AVASTIN®

bevacizumab (rch)

CAS 216974-75-3

Bevacizumab is an immunoglobulin G (IgG) composed of two identical light chains, consisting of 214 amino acid residues and two 453 residue heavy chains containing an N-linked oligosaccharide and has a molecular weight of approximately 149,000 daltons.

DESCRIPTION

AVASTIN is a clear to slightly opalescent, colourless to pale brown sterile solution for intravenous (IV) infusion. AVASTIN is available in 100 mg and 400 mg single dose vials containing 4 mL and 16 mL, respectively of bevacizumab (25 mg/mL). AVASTIN also contains α,α-trehalose dihydrate, monobasic monohydrate sodium phosphate, dibasic sodium phosphate, polysorbate 20 and water for injections.

PHARMACOLOGY

Mechanism of Action

AVASTIN is an antineoplastic agent containing the active ingredient, bevacizumab. Bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab contains human framework regions with antigen binding regions of a humanised murine antibody that binds to VEGF. Bevacizumab is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin and is purified by a process that includes specific viral inactivation and removal steps. Gentamicin is detectable in the final product at ≤ 0.35 ppm.

AVASTIN inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralising the biologic activity of VEGF reduces the vascularisation of tumours, thereby inhibiting tumour growth. Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumour activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was inhibited and microvascular permeability was reduced.

PHARMACOKINETICS

The pharmacokinetics of bevacizumab were characterised in patients with various types of solid tumours. The doses tested were 0.1-10 mg/kg weekly in phase I; 3-20 mg/kg every two weeks (q2w) or every three weeks (q3w) in phase II; 5 mg/kg (q2w) or 15 mg/kg q3w in phase III. In all clinical trials, bevacizumab was administered as an IV infusion.

As observed with other antibodies, the pharmacokinetics of bevacizumab are well described by a two-compartment model. Overall, in all clinical trials, bevacizumab disposition was characterised by a low clearance, a limited volume of the central compartment (Vc), and a long elimination half-life. This enables target therapeutic bevacizumab plasma levels to be maintained with a range of administration schedules (such as one administration every 2 or 3 weeks).

In the population pharmacokinetics analysis there was no significant difference in the pharmacokinetics of bevacizumab in relation to age (no correlation between bevacizumab clearance and subject age [the median age was 59 years with 5th and 95th percentiles of 37 and 76 years]).

Low albumin and high alkaline phosphatase levels are generally indicative of disease severity and tumour burden. Bevacizumab clearance was approximately 20% higher either in subjects with low levels of serum albumin or in subjects with elevated alkaline phosphatase levels when compared with the typical subject with median values of albumin and/or alkaline phosphatase.

Absorption and Bioavailability
Not applicable.

Distribution
The typical value for Vc was 2.66 L and 3.25 L for female and male subjects, respectively, which is in the range that has been described for IgGs and other monoclonal antibodies. After correcting for body weight, male subjects had a larger Vc (+22%) than females.

Metabolism
Assessment of bevacizumab metabolism in rabbits following a single IV dose of ^{125}I- bevacizumab suggested that its metabolic profile was similar to that expected for a native IgG molecule which does not bind VEGF.

Elimination
The pharmacokinetics of bevacizumab are linear at doses ranging from 1.5 to 10 mg/kg/wk.

The value for clearance is, on average, equal to 0.207 and 0.262 L/day for female and male subjects, respectively. After correcting for body weight, male subjects had a higher bevacizumab clearance (+26%) than females. According to the bi-compartmental model, the initial half-life (α) is 1.4 days for both sexes, and the terminal (β) half-life estimate is 20 days for a typical female subject and 19 days for a typical male.

Pharmacokinetics in Special Populations
The population pharmacokinetics of bevacizumab were analysed to evaluate the effects of demographic characteristics. The results showed no significant difference in the pharmacokinetics of bevacizumab in relation to age.

Children and adolescents: The pharmacokinetics of bevacizumab have been studied in a limited number of paediatric patients. The resulting pharmacokinetic data suggest that the volume of distribution and clearance of bevacizumab were comparable to that in adults with solid tumours.

Renal impairment: No formal studies have been conducted to examine the pharmacokinetics of bevacizumab in subjects with renal impairment.

Hepatic impairment: No formal studies have been conducted to examine the pharmacokinetics of bevacizumab in subjects with hepatic impairment.

CLINICAL TRIALS

Metastatic Colorectal Cancer
The safety and efficacy of AVASTIN in metastatic colorectal cancer were studied in two randomised, active-controlled clinical trials. AVASTIN was combined with two chemotherap y regimens:

- **AVF2107g**: A weekly schedule of irinotecan/bolus fluorouracil/leucovorin† (IFL) for a total of 4 weeks of each 6 week-cycle
- **AVF0780g:** In combination with bolus fluorouracil/leucovorin† (FU/LV) for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen)

Two additional studies were conducted in first (NO16966) and second line (E3200) treatment of metastatic carcinoma of the colon or rectum, with AVASTIN administered in the following dosing regimens, in combination with FOLFOX-4 (FU/LV/Oxaliplatin) and XELOX (Capecitabine/Oxaliplatin):

NO16966: AVASTIN 7.5 mg/kg of body weight every 3 weeks in combination with oral capecitabine and intravenous oxaliplatin (XELOX) or AVASTIN 5 mg/kg every 2 weeks in combination with leucovorin† plus fluorouracil bolus, followed by fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4).

E3200: AVASTIN 10 mg/kg of body weight every 2 weeks in combination with leucovorin† and fluorouracil bolus, followed by fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4).

† The Australian Approved Name for leucovorin is folinic acid

Study AVF2107g

This was a phase III randomised, double-blind, active-controlled clinical trial evaluating AVASTIN in combination with IFL as first-line treatment for metastatic colorectal cancer. Eight hundred and thirteen patients were randomised to receive IFL plus placebo (Arm 1) or IFL plus AVASTIN (Arm 2), see Table 1. A third group of 110 patients received FU/LV plus AVASTIN (Arm 3). Enrolment in Arm 3 was discontinued, as pre-specified, once safety of AVASTIN with the IFL regimen was established and considered acceptable. The median age of patients was 60 years (range 21 -88), 60% were male.

Table 1: Treatment regimens in study AVF2107g

	Treatment	Starting Dose	Schedule
Arm 1	Irinotecan Fluorouracil Folinic acid	125 mg/m^2 IV 500 mg/m^2 IV 20 mg/m^2 IV	Given once weekly for 4 weeks every 6 weeks
	Placebo	IV	Every 2 weeks
Arm 2	Irinotecan Fluorouracil Folinic acid	125 mg/m^2 IV 500 mg/m^2 IV 20 mg/m^2 IV	Given once weekly for 4 weeks every 6 weeks
	AVASTIN	5 mg/kg IV	Every 2 weeks
Arm 3	Fluorouracil Folinic acid	500 mg/m^2 IV 500 mg/m^2 IV	Given once weekly for 6 weeks every 8 weeks
	AVASTIN	5 mg/kg IV	Every 2 weeks

Fluorouracil: IV bolus injection immediately after folinic acid
Folinic acid: IV bolus injection (over 1- 2 minutes) immediately after each irinotecan dose

The primary efficacy endpoint of the trial was overall survival. At the time of data cut-off, 399 deaths had occurred in patients randomised to Arm 1 (n = 225) and Arm 2 (n = 174). The addition of AVASTIN to IFL resulted in a statistically significant increase in overall survival. Results are presented in Table 2 and Figure 1. The clinical benefit of AVASTIN, as measured by survival, progression-free survival and objective response, was seen in all pre-specified patient subgroups, see Figure 2.

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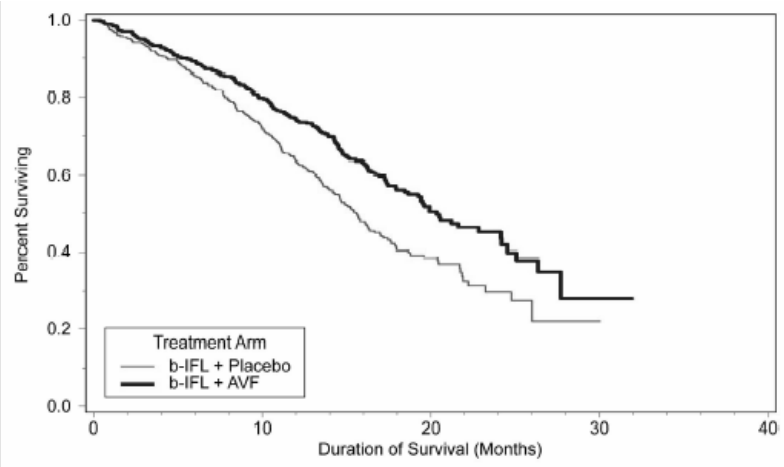
Table 2: Efficacy results for study AVF2107g

	Arm 1 IFL plus placebo (n=411)	Arm 2 IFL plus AVASTIN[a] (n=402)	Arm 3 FU/LV plus AVASTIN[a] (n=110[b])
Overall Survival			
Median (months)	15.6	20.3	18.3
Hazard ratio[c] (95% CI)	0.660 (0.54, 0.81)		
p-value (log rank)	0.00004		–
Progression-Free Survival			
Median (months)	6.2	10.6	8.8
Hazard ratio (95% CI)	0.54 (0.45, 0.66)		
p-value (log rank)	<0.0001		–
Overall Response Rate			
Rate (percent)	34.8	44.8	40.0
Between-arm difference (%) (95% CI)	10 (3.3, 16.7)		–
p-value (log rank)	0.0036		–
Duration of Response			
Median (months)	7.1	10.4	8.5
25–75 percentile (months)	4.7-11.8	6.7-15.0	5.5-11.9

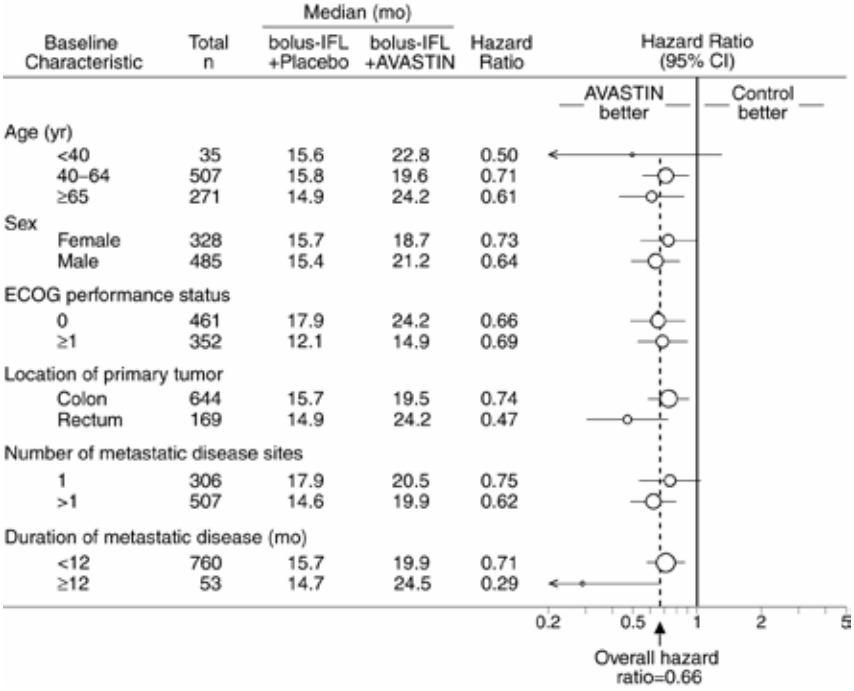
[a] 5 mg/kg every 2 weeks, [b] Recruitment stopped as per protocol, [c] Relative to control arm

Figure 1: Plot of Kaplan Meier estimates for survival in study AVF2107g



IFL =irinotecan/ fluorouracil/ leucovorin (folinic acid); AVF = AVASTIN

Figure 2: Duration of survival by baseline risk factor in study AVF2107g

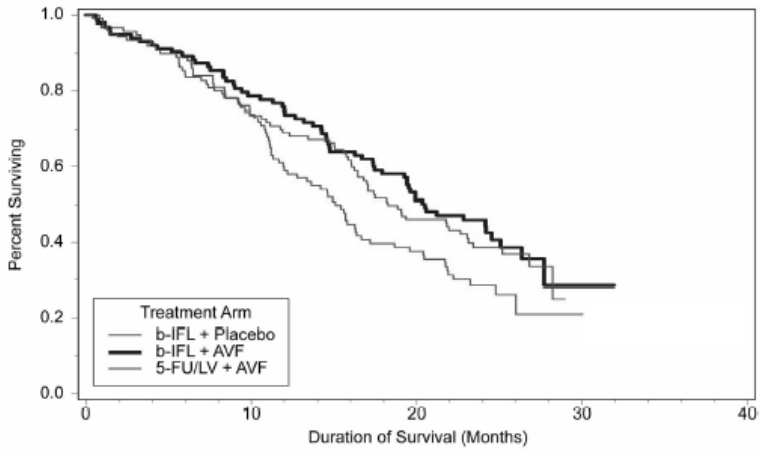


CI= interval; IFL= irinotecan/fluorouracil/ leucovorin (folinic acid);.

Hazard ratio <1 indicates a lower hazard of death in the IFL plus AVASTIN arm compared with the IFL plus placebo arm. Size of circle is proportional to the number of patients in the subgroup. Confidence interval is indicated by the horizontal line.

Results for the 110 patients in Arm 3 were compared to the first 100 patients enrolled in Arm 1 and Arm 2. There was a trend towards prolonged survival in the AVASTIN plus FU/LV arm as compared to the IFL plus placebo arm in this subset of patients, see Figure 3. Although the results did not show a statistical difference, the results were consistently better for the AVASTIN plus FU/LV arm than for IFL plus placebo arm for all efficacy parameters measured.

Figure 3: Plot of Kaplan Meier Estimates for survival in study AVF2107g: Patients enrolled in Arm 3 and concurrently enrolled patients in Arms 1 and 2



IFL = irinotecan/ fluorouracil/ leucovorin (folinic acid); AVF = AVASTIN

Study AVF0780g

This was a phase II randomised, active-controlled, open-labelled clinical trial investigating AVASTIN in combination with FU/LV as first-line treatment of metastatic colorectal cancer. Seventy one patients were randomised to receive bolus FU/LV or FU/LV plus AVASTIN (5 mg/kg every 2 weeks). A third group of 33 patients received bolus FU/LV plus AVASTIN (10 mg/kg every 2 weeks). Patients were treated until disease progression. The median age was 64 years (range 23-85), 57% were male. The primary efficacy endpoints of the trial were objective response rate and progression-free survival. The addition of AVASTIN (5 mg/kg ever y two weeks) to FU/LV resulted in higher objective response rates, longer progression-free survival and a trend in longer survival, compared with FU/LV chemotherapy alone, see Table 3. This efficacy data is consistent with the results from study AVF2107g.

Table 3: Efficacy results for study AVF0780g

	FU/LV (n=36)	FU/LV plus AVASTIN[a] (n=35)	FU/LV plus AVASTIN[b] (n=33)
Overall Survival			
Median (months)	13.6	17.7	15.2
Hazard ratio[c]	-	0.52	1.01
p-value (log-rank)	-	0.073	0.978
Progression-Free Survival			
Median (months)	5.2	9.0	7.2
Hazard ratio[c]	-	0.44	0.69
p-value (log-rank)	-	0.005	0.217
Overall Response Rate			
Rate[d] (percent) (95% CI)	16.7 (7.0-33.5)	40.0 (24.4-57.8)	24.2 (11.7-42.6)
p-value (log-rank)	-	0.03	0.43
Duration of Response			
Median (months)	NR	9.3	5.0
25–75 percentile (months)	5.5 - NR	6.1 - NR	3.8–7.8

[a] 5 mg/kg every 2 weeks, [b] 10 mg/kg every 2 weeks, [c] Relative to control arm, [d] independent review
NR = Not reached

Study NO16966

This was a phase III randomised, double-blind (for bevacizumab), clinical trial investigating AVASTIN 7.5 mg/kg in combination with oral capecitabine and IV oxaliplatin (XELOX), administered on a 3-weekly schedule; or AVASTIN 5 mg/kg in combination with leucovorin with fluorouracil bolus, followed by fluorouracil infusional, with IV oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule. The study contained two parts (see Table 4): an initial unblinded 2-arm part (Part I) in which patients were randomised to two different treatment groups (XELOX and FOLFOX-4) and a subsequent 2 x 2 factorial 4-arm part (Part II) in which patients were randomised to four treatment groups (XELOX + placebo, FOLFOX-4 + placebo, XELOX + AVASTIN, FOLFOX-4 + AVASTIN). In Part II, treatment assignment was double-blind with respect to AVASTIN.

Approximately 350 patients were randomised into each of the four study arms in Part II of the trial.

Table 4: Treatment Regimens in Study N016966 (mCRC)

	Treatment	Starting Dose	Schedule
FOLFOX-4 or FOLFOX-4 + AVASTIN	Oxaliplatin Leucovorin† Fluorouracil	85 mg/m^2 IV 2 h 200 mg/m^2 IV 2 h 400 mg/m^2 IV bolus, 600 mg/ m^2 IV 22 h	Oxaliplatin on Day 1 Leucovorin† on Day 1 and 2 Fluorouracil IV bolus/infusion, each on Days 1 and 2
	Placebo or AVASTIN	5 mg/kg IV 30-90 min	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX+ AVASTIN	Oxaliplatin Capecitabine	130 mg/m^2 IV 2 h 1000 mg/m^2 oral bid	Oxaliplatin on Day 1 Capecitabine oral bid for 2 weeks (followed by 1 week off treatment)
	Placebo or AVASTIN	7.5 mg/kg IV 30-90 min	Day 1, prior to XELOX, q 3 weeks
Fluorouracil:	IV bolus injection immediately after leucovorin		

† The Australian Approved Name for leucovorin is folinic acid

The primary efficacy parameter of the trial was the duration of progression-free survival (PFS). In this study, there were two primary objectives: to show that XELOX was non-inferior to FOLFOX-4 and to show that AVASTIN in combination with FOLFOX-4 or XELOX chemotherapy was superior to chemotherapy alone. Both co-primary objectives were met.

Superiority of the AVASTIN containing arms versus the chemotherapy alone arms in the overall comparison was demonstrated in terms of progression-free survival in the ITT population (See Table 5).

Secondary PFS analyses, based on Independent Review Committee and 'on-treatment'-based response assessments, confirmed the significantly superior clinical benefit for patients treated with AVASTIN.

Table 5: Key efficacy results for the superiority analysis (ITT population, Study NO16966)

Endpoint (months)	FOLFOX-4 or XELOX + Placebo (n=701)	FOLFOX-4 or XELOX + Bevacizumab (n=699)	P Value
Primary endpoint			
Median PFS**	8.0	9.4	0.0023
Hazard ratio (97.5% CI)a	0.83 (0.72 - 0.95)		
Secondary endpoints			
Median PFS (on treatment)**b	7.9	10.4	<0.0001
Hazard ratio (97.5% CI)	0.63 (0.52 - 0.75)		
Overall response rate (Investigator Assessment)**	49.2%,	46.5%	
Median overall survival*	19.9	21.2	0.0769
Hazard ratio (97.5% CI)	0.89 (0.76 - 1.03)		

* Overall survival analysis at clinical cut-off 31 January 2007
** Primary analysis at clinical cut-off 31 January 2006

[a] relative to control arm

[b] PFS on-treatment: based on investigator tumour assessments and death events that occurred no later than 28 days after the last confirmed intake of any study medication in the primary study treatment phase (5-FU, oxaliplatin, capecitabine, or bevacizumab/placebo, which ever was taken last)

Overall response rate was similar in the chemotherapy plus AVASTIN arm (46.5%) and in chemotherapy alone arm (49.2%).

Study ECOG E3200

This was a phase III randomised, active-controlled, open-label study investigating AVASTIN 10 mg/kg in combination with leucovorin with fluorouracil bolus and then fluorouracil infusional, with intravenous oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule in previously-treated patients (second line) with advanced colorectal cancer. In the chemotherapy arms, the FOLFOX-4 regimen used the same doses and schedule as shown in Table 4 for Study NO16966.

The primary efficacy parameter of the trial was overall survival, defined as the time from randomisation to death from any cause. Eight hundred and twenty-nine patients were randomised (292 FOLFOX-4, 293 AVASTIN +_FOLFOX-4 and 244 AVASTIN monotherapy). The addition of AVASTIN to FOLFOX-4 resulted in a statistically significant prolongation of survival. Statistically significant improvements in progression-free survival and objective response rate were also observed (see Table 6).

Table 6: Efficacy Results for Study E3200

	E3200	
	FOLFOX-4	FOLFOX-4 + Avastin[a]
Number of Patients	292	293
Overall Survival		
Median (months)	10.8	13.0
95% confidence interval	10.12 – 11.86	12.09 – 14.03
Hazard ratio[b] 95% confidence interval	0.751 (0.632, 0.893) (p-value = 0.0012)	
Progression-Free Survival Median (months) Hazard ratio 95% confidence interval	4.5 0.518 (0.416, 0.646) (p-value < 0.0001)	7.5
Objective Response Rate Rate	8.6 % (p-value < 0.0001)	22.2 %

a 10 mg/kg every 2 weeks
b Relative to control arm

No significant difference was observed in the duration of overall survival between patients who received AVASTIN monotherapy compared to patients treated with FOLFOX-4. Progression-free survival and objective response rate were inferior in the AVASTIN monotherapy arm compared to the FOLFOX-4 arm.

Locally recurrent or metastatic Breast Cancer

(Note that the efficacy and safety of the combination of bevacizumab and paclitaxel have not been compared with anthracycline-based therapies for first-line therapy in metastatic breast cancer. The efficacy of the combination of bevacizumab and paclitaxel in second and third line treatment of metastatic breast cancer has not been demonstrated.)

E2100 was an open-label, randomised, active controlled, multicentre clinical trial evaluating AVASTIN in combination with paclitaxel for locally recurrent or metastatic breast cancer in patients who had not previously received chemotherapy for locally recurrent and metastatic disease. Prior hormonal therapy for the treatment of metastatic disease was allowed. Adjuvant taxane therapy was allowed only if it was completed at least 12 months prior to study entry.

Patients were randomised to paclitaxel alone (90 mg/m2 IV over 1 hour once weekly for three out of four weeks) or in combination with AVASTIN (10 mg/kg IV infusion every two weeks). Patients were to continue assigned study treatment until disease progression. In cases where

patients discontinued chemotherapy prematurely, treatment with AVASTIN as a single agent was continued until disease progression. The primary endpoint was progression free survival (PFS), as assessed by investigators. In addition, an independent review of the primary endpoint was also conducted.

Of the 722 patients in the study, the majority of patients (90%) had HER2-negative disease. A small number of patients had HER-2 receptor status that was either unknown (8%) or positive (2%). Patients who were HER2-positive had either received previous treatment with trastuzumab or were considered unsuitable for trastuzumab. The majority (65%) of patients had received adjuvant chemotherapy including 19% who had prior taxanes and 49% who had prior anthracyclines. The patient characteristics were similar between the study arms.

The results of this study are presented in Table 7 and Figure 4. The addition of bevacizumab to paclitaxel chemotherapy resulted in a significant reduction of risk of disease progression or death, as measured by PFS (HR = 0.42; p< 0.0001). The resulting median PFS in bevacizumab-containing arm was 11.4 months compared with 5.8 months in the control arm. The small improvement in overall survival was not statistically significant.

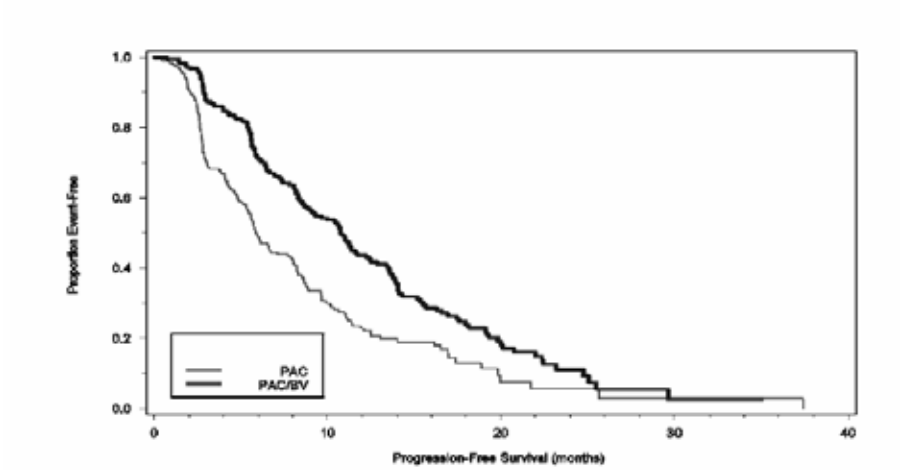
Table 7: Study E2100 Efficacy Results: Eligible Patients

Progression-free survival				
	Investigator Assessment*		IRF Assessment	
	Paclitaxel (n=354)	Paclitaxel/AVASTIN (n=368)	Paclitaxel (n=354)	Paclitaxel/AVASTIN (n=368)
Median PFS (months)	5.8	11.4	5.8	11.3
HR (95% CI)	0.421 (0.343 ; 0.516)		0.483 (0.385 ; 0.607)	
p-value	< 0.0001		< 0.0001	
Response rates (for patients with measurable disease)				
	Investigator Assessment		IRF Assessment	
	Paclitaxel (n=243)	Paclitaxel/AVASTIN (n=229)	Paclitaxel (n=243)	Paclitaxel/AVASTIN (n=229)
% pts with objective response	23.4	48.0	22.2	49.8
p-value	< 0.0001		< 0.0001	

* primary analysis; IRF = independent review facility

Overall Survival (Investigator assessment)		
	Paclitaxel (n=354)	Paclitaxel/AVASTIN (n=368)
Median OS (months)	24.8	26.5
HR (95% CI)	0.869 (0.722 ; 1.046)	
p-value	0.1374	

Figure 4: Kaplan-Meier curves for progression free survival in study E2100



The efficacy and safety of bevacizumab in combination with anthracycline-based therapies have not been studied for first-line therapy in metastatic breast cancer.

Advanced, metastatic or recurrent Non-Small Cell Lung Cancer

The safety and efficacy of AVASTIN in the first-line treatment of patients with non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology, was studied in addition to carboplatin/paclitaxel-based chemotherapy in study E4599 (n = 878). E4599 was an open- label, randomised, active-controlled, multicentre clinical trial evaluating AVASTIN as first-line treatment of patients with locally advanced (stage IIIB with malignant pleural effusion), metastatic or recurrent NSCLC other than predominantly squamous cell histology.

Patients were randomised to platinum-based chemotherapy (paclitaxel 200 mg/m^2 and carboplatin AUC = 6.0, both by IV infusion) (PC) on day 1 of every 3-week cycle for up to 6 cycles or PC in combination with AVASTIN at a dose of 15 mg/kg IV infusion day 1 of every 3-week cycle. Patients with predominant squamous histology (mixed cell type tumours only), central nervous system (CNS) metastasis, gross haemoptysis (≥½ tsp of red blood), clinically significant cardiovascular disease and medically uncontrolled hypertension were excluded. Other exclusion criteria were: therapeutic anticoagulation, regular use of aspirin (> 325 mg/day, NSAIDs or other agents known to inhibit platelet function, radiation therapy within 21 days of enrolment and major surgery within 28 days before enrolment.

Among 878 patients randomised to the two arms, the median age was 63, 46% were female, 43% were ≥ age 65, and 28% had 5% weight loss at study entry. 11% had recurrent disease and of ≥ the remaining 89% with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had Stage IV disease.

After completion of six cycles of carboplatin-paclitaxel chemotherapy or upon premature discontinuation of chemotherapy, patients on the AVASTIN + carboplatin–paclitaxel arm continued to receive AVASTIN as a single agent every 3 weeks until disease progression.

During the study, of the patients who received trial treatment, 32.2% (136/422) of patients received 7-12 administrations of AVASTIN and 21.1% (89/422) of patients received 13 or more administrations of AVASTIN.

The primary endpoint was overall survival (OS). The secondary endpoints, PFS (progression free survival) and ORR (overall response rate), were based on investigator assessment and were not independently verified.

Overall survival was statistically significantly higher for patients receiving AVASTIN + PC chemotherapy compared with those receiving PC alone. Results are presented in Table 8.

Table 8: Efficacy results for study E4599

	Arm 1 Carboplatin/ Paclitaxel	Arm 2 Carboplatin/ Paclitaxel + Avastin 15 mg/kg q 3 weeks
Number of Patients	444	434
Overall Survival		
Median (months)	10.3	12.3
Hazard ratio		0.80
		95% CI (0.69, 0.93)
p-value[a]		p = 0.003
Progression-Free Survival		
Median (months)	4.8	6.4
Hazard ratio		0.65
		95% CI (0.56, 0.76)
p-value[a]		p < 0.0001
Overall Response Rate		
Rate (percent)	12.9	29.0
p-value[b]		p < 0.0001

[a] stratified logrank test
[b] stratified χ^2 test includes patients with measurable disease at baseline.

Advanced and/or metastatic Renal Cell Cancer

Study BO17705

BO17705 was a multicentre, randomised, double-blind phase III trial conducted to evaluate the efficacy and safety of AVASTIN in combination with interferon (IFN)-alfa-2a (Roferon®) versus IFN-alfa-2a alone as first-line treatment in metastatic renal cell cancer (mRCC). The 649 randomised patients (641 treated) had clear cell mRCC, Karnofsky Performance Status (KPS) of ≥ 70%, no CNS metastases and adequate organ function. IFN-alfa-2a (x3/week at a recommended dose of 9 MIU) plus AVASTIN (10mg/kg q2w) or placebo was given until disease progression. For patients who were unable to tolerate IFN-alfa-2a treatment, treatment with AVASTIN was permitted to continue in the absence of progressive disease. Patients were stratified according to country and Motzer score and the treatment arms were shown to be well balanced for the prognostic factors.

At the data cut-off, 505 progression events had occurred, 111 patients remained on treatment, 287 had discontinued (discontinuations of trial treatment due to adverse events were 12% with IFN vs. 28% with IFN-alfa-2a/AVASTIN), and 251 died. Ninety seven (97) patients in the IFN alfa-2a arm and 131 patients in the AVASTIN arm reduced the dose of IFN alfa-2a from 9 MIU to either 6 or 3 MIU three times a week as pre-specified in the protocol. The addition of AVASTIN to IFN-alfa-2a significantly increased PFS and objective tumour response rate (see Table 9). The overall survival data were not mature at the time of the interim analysis. Median overall survival was 19.8 months for the IFN + placebo arm and had not been reached for the AVASTIN + IFN arm (p=0.670).

Table 9: Efficacy Results for Study BO17705

	BO17705	
	IFN + Placebo	IFN + AVASTIN
Number of Patients	322	327
Progression-Free Survival		
Median (months)	5.4	10.2
Hazard ratio	0.63 (p-value < 0.0001)	
Objective Response Rate (%) in Patients with Measurable Disease		
n	289	306
Response rate	12.8 %	31.4 % (p-value < 0.0001)

Grade IV Glioma*

Study AVF3708g

The efficacy and safety of AVASTIN as treatment for patients with GBM was studied in an open-label, multicentre, randomised, non-comparative study (AVF3708g).

Patients in first or second relapse after prior radiotherapy (completed at least 8 weeks prior to receiving AVASTIN) and temozolomide, were randomised (1:1) to receive AVASTIN (10mg/kg IV infusion every 2 weeks) or AVASTIN plus irinotecan (125 mg/m^2 IV or 340 mg/m^2 IV for patients on enzyme-inducing anti-epileptic drugs every 2 weeks) until disease progression or until unacceptable toxicity. The primary endpoints of the study were 6-month progression-free survival (PFS) and objective response rate (ORR) as assessed by an independent review facility. Other outcome measures were duration of PFS, duration of response and overall survival. Results are summarised in Table 10.

Table 10: Efficacy Results from Study AVF3708g

	AVASTIN		Historical controls[#]
Number of patients	85		225
	IRF	Inv	-
Primary endpoints			
6-month progression-free survival (97.5% CI)	42.6% (29.6%, 55.5%)	43.6% (33.0, 54.3)	15% (p < 0.0001)
Objective Response Rate (ORR) (97.5% CI)	28.2% (18.5%, 40.3%)	41.2% (30.6, 52.3)	5% (p < 0.0001)
Secondary endpoints			
Progression-free survival (months) Median (95% CI)	4.2 (2.9, 5.8)	4.2 (3.0, 6.9)	2.1
Duration of objective response (months) Median (95% CI)	5.6 (3.0, 5.8)	8.1 (5.5, *)	-
Overall survival (months) Median (95% CI)	9.3 (8.2, *)	9.3 (8.2, *)	5.7

ORR and progression were determined using modified Macdonald criteria; CI = confidence interval; Inv = Investigator's assessment; IRF = Independent Review Facility [#] protocol-defined statistical comparison with the integrated analysis of Wong et al(1999). Upper limit of the CI could not be obtained*

The majority of patients who were receiving steroids at baseline, including responders and non-responders, were able to reduce their steroid utilisation over time while receiving AVASTIN. The majority of patients experiencing an objective response or prolonged PFS (at week 24) were able to maintain or improve their neurocognitive function at the time of response and at week 24, respectively, compared to baseline. The majority of patients that remained in the study and were progression free at 24 weeks, had a Karnofsky performance status (KPS) that remained stable.

INDICATIONS

Metastatic Colorectal Cancer

AVASTIN (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of patients with metastatic colorectal cancer.

Locally recurrent or metastatic Breast Cancer

AVASTIN (bevacizumab) in combination with paclitaxel is indicated for the first-line treatment of metastatic breast cancer in patients in whom an anthracycline-based therapy is contraindicated. (see Clinical Trials)

Advanced, metastatic or recurrent non-squamous Non Small Cell Lung Cancer (NSCLC)

AVASTIN (bevacizumab), in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent, non-squamous, non-small cell lung cancer.

Advanced and/or metastatic Renal Cell Cancer

AVASTIN (bevacizumab) in combination with interferon alfa-2a is indicated for treatment of patients with advanced and/or metastatic renal cell cancer.

Grade IV Glioma*

AVASTIN (bevacizumab) as a single agent, is indicated for the treatment of patients with Grade IV glioma after relapse or disease progression after standard therapy, including chemotherapy.*

CONTRAINDICATIONS

AVASTIN is contraindicated in patients with:

- known hypersensitivity to any components of the product; Chinese hamster ovary cell products or other recombinant human or humanised antibodies

PRECAUTIONS

Gastrointestinal Perforations

Patients may be at increased risk for the development of gastrointestinal perforation when treated with AVASTIN. AVASTIN should be permanently discontinued in patients who develop gastrointestinal perforation.

AVASTIN has been associated with serious cases of gastrointestinal perforation. Gastrointestinal perforations have been reported in clinical trials with an incidence of less than 1% in patients with metastatic breast cancer or non-squamous non-small cell lung cancer, and up to 2% in patients with metastatic colorectal cancer or metastatic renal cell cancer. Cases of GI perforations have also been observed in patients with relapsed glioblastoma. Fatal outcome was reported in approximately a third of serious cases of gastrointestinal perforations, which represents between 0.2% - 1% of all AVASTIN treated patients.

The presentation of these events varied in type and severity, ranging from free air seen on the plain abdominal X-ray, which resolved without treatment, to intestinal perforation with abdominal abscess and fatal outcome. In some cases underlying intra-abdominal inflammation was present, either from gastric ulcer disease, tumour necrosis, diverticulitis or chemotherapy-associated colitis. A causal association of intra-abdominal inflammatory process and gastrointestinal perforation to AVASTIN has not been established.

Hypertension

An increased incidence of hypertension was observed in patients treated with AVASTIN. Clinical

safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre-existing hypertension should be adequately controlled before starting AVASTIN treatment. There is no information on the effect of AVASTIN in patients with uncontrolled hypertension at the time of initiating AVASTIN therapy. Monitoring of blood pressure is recommended during AVASTIN therapy.

In most cases hypertension was controlled adequately using standard anti-hypertensive treatment appropriate for the individual situation of the affected patient. AVASTIN should be permanently discontinued if medically significant hypertension can not be adequately controlled with antihypertensive therapy, or if, the patient develops hypertensive crisis or hypertensive encephalopathy (see ADVERSE EFFECTS-Post-Marketing Experience).

An increased incidence of hypertension (all grades) of up to 34% has been observed in patients treated with AVASTIN compared with up to 14% in the comparator arm. In clinical trials across all indications the overall incidence of Grade 3-4 hypertension in patients receiving AVASTIN ranged from 0.4% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of patients treated with AVASTIN compared to up to 0.2% patients treated with the same chemotherapy alone.

Hypertension was generally treated with oral anti-hypertensives such as angiotensin-converting enzyme inhibitors, diuretics and calcium-channel blockers. It rarely resulted in discontinuation of AVASTIN treatment or hospitalisation.

Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal (see ADVERSE EFFECTS-Post-Marketing Experience). The risk of AVASTIN-associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy.

Wound Healing

AVASTIN may adversely affect the wound healing process, AVASTIN therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experience wound healing complications during AVASTIN therapy, AVASTIN should be withheld until the wound is fully healed. AVASTIN therapy should be withheld for elective surgery.

Across metastatic colorectal cancer clinical trials there was no increased risk of post-operative bleeding or wound healing complications observed in patients who underwent major surgery between 28-60 days prior to starting AVASTIN therapy. An increased incidence of post- operative bleeding or wound healing complications occurring within 60 days of major surgery was observed if the patient was being treated with AVASTIN at the time of surgery. The incidence varied between 10% (4/40) and 20% (3/15).

In locally recurrent and metastatic breast cancer, National Cancer Institute-Common Toxicit y Criteria (NCI-CTC) Grade 3 - 5 wound healing complications were observed in 1.1% of patients receiving AVASTIN compared with up to 0.9% of patients in the control arms.

In Study AVF3708g, patients with relapsed GBM, the incidence of post-operative wound healing complications (craniotomy site wound dehiscence and cerebrospinal fluid leak) was 3.6% in patients treated with single-agent AVASTIN and 1.3% in patients treated with AVASTIN and irinotecan.

Thromboembolism

Arterial thromboembolic events

An increased incidence of arterial thromboembolic events has been observed in patients treated with AVASTIN across indications including cerebrovascular accidents, myocardial infarction, transient ischaemic attacks, and other arterial thromboembolic events.

In clinical trials, the overall incidence ranged up to 3.8% in the AVASTIN-containing arms compared with up to 1.7% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving AVASTIN in combination with chemotherapy compared to 0.5% of patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischaemic attacks) were reported in up to 2.3% of AVASTIN treated patients versus 0.5% of patients in the control group; myocardial infarction was reported in 1.4% of AVASTIN treated versus 0.7% of patients in the observed control group.

AVASTIN should be permanently discontinued in patients who develop arterial thromboembolic events.

Patients receiving AVASTIN plus chemotherapy with a history of arterial thromboembolism or age greater than 65 years have an increased risk of developing arterial thromboembolic events during AVASTIN therapy. Caution should be taken when treating such patients with AVASTIN.

Venous thromboembolic events

In clinical trials across indications, the overall incidence of venous thromboembolic events ranged from 2.8% to 17.3% in the AVASTIN containing arms compared to 3.2% to 15.6% in the chemotherapy control arms. Venous thromboembolic events include deep venous thrombosis and pulmonary embolism.

Patients may be at risk of developing venous thromboembolic events, including pulmonary embolism under AVASTIN treatment. AVASTIN should be discontinued in patients with life-threatening (Grade 4) pulmonary embolism, patients with ≤ Grade 3 need to be closely monitored.

Grade 3-5 venous thromboembolic events have been reported in up to 7.8% of patients treated with chemotherapy plus bevacizumab compared with up to 4.9% in patients with chemotherap y alone. Patients who have experienced a venous thromboembolic event may be at higher risk for a recurrence if they receive AVASTIN in combination with chemotherapy versus chemotherap y alone.

Haemorrhage

Patients treated with AVASTIN have an increased risk of haemorrhage, especially tumour-associated haemorrhage. AVASTIN should be permanently discontinued in patients who experience Grade 3 or 4 bleeding during AVASTIN therapy.

In clinical trials across all indications the overall incidence of NCI-CTC Grade 3 - 5 bleeding events ranged from 0.4% to 5% in AVASTIN-treated patients, compared to 0 to 2.9% of patients in the chemotherapy control group. Haemorrhagic events observed in AVASTIN clinical trials were predominantly tumour-associated haemorrhage and minor mucocutaneous haemorrhage (e.g. epistaxis).

The risk of Central Nervous System (CNS) haemorrhage has not been evaluated in randomised clinical studies with AVASTIN. Patients with untreated CNS metastases have been routinely excluded based on imaging procedures or signs and symptoms. Patients should be monitored for signs and symptoms of CNS bleeding, and AVASTIN treatment discontinued in case of intracranial bleeding*.

There is no information on the safety profile of AVASTIN in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting AVASTIN therapy, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating AVASTIN therapy in these patients. However, patients who developed venous thrombosis while receiving AVASTIN therapy did not appear to have an increased rate of Grade 3 or above bleeding when treated with full dose of warfarin and AVASTIN concomitantly.

Tumour-associated haemorrhage

Major or massive pulmonary haemorrhage/haemoptysis has been observed primarily in studies in patients with non-small cell lung cancer (NSCLC). Possible risk factors include squamous cell histology, treatment with antirheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, AVASTIN therapy, previous medical history of atherosclerosis, central tumour location and cavitation of tumours prior to or during therapy. The only variables that showed statistically significant correlations with bleeding were AVASTIN therapy and squamous cell histology. Patients with NSCLC of known squamous cell histology or mixed cell type with predominant squamous cell histology were excluded from subsequent studies, while patients with unknown tumour histology were included.

In patients with NSCLC excluding predominant squamous histology, all grade events were seen with a frequency of up to 9% when treated with AVASTIN plus chemotherapy compared with 5% in the patients treated with chemotherapy alone. Grade 3-5 events have been observed in up to 2.3% of patients treated with AVASTIN plus chemotherapy as compared with < 1% with chemotherapy alone. Major or massive pulmonary haemorrhage/haemoptysis can occur suddenly and up to two thirds of the serious pulmonary haemorrhages resulted in a fatal outcome.

In metastatic colorectal cancer trials gastrointestinal haemorrhage was reported as tumour-associated.

Gastrointestinal haemorrhages, including rectal bleeding and melaena have been reported in colorectal patients, and have been assessed as tumour-associated haemorrhages.

Tumour-associated haemorrhages have also been seen rarely in other tumour types and locations and include cases of CNS bleeding in a patients with CNS metastases and glioblastoma (GBM).

The incidence of CNS bleeding in patients with untreated CNS metastases receiving AVASTIN has not been evaluated in randomised clinical studies. In an exploratory retrospective analysis of data from 13 completed randomised trials in patients with various tumour types, 3 patients out of 91 (3.3%) with brain metastases experienced CNS bleeding (all Grade 4) when treated with AVASTIN, compared to 1 case (Grade 5) out of 96 patients (1%) that were not exposed to AVASTIN. In two ongoing studies in patients with treated brain metastases, one case of Grade 2 CNS haemorrhage was reported in 83 subjects treated with AVASTIN (1.2%) at the time of interim safety analysis.

Intracranial haemorrhage can occur in patients with relapsed GBM. In study AVF3708g, CNS haemorrhage was reported in 2.4% (2/84) of patients in the single-agent AVASTIN arm (Grade 1) and in 3.8% (3/79) of patients treated with AVASTIN and irinotecan (Grades 1, 2 and 4).

Mucocutaneous haemorrhage

Mucocutaneous haemorrhages were seen in up to 50% of patients treated with AVASTIN, across all AVASTIN clinical trials. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in AVASTIN treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous haemorrhage (e.g. epistaxis) may be dose-dependent. There have been less common events of minor mucocutaneous haemorrhage in other locations such as gingival bleeding or vaginal bleeding.

Pulmonary haemorrhage/haemoptysis

Patients with non-small cell lung cancer treated with AVASTIN may be at risk for serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis. Patients with recent pulmonary haemorrhage/haemoptysis (> 1/2 teaspoon red blood) should not be treated with AVASTIN.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

There have been rare reports of AVASTIN-treated patients developing signs and symptoms that are consistent with Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a rare neurological disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of RPLS requires confirmation by brain imaging. In patients developing RPLS, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of AVASTIN. The safety of reinitiating AVASTIN therapy in patients previously experiencing RPLS is not known (see ADVERSE EFFECTS-Post-Marketing Experience).

Proteinuria

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with AVASTIN. There is evidence suggesting that Grade 1 proteinuria may be dose-dependent. Testing for proteinuria is recommended prior to the start of AVASTIN therapy. In most clinical studies urine protein levels of ≥ 2g/24 hrs led to the holding of AVASTIN until recovery to < 2g/24 hrs.

In clinical trials, the incidence of proteinuria was higher in patients receiving AVASTIN in combination with chemotherapy compared to those who received chemotherapy alone. Grade 4 proteinuria (nephrotic syndrome) was uncommon in patients with AVASTIN. In the event of Grade 4 proteinuria AVASTIN treatment should be permanently discontinued.

In clinical trials, proteinuria has been reported within the range of 0.7% to 38% of patients receiving AVASTIN. Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome. Grade 3 proteinuria was reported in < 3% of treated patients, except in advanced and/or metastatic renal cell cancer where it was reported in up to 7% of patients. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of treated patients. The proteinuria seen in AVASTIN clinical trials was not associated with renal impairment and rarely required permanent discontinuation of AVASTIN therapy.

Congestive Heart Failure

Events consistent with congestive heart failure (CHF) were reported in clinical trials in all cancer indications studied to date. The symptoms ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF, such as pre-existing coronary heart disease or concomitant cardiotoxic therapy.

In phase III studies (AVF2119g and E2100) in patients with metastatic breast cancer an increase of CHF Grade 3 or more with AVASTIN was seen. CHF was reported in up to 3.5% of patients treated with AVASTIN compared with up to 0.9% in the control arms. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy.

In most clinical trials of AVASTIN, patients with pre-existing CHF of NYHA II - IV were excluded, therefore, no information is available on the risk of CHF in this population.

Prior anthracyclines exposure and/or prior radiation to the chest wall may be possible risk factors for the development of CHF.

Caution should be exercised when treating patients with clinically significant cardiovascular disease or pre-existing congestive heart failure with AVASTIN.

Neutropenia
Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus AVASTIN in comparison to chemotherapy alone.

Fistulae
Patients may be at increased risk for the development of fistulae when treated with AVASTIN. AVASTIN use has been associated with serious cases of fistulae including events resulting in death.

In AVASTIN clinical trials, gastrointestinal fistulae have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer, but were also reported less commonly in patients with other types of cancer. Uncommon (≥ 0.1% to < 1%) reports of other types of fistulae that involve areas of the body other than the gastrointestinal tract (e.g. bronchopleural, urogenital, biliary fistulae) were observed across various indications. Fistulae have also been reported in post-marketing experience.

Events were reported at various time points during treatment ranging from one week to greater than 1 year from initiation of AVASTIN, with most events occurring within the first 6 months of therapy.

Permanently discontinue AVASTIN in patients with tracheo-oesophageal fistula or any Grade 4 fistula. Limited information is available on the continued use of AVASTIN in patients with other fistulae. In cases of internal fistula not arising in the gastrointestinal tract, discontinuation of AVASTIN should be considered.

Hypersensitivity Reactions, Infusion Reactions
Patients may be at risk of developing infusion/hypersensitivity reactions. Close observation of the patient during and following the administration of AVASTIN is recommended. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered.

Carcinogenesis and Mutagenesis
Studies to evaluate the carcinogenic and mutagenic potential of AVASTIN have not been performed.

Effects on Fertility
No specific studies in animals have been performed to evaluate the effect of bevacizumab on fertility. No adverse effect on the male reproductive organ was observed in repeat dose toxicity studies in cynomolgus monkeys, but inhibition of ovarian function was observed in females. This was characterised by decreases in ovarian and/or uterine weight and the number of corpora lutea, a reduction in endometrial proliferation and an inhibition of follicular maturation in cynomolgus monkeys treated with AVASTIN. The lowest dose tested in the 26 week study (2 mg/kg weekly which corresponds to 0.6-fold the human therapeutic dose based on AUC) caused a reduction in uterine weight, however the reduction was not statistically significant. In rabbits, administration of 50 mg/kg of bevacizumab IV for 3 or 4 doses every 4 days resulted in decreases in ovarian and/or uterine weight and number of corpora lutea. The changes in both monkeys and rabbits were reversible upon cessation of treatment. The inhibition of angiogenesis following

administration of bevacizumab is likely to result in an adverse effect on female fertility.

Use in Pregnancy – Category D

There are no adequate and well-controlled studies in pregnant women. IgGs are known to cross the placental barrier, and AVASTIN may inhibit angiogenesis in the foetus. Angiogenesis has been shown to be critically important to foetal development. The inhibition of angiogenesis following administration of AVASTIN could result in an adverse outcome of pregnancy. Therefore, AVASTIN should not be used during pregnancy.

In women with childbearing potential, appropriate contraceptive measures are recommended during AVASTIN therapy. Based on pharmacokinetic considerations, contraceptive measures are recommended for at least 6 months following the last dose of AVASTIN.

Bevacizumab has been shown to be embryotoxic and teratogenic when administered to rabbits. Observed effects included decreases in foetal body weights, an increased number of foetal resorptions and an increased incidence of specific gross and skeletal foetal alterations. Adverse foetal outcomes were observed at all tested doses. At the lowest dose tested, maternal serum AUC values were about 0.7-fold those observed in humans at the recommended clinical dose.

Use in Lactation

Immunoglobulins are excreted in milk, although there are no data specifically for bevacizumab excretion in milk. Since bevacizumab could harm infant growth and development, women should be advised to discontinue breastfeeding during AVASTIN therapy and not to breast feed for at least 6 months following the last dose of AVASTIN.

Interactions with Other Medicines

Effect of antineoplastic agents on bevacizumab pharmacokinetics

No clinically relevant pharmacokinetic interaction of co-administered chemotherapy on AVASTIN disposition has been observed based on the results of a population pharmacokinetic analysis. There was no difference in clearance of AVASTIN in patients treated with single-agent AVASTIN compared to patients receiving AVASTIN in combination with the bolus-IFL regimen. The effect of other co-administered chemotherapies (FU-LV, carboplatin-paclitaxel, capecitabine or doxorubicin) on AVASTIN clearance is considered not clinically significant.

Effect of bevacizumab on the pharmacokinetics of other antineoplastic agents

Results from a drug-drug interaction study, AVF3135g, demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan and its active metabolite SN38.

Results from study NP18587 demonstrated no significant effect of bevacizumab on the pharmacokinetic of capecitabine and its metabolites, and on the pharmacokinetics of oxaliplatin, as determined by measurement of free and total platinum.

Results from study B017705 demonstrated no significant effect of bevacizumab on the pharmacokinetics of interferon alfa-2a.

Combination of bevacizumab and sunitinib malate

In two clinical studies of metastatic renal cell carcinoma, microangiopathic haemolytic anaemia (MAHA) was reported in 7 of 19 patients treated with bevacizumab (10 mg/kg every two weeks) and sunitinib malate (50 mg daily) combination.

MAHA is a haemolytic disorder which can present with red cell fragmentation, anaemia, and thrombocytopenia. In addition, hypertension (including hypertensive crisis), elevated creatinine,

and neurological symptoms were observed in some of these patients. All of these findings were reversible upon discontinuation of bevacizumab and sunitinib malate (see PRECAUTIONS-Hypertension, Proteinuria and RPLS).

Radiotherapy

The safety and efficacy of concomitant administration of radiotherapy and AVASTIN have not been established.

Use in Children

The safety and effectiveness of AVASTIN in children and adolescent patients have not been studied.

Use in Elderly

In randomised clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic events including cerebrovascular accidents, transient ischaemic attacks and myocardial infarction, as compared to those aged ≤ 65 years when treated with AVASTIN.

Other reactions with a higher frequency seen in patients over 65 were Grade 3-4 leucopenia and thrombocytopenia; and all grade neutropenia, diarrhoea, nausea, headache and fatigue.

No increase in the incidence of other reactions including gastrointestinal perforation, wound healing complications, hypertension, proteinuria, congestive heart failure and haemorrhage, was observed in elderly patients (> 65 years) receiving AVASTIN as compared to those aged ≥65 years treated with AVASTIN.

Effects on the Ability to Drive or Operate Machines

No studies on the effects on the ability to drive and use machines have been performed. However, there is no evidence that AVASTIN treatment results in an increase in adverse events that might lead to impairment of the ability to drive or operate machinery or impairment of mental ability.

ADVERSE EFFECTS

Experience from Clinical Trials

Clinical trials have been conducted in more than 3500 patients with various malignancies treated with AVASTIN, predominantly in combination with chemotherapy. The safety profile from the clinical trial population is presented in this section.

The most serious adverse drug reactions were:

- Gastrointestinal Perforations (see PRECAUTIONS)
- Haemorrhage including pulmonary haemorrhage/haemoptysis, which is more common in NSCLC patients (see PRECAUTIONS)
- Arterial thromboembolism (see PRECAUTIONS)

Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with AVASTIN therapy are likely to be dose-dependent (see PRECAUTIONS).

The most frequently observed adverse drug reactions across clinical trials in patients receiving

AVASTIN were hypertension, fatigue or asthenia, diarrhoea and abdominal pain.

Table 11 lists adverse drug reactions associated with the use of AVASTIN in combination with different chemotherapy regimens in multiple indications. These reactions had occurred either with at least a 2% difference compared to the control arm (NCI-CTC Grade 3 - 5 reactions) or with at least a 10% difference compared to the control arm (NCI-CTC Grade 1 - 5 reactions), in

at least one of the major clinical trials. The adverse drug reactions listed in Table 11 fall into the following categories: Very Common (≥10%) and Common (≥1% - < 10%). Adverse drug reactions have been included in the appropriate category in Table 11 according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping adverse drug reactions are presented in order of decreasing seriousness. Some of the adverse reactions are reactions commonly seen with chemotherapy (e.g. palmar-plantar erythrodysaesthesia syndrome with capecitabine and peripheral sensory neuropathy with paclitaxel or oxaliplatin); however, an exacerbation by AVASTIN therapy cannot be excluded.

Table 11: Very Common and Common Adverse Drug Reactions

System Organ Class (SOC)	*NCI-CTC Grade 3-5 Reactions (≥ 2% difference between the study arms in at least one clinical trial)*		*All Grade Reactions (≥ 10% difference between the study arms in at least one clinical trial)*
	Very common	*Common*	*Very Common*
Infections and infestations		Sepsis Abscess Infection	
Blood and the lymphatic systems disorders	Leucopenia Neutropenia Thrombocytopenia	Febrile neutropenia Anaemia	
Metabolism and nutrition disorders		Dehydration	Anorexia
Nervous system disorders	Peripheral sensory neuropathy	Cerebrovascular accident Syncope Somnolence Headache	Dysgeusia Headache
Eye disorders			Eye disorder
Cardiac disorders		Cardiac failure congestive Supraventricular tachycardia	
Vascular disorders	Hypertension	Thromboembolism (arterial) Deep vein thrombosis Haemorrhage	Hypertension
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism Dyspnoea Hypoxia Epistaxis	Dyspnoea Epistaxis Rhinitis
Gastrointestinal disorders	Diarrhoea Nausea Vomiting	Intestinal Perforation Ileus Intestinal obstruction Abdominal pain Gastrointestinal disorder	Constipation Stomatitis Rectal haemorrhage
Skin and subcutaneous tissue disorders		Palmar-plantar erythrodysaesthesia syndrome	Exfoliative dermatitis Dry skin Skin discolouration
Musculoskeletal, connective tissue and bone disorders		Muscular weakness	
Renal and urinary disorders		Proteinuria Urinary Tract Infection	Proteinuria
General disorders and administration site conditions	Asthenia Fatigue	Pain Lethargy	Pyrexia Asthenia Pain

Laboratory Abnormalities
Decreased neutrophil count, decreased white blood count and presence of urine protein may be associated with AVASTIN treatment.

Across clinical trials, the following Grade 3 and 4 laboratory abnormalities were seen with an increased (≥ 2%) incidence in patients treated with AVASTIN compared to those in the control groups: hyperglycaemia, decreased haemoglobin, hypokalaemia, hyponatraemia, decreased white blood cell count, increased prothrombin time and normalised ratio.

Post-Marketing Experience

Table 12: Adverse reactions reported in post-marketing setting

System Organ Class (SOC)	Reactions (frequency*)
Nervous system disorders	Hypertensive encephalopathy (very rare) (see PRECAUTIONS) Reversible Posterior Leukoencephalopathy Syndrome (rare) (see PRECAUTIONS)
Vascular disorders	Renal Thrombotic Microangiopathy, clinically manifested as proteinuria (not known) (see PRECAUTIONS).
Respiratory, thoracic and mediastinal disorders	Nasal septum perforation (not known) Pulmonary hypertension (not known) Dysphonia (common)
Gastrointestinal disorders	Gastrointestinal ulcer (not known)
Immune system disorders	Hypersensitivity, infusion reactions (not known); possibly associated with the following co-manifestations: dyspnoea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting (see Precautions)

* if specified, the frequency has been derived from clinical trial data

DOSAGE AND ADMINISTRATION

Recommended Dose

Metastatic Colorectal Cancer

The recommended dose of AVASTIN, administered as an intravenous infusion, is as follows;

*First-line treatmen*t*: 5 mg/kg of body weight given once every 2 weeks or
7.5 mg/kg of body weight given once every 3 weeks

*Second-line treatmen*t*: 10 mg/kg of body weight given every 2 weeks or
15 mg/kg of body weight given once every 3 weeks.

It is recommended that AVASTIN treatment be continued until progression of the underlying disease.

Locally recurrent or metastatic Breast Cancer

The recommended dose of AVASTIN is 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

It is recommended that AVASTIN treatment be continued until progression of the underlying disease.

Advanced, metastatic or recurrent non-squamous Non-Small Cell Lung Cancer

The recommended dose of AVASTIN in combination with carboplatin and paclitaxel is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

AVASTIN is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by AVASTIN as a single agent until disease progression.

Advanced and/or metastatic Renal Cell Cancer

The recommended dose of AVASTIN is 10 mg/kg given once every 2 weeks as an intravenous infusion.

It is recommended that AVASTIN treatment be continued until progression of the underlying disease.

AVASTIN should be given in combination with interferon (IFN)-alfa-2a (Roferon®) (3 times a week at a recommended dose of 9 MIU) (see CLINICAL TRIALS).

Grade IV Glioma*

The recommended dose of AVASTIN is 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion*.

It is recommended that AVASTIN treatment be continued until progression of the underlying disease.

Dose reduction

Dose reduction of AVASTIN for adverse reactions is not recommended. If indicated, AVASTIN should either be discontinued or temporarily suspended (see PRECAUTIONS).

Special Dosage Instructions

Children and adolescents: The safety and efficacy of AVASTIN in children and adolescents have not been studied.

Elderly: No dose adjustment is required in the elderly.

Renal impairment: The safety and efficacy of AVASTIN have not been studied in patients with renal impairment.

Hepatic impairment: The safety and efficacy of AVASTIN have not been studied in patients with hepatic impairment.

Preparing the Infusion

AVASTIN should be prepared by a healthcare professional using aseptic technique. Withdraw the necessary amount of bevacizumab and dilute to the required administration volume with 0.9% sodium chloride solution. The concentration of the final bevacizumab solution should be kept within the range of 1.4 - 16.5 mg/mL.

No incompatibilities between AVASTIN and polyvinyl chloride or polyolefin bags have been observed.

AVASTIN infusions should not be administered or mixed with dextrose or glucose solutions.

Method of Administration

The initial AVASTIN dose should be delivered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60 minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

Do not administer as an intravenous push or bolus.

OVERDOSAGE

The highest dose tested in humans (20 mg/kg body weight, IV) was associated with severe migraine in several patients. Treatment of overdose should consist of general supportive measures. Contact the Poisons Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

AVASTIN is available as:

- 100 mg pack containing one 4 mL single-dose vial
- 400 mg pack containing one 16 mL single-dose vial

Store vials at 2-8°C. (Refrigerate. Do not freeze.) Do not shake.

Protect from light. Keep vial in outer carton due to light sensitivity until use.

AVASTIN does not contain any antimicrobial agent; therefore care must be taken to ensure the sterility of the prepared solution. Product is for single use in one patient only. Discard any residue. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

Chemical and physical in-use stability has been demonstrated for 48 hours at 2-30°C in 0.9% sodium chloride solution. To reduce microbiological hazard, the product should be used as soon as practicable after preparation. If storage is necessary, in-use storage times and conditions are the responsibility of the user and would not be longer than 24 hours at 2-8°C.

Disposal of Medicines

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

POISON SCHEDULE

Prescription Only Medicine (S4)

SPONSOR

Roche Products Pty Limited

ABN 70 000 132 865

4−10 Inman Road

Dee Why NSW 2099

AUSTRALIA

Roche

Customer enquiries: 1800 233 950

TGA Approval Date: 10 February 2010

** Please note changes in Product Information*