1.14.1.3 Labeling Text

AVASTIN™
(Bevacizumab)

For Intravenous Use

WARNINGS

Gastrointestinal Perforations/Wound Healing Complications

AVASTIN administration can result in the development of gastrointestinal perforation and wound dehiscence, in some instances resulting in fatality. Gastrointestinal perforation, sometimes associated with intra-abdominal abscess, occurred throughout treatment with AVASTIN (i.e., was not correlated to duration of exposure). The incidence of gastrointestinal perforation in patients receiving bolus-IFL with AVASTIN was 2%. The typical presentation was reported as abdominal pain associated with symptoms such as constipation and vomiting. Gastrointestinal perforation should be included in the differential diagnosis of patients presenting with abdominal pain on AVASTIN. AVASTIN therapy should be permanently discontinued in patients with gastrointestinal perforation or wound dehiscence requiring medical intervention. The appropriate interval between termination of AVASTIN and subsequent elective surgery required to avoid the risks of impaired wound healing/wound dehiscence has not been determined. (See **WARNINGS: Gastrointestinal Perforations/Wound Healing Complications** and **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

Hemorrhage

Serious, and in some cases fatal, hemoptysis has occurred in patients with non–small cell lung cancer treated with chemotherapy and AVASTIN. In a small study, the incidence of serious or fatal hemoptysis was 31% in patients with squamous histology and 4% in patients with adenocarcinoma receiving AVASTIN as compared to no cases in patients treated with chemotherapy alone. Patients with recent hemoptysis should not receive AVASTIN. (See **WARNINGS: Hemorrhage** and **DOSAGE AND ADMINISTRATION: Dose Modifications**.)

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 (1). Bevacizumab is produced in a Chinese Hamster Ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin and has a molecular weight of approximately 149 kilodaltons. AVASTIN is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous (IV) 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.

CLINICAL PHARMACOLOGY

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.

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, by gender, and by 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 a randomized study of 813 patients (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.

Special Populations

Analyses of demographic data suggest that no dose adjustments are necessary for age or sex.

Patients with renal impairment. No studies have been conducted to examine the pharmacokinetics of Bevacizumab in patients with renal impairment.

Patients with hepatic dysfunction. No studies have been conducted to examine the pharmacokinetics of Bevacizumab in patients with hepatic impairment.

CLINICAL STUDIES

The safety and efficacy of AVASTIN in the initial treatment of patients with metastatic carcinoma of the colon and rectum were studied in two randomized, controlled clinical trials in combination with intravenous 5-fluorouracil–based chemotherapy.

AVASTIN in Combination with Bolus-IFL

Study 1 was a randomized, double-blind, active-controlled clinical trial evaluating AVASTIN as first-line treatment of metastatic carcinoma of the colon or rectum. Patients were randomized to bolus-IFL (irinotecan 125 mg/m^2 IV, 5-fluorouracil 500 mg/m^2 IV, and leucovorin 20 mg/m^2 IV 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.

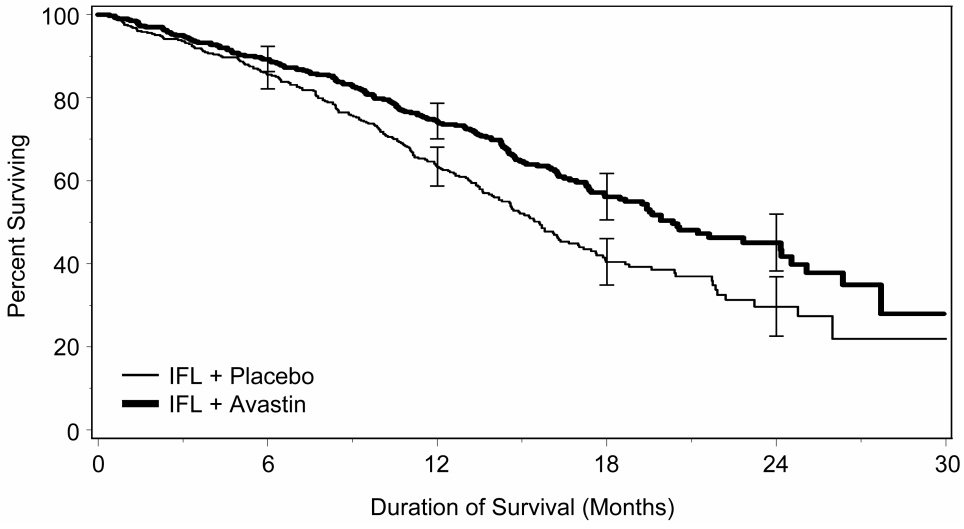
Of the 813 patients randomized to Arms 1 and 2, the median age was 60, 40% were female, and 79% were Caucasian. Fifty-seven percent had an ECOG performance status of 0. Twenty-one percent had a rectal primary and 28% received prior adjuvant chemotherapy. In the majority of patients, 56%, the dominant site of disease was extra-abdominal, while the liver was the dominant site in 38% of patients. The patient characteristics were similar across the study arms. The primary endpoint of this trial was overall survival. Results are presented in Table 1 and Figure 1.

Table 1
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)	6.4	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 logrank test.
[b] $p < 0.01$ by χ^2 test.

Figure 1
Duration of Survival in Study 1



Error bars represent 95% confidence intervals.

The clinical benefit of AVASTIN, as measured by survival in the two principal arms, was seen in all subgroups tested. The subgroups examined

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