55)	CT[b]+Avastin (N=60)	CT[b] (N=63)	CT[b]+Avastin (N=57)	CT[b] (N=64)	CT[b]+Avastin (N=62)
PFS per Investigator						
Median (months) (95% CI)	3.9 (3.5, 5.5)	9.6 (7.8, 11.5)	2.1 (1.9, 2.3)	6.2 (5.3, 7.6)	3.5 (1.9, 3.9)	5.1 (3.9, 6.3)
HR (95% CI)[a]	0.47 (0.31, 0.72)		0.24 (0.15, 0.38)		0.47 (0.32, 0.71)	
Overall Survival						
Median (months) (95% CI)	13.2 (8.2, 19.7)	22.4 (16.7, 26.7)	13.3 (10.4, 18.3)	13.8 (11.0, 18.3)	14.1 (9.9, 17.8)	13.7 (11.0, 18.3)
HR (95% CI)[a]	0.64 (0.41, 1.01)		1.12 (0.73, 1.73)		0.94 (0.63, 1.42)	
Objective Response Rate						
Number of Patients with Measurable Disease at Baseline	43	45	50	46	51	51
Rate, % (95% CI)	30 (17, 44)	53 (39, 68)	2 (0, 6)	17 (6, 28)	8 (0, 15)	16 (6, 26)
Median of Response Duration (months)	6.8	11.6	NE	5.2	4.6	8.0

[a] per stratified Cox proportional hazards model
[b] chemotherapy
NE= Not Estimable

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

Study 11

Study 11 was a randomized, double-blind, placebo-controlled trial (AVF4095g; OCEANS) studying Avastin plus chemotherapy versus chemotherapy alone in the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior chemotherapy in the recurrent setting or prior bevacizumab treatment (n=484). Patients were randomized (1:1) to receive carboplatin (AUC4, Day 1) and gemcitabine (1000 mg/m^2 on Days 1 and 8) and concurrent placebo every 3 weeks for 6 to 10 cycles followed by placebo alone until disease progression or unacceptable toxicity (n=242) or carboplatin (AUC4, Day 1) and gemcitabine (1000 mg/m^2 on Days 1 and 8) and concurrent Avastin (15 mg/kg Day 1) every 3 weeks for 6 to 10 cycles followed by Avastin (15 mg/kg every 3 weeks) as a single agent until disease progression or unacceptable toxicity (n=242).

The main efficacy outcome measures was investigator-assessed PFS. Secondary outcome measures were ORR and OS.

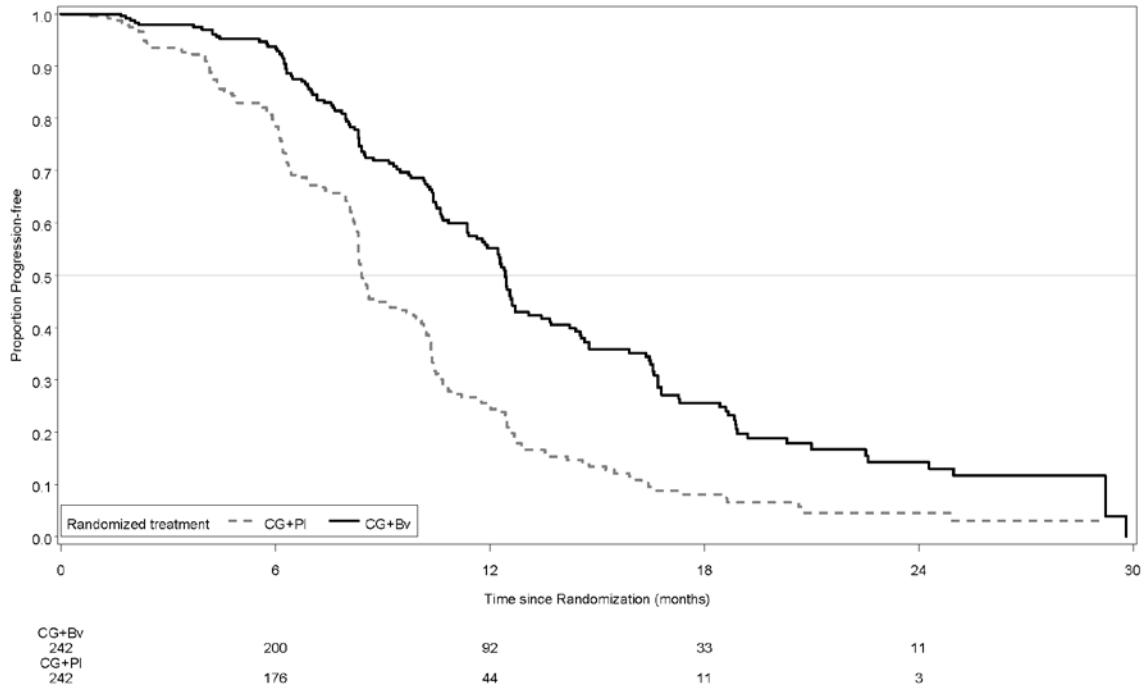
The median age was 61 years (range 28–87 years) and 37% of patients were ≥ age 65. All patients had measurable disease at baseline, 74% had baseline CA-125 levels greater than the ULN (35 U/mL). The platinum-free interval (PFI) was 6–12 months in 42 % of patients and > 12 months in 58% of patients. The ECOG performance status was 0 or 1 for 99.8% of patients.

A statistically signficant prolongation in PFS was demonstrated among Avastin plus chemotherapy-treated patients compared to those receiving placebo plus chemotherapy (Table 14 and Figure 7). Independent radiology review of PFS was consistent with investigator assessment (HR=0.45, 95% CI=[0.35, 0.58]). Overall survival was not significantly improved with the addition of Avastin to chemotherapy [HR=0.95, 95% CI (0.77, 1.17)].

Table 14
Investigator Assessed Efficacy Results from Study 11

	Crb + Gem + Placebo (n=242)	Crb + Gem + Bev (n=242)
Progression Free Survival		
Median PFS (months)	8.4	12.4
Hazard ratio (95% CI)	0.46 (0.37, 0.58)	
p –value	< 0.0001	
Objective Response Rate		
% patients with objective response	57%	78%
p –value	< 0.0001	

Figure 7
Progression-Free Survival Based on Investigator Assessment for Study 11



Study 12

Study 12 was a randomized, controlled, open-label trial (GOG-0213) studying Avastin plus chemotherapy versus chemotherapy alone in the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have not received more than one previous regimen of chemotherapy (n=673). Patients were randomized (1:1) to receive carboplatin (AUC5) and paclitaxel (175 mg/m^2 IV over 3 hours) every 3 weeks for 6 to 8 cycles (n=336) or carboplatin (AUC5) and paclitaxel (175 mg/m^2 IV over 3 hours) and concurrent Avastin (15 mg/kg) every 3 weeks for 6 to 8 cycles followed by Avastin (15 mg/kg every 3 weeks) as a single agent until disease progression or unacceptable toxicity (n=337).

The main efficacy outcome measure was OS. Other additional efficacy outcomes were investigator-assessed PFS, and ORR.

The median age was 60 years (range 23–85 years) and 33% of patients were ≥ age 65. Eighty-three percent had measurable disease at baseline, 74% had abnormal CA-125 levels at baseline.

There were 69 (10.3%) patients who had received prior bevacizumab. Twenty-six percent had a platinum-free interval (PFI) of 6−12 months and 74% had a PFI of >12 months. GOG Performance Status was 0 or 1 for 99% of the patients.

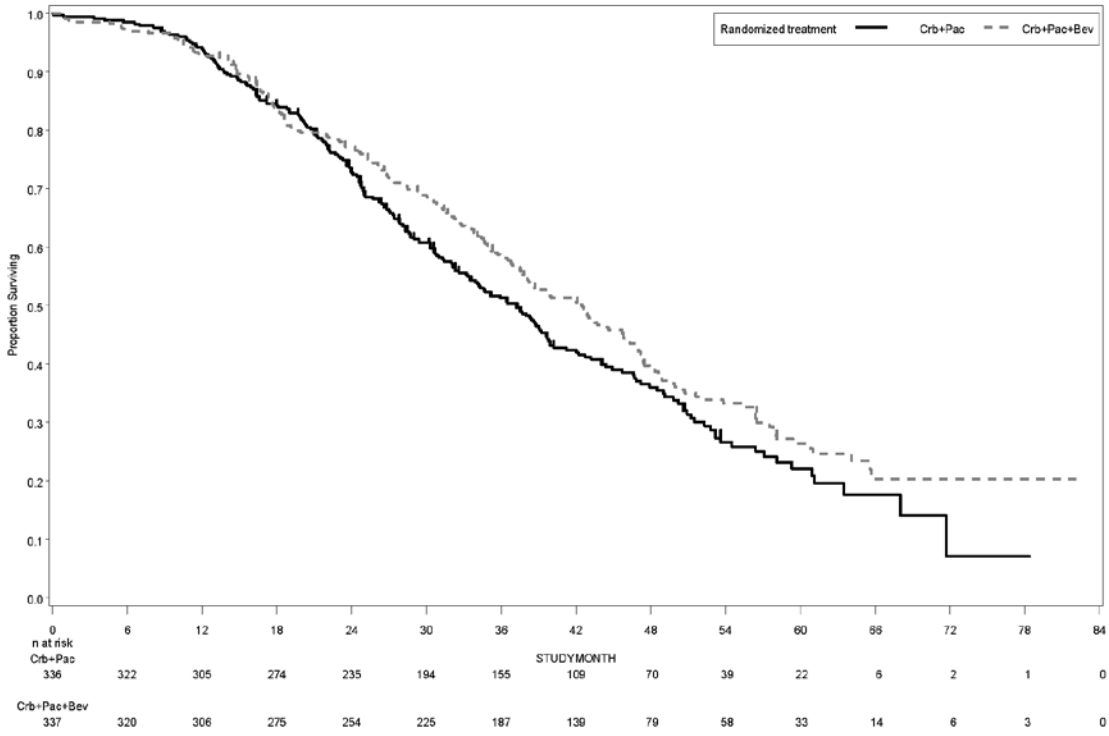
Study results are presented in Table 15 and Figure 8.

Table 15
Efficacy Results from Study 12

	Carboplatin + Paclitaxel (n=336)	Carboplatin + Paclitaxel + Bevacizumab (n=337)
Overall Survival (OS)		
Median OS (months)	37.3	42.6
Hazard ratio (95% CI) (IVRS)[a]	0.84 (0.69, 1.01)	
Hazard ratio (95% CI) (eCRF)[b]	0.82 (0.68, 0.996)	
Progression-free Survival (PFS)		
Median PFS (months)	10.4	13.8
Hazard ratio (95% CI) (IVRS)[a]	0.61 (0.51, 0.72)	
Objective Response Rate		
Number of patients with measurable disease at baseline	286	274
Rate, %	159 (56%)	213 (78%)

[a] Hazard ratio was estimated from Cox proportional hazards models stratified by the duration of treatment free-interval prior to enrolling onto this study per IVRS (interactive voice response system) and secondary surgical debulking status.
[b] Hazard ratio was estimated from Cox proportional hazards models stratified by the duration of platinum free-interval prior to enrolling onto this study per eCRF (electronic case report form) and secondary surgical debulking status.

Figure 8
Overall Survival ITT Population of Study 12



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 increased risk for ovarian failure following Avastin treatment.

Embryo-fetal Toxicity

- Advise female patients that Avastin may cause fetal harm and to inform their healthcare provider with a known or suspected pregnancy. [*See Warnings and Precautions (5.11), Use in Specific Populations (8.1).*]
- Advise females of reproductive potential to use effective contraception during treatment with Avastin and for 6 months after the last dose of Avastin. [*See Use in Specific Populations (8.3).*]

Lactation

- Advise nursing women that breastfeeding is not recommended during treatment with Avastin. [*See Use in Specific Populations (8.2).*]

Avastin® (bevacizumab)

Manufactured by:
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