

CORE DATA SHEET VS 32.0

AVASTIN®

January 2015

Bevacizumab

Information as set forth in this label only applies to AVASTIN

1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

Anti-neoplastic agent

ATC Code: L01X C07

1.2 TYPE OF DOSAGE FORM

Concentrate for solution for infusion.

1.3 ROUTE OF ADMINISTRATION

Clear to slightly opalescent, colourless to pale brown, sterile liquid for intravenous (IV) infusion.

Avastin is not formulated for intravitreal use (*see section 2.4.1 Warnings and Precautions, General*).

1.4 STERILE / RADIOACTIVE STATEMENT

Sterile.

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Bevacizumab (humanised anti-VEGF monoclonal antibody).

Avastin is supplied in 100 mg and 400 mg preservative-free, single-use vials containing 4 mL or 16 mL of Avastin (25 mg/mL).

Each Avastin 100 mg vial contains 100 mg of bevacizumab.

Each Avastin 400 mg vial contains 400 mg of bevacizumab.

List of Excipients: trehalose dihydrate, sodium phosphate, polysorbate 20 (produced from genetically modified maize), water for injection.

1.6 THERAPEUTIC INDICATION(S)

Metastatic Colorectal Cancer (mCRC)

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

Avastin is indicated in combination with an irinotecan- or oxaliplatin-containing chemotherapy regimen in the second-line treatment of patients with metastatic colorectal cancer with previous oxaliplatin or irinotecan-based chemotherapy with or without Avastin.

Locally recurrent or metastatic Breast Cancer (mBC)

Avastin in combination with standard cytotoxic chemotherapy is indicated for first-line treatment of patients with locally recurrent or metastatic breast cancer.

Avastin in combination with taxanes, capecitabine or gemcitabine, is indicated for the treatment of patients with metastatic breast cancer after failure of first-line cytotoxic chemotherapy.

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

Avastin, in addition to platinum-based chemotherapy, 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 (mRCC)

Avastin in combination with interferon alfa-2a is indicated for first-line treatment of patients with advanced and/or metastatic renal cell cancer.

Malignant Glioma (WHO Grade IV) - Glioblastoma

Avastin, as a single agent, or in combination with irinotecan, is indicated for the treatment of patients with glioblastoma after relapse or disease progression.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

Avastin, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer. Avastin, in combination with carboplatin and gemcitabine is indicated for the treatment of patients with recurrent, platinum-sensitive, epithelial ovarian, fallopian tube, or primary peritoneal cancer (with a platinum-free interval of at least 6 months).

Avastin in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens

Cervical Cancer

Avastin in combination with paclitaxel and cisplatin or paclitaxel and topotecan is indicated for the treatment of persistent, recurrent, or metastatic carcinoma of the cervix.

1.7 DOSAGE AND ADMINISTRATION

General

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

Avastin should be prepared by a healthcare professional using aseptic technique (*see section 4.2 Special Instructions for Use, Handling and Disposal*).

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.

Dose reduction of Avastin for adverse events is not recommended. If indicated, Avastin should either be permanently discontinued or temporarily suspended as described in section 2.4.1 Warnings and Precautions, General.

Avastin is not formulated for intravitreal use (*see section 2.4.1 Warnings and Precautions, General*).

Metastatic Colorectal Cancer (mCRC)

The recommended dose of Avastin, administered as an intravenous infusion, is as follows:

First-line treatment: 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 treatment: 5 mg/kg or 10 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg 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. Patients previously treated with Avastin can continue with Avastin treatment following first progression (*see section 3.1.2 study ML18147*).

Locally recurrent or metastatic Breast Cancer (mBC)

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-Small Cell Lung Cancer (NSCLC)

Avastin is administered in addition to platinum- based chemotherapy for up to 6 cycles of treatment followed by Avastin as a single agent until disease progression.

The recommended dose of Avastin when used in addition to cisplatin- based chemotherapy is 7.5 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

The recommended dose of Avastin when used in addition to carboplatin-based chemotherapy is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

Advanced and/or metastatic Renal Cell Cancer (mRCC)

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

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

Malignant Glioma (WHO Grade IV) - Glioblastoma

The recommended dose of Avastin, administered as an intravenous infusion, is as follows:

10 mg/kg of body weight given once 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.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

The recommended dose of Avastin administered as an intravenous infusion is as follows.

Front-line treatment:

15 mg/kg of body weight given once every 3 weeks
when administered in addition to carboplatin and
paclitaxel for up to six cycles of treatment followed by
continued use of Avastin as single agent for 15 months
or until disease progression, whichever occurs earlier.

Treatment of recurrent disease:

Platinum sensitive:

15 mg/kg of body weight given once every 3 weeks
when administered in combination with carboplatin and
gemcitabine for 6 cycles and up to 10 cycles followed
by continued use of Avastin as single agent until
disease progression.

Platinum resistant:

10 mg/kg body weight given once every 2 weeks when
administered in combination with one of the following
agents – paclitaxel, topotecan (given weekly) or
pegylated liposomal doxorubicin (*see section 3.1.2,*
study MO22224 for chemotherapy regimens).

Alternatively, 15 mg/kg every 3 weeks when administered in combination with topotecan given on days 1-5, every 3 weeks (*see section 3.1.2, study MO22224 for chemotherapy regimen*).

It is recommended that treatment be continued until disease progression.

Cervical Cancer

Avastin is administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin or paclitaxel and topotecan (*see section 3.1.2 study GOG-0240 for further details on the chemotherapy regimens*).

The recommended dose of Avastin is 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.

1.7.1 SPECIAL DOSAGE INSTRUCTIONS

Children and adolescents: The safety and efficacy of Avastin in children and adolescents has not been established.

Elderly: No dose adjustment is required in the elderly.

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

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

1.8 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.
- § Pregnancy

1.9 WARNINGS AND PRECAUTIONS

1.9.1 GENERAL

In order to improve traceability of biological medicinal products, the trade name and the batch number of the administered product should be clearly recorded (or stated) in the patient file.

Gastrointestinal Perforations and Fistulae Patients may be at increased risk for the development of gastrointestinal perforation (*see section 2.6.1 Undesirable Effects, Clinical Trials*) and gallbladder perforation (*see section 2.6.2 Undesirable Effects, Post Marketing*) when treated with Avastin. Avastin should be permanently discontinued in patients who develop gastrointestinal perforation. *Patients treated for persistent, recurrent, or metastatic cervical cancer with Avastin may be at increased risk of fistulae between the vagina and any part of the GI tract (Gastrointestinal_vaginal fistulae) (see section 2.6.1 Gastrointestinal Perforations and Fistulae).*

Non-GI Fistulae (see section 2.6.1 Clinical Trials, Undesirable Effects)

Patients may be at increased risk for the development of fistulae when treated with Avastin (*see section 2.6.1. Undesirable Effects, Clinical Trials*).

Permanently discontinue Avastin in patients with tracheoesophageal (TE) 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 GI tract, discontinuation of Avastin should be considered.

Haemorrhage (see section 2.6.1 Undesirable Effects, Clinical Trials)

Patients treated with Avastin have an increased risk of haemorrhage, especially tumour-associated haemorrhage (*see section 2.6.1 Haemorrhage*). Avastin should be permanently discontinued in patients who experience Grade 3 or 4 bleeding during Avastin therapy.

Patients with untreated CNS metastases were routinely excluded from clinical trials with Avastin, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS haemorrhage in such patient has not been prospectively evaluated in randomised clinical studies (*see section 2.6.1 Haemorrhage*). Patients should be monitored for signs and symptoms of CNS bleeding, and Avastin treatment discontinued in cases 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 treatment, 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.

Severe Eye Infections Following Compounding for Unapproved Intravitreal Use (see section 2.6.2 Undesirable Effects, Postmarketing) Individual cases and clusters of serious ocular adverse events have been reported (including infectious endophthalmitis and other ocular inflammatory conditions) following unapproved intravitreal use of Avastin compounded from vials approved for intravenous administration in cancer patients. Some of these events have resulted in various degrees of visual loss, including permanent blindness.

Pulmonary Haemorrhage/Haemoptysis (see section 2.6 Undesirable Effects)

Patients with non-small cell lung cancer treated with Avastin may be at risk for serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis (see section 2.6.1 Haemorrhage). Patients with recent pulmonary haemorrhage/haemoptysis (>1/2 teaspoon red blood) should not be treated with Avastin.

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 (see section 2.6.1 Undesirable Effects, Clinical Trials).

In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. Avastin should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if, the patient develops hypertensive crisis or hypertensive encephalopathy (see sections 2.6.1 Undesirable Effects, Clinical Trials and 2.6.2 Undesirable Effects, Post Marketing).

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been rare reports of Avastin-treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephalopathy Syndrome (PRES), 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 PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, 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 PRES is not known (see sections 2.6.1 Undesirable Effects, Clinical Trials and 2.6.2 Undesirable Effects, Post-Marketing).

Arterial Thromboembolism

In clinical trials, the incidence of arterial thromboembolism events including cerebrovascular accidents, transient ischaemic attack (TIA) and myocardial infarction (MI) was higher in patients receiving Avastin in combination with chemotherapy compared to those who received chemotherapy alone.

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

Patients receiving Avastin plus chemotherapy with a history of arterial thromboembolism, diabetes 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 Thromboembolism (see section 2.6 Undesirable Effects)

Patients may be at risk of developing venous thromboembolic events, including pulmonary embolism under Avastin treatment.

Patients treated for persistent, recurrent, or metastatic cervical cancer with Avastin may be at increased risk of venous thromboembolic events (*see section 2.6.1 Venous thromboembolism*).

Avastin should be discontinued in patients with life-threatening (Grade 4) venous thromboembolic events, including pulmonary embolism. Patients with thromboembolic events \leq Grade 3 need to be closely monitored.

Congestive Heart Failure (see section 2.6 Undesirable Effects)

Events consistent with congestive heart failure (CHF) were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation.

Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with Avastin.

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 were present.

In patients in AVF3694g who received treatment with anthracyclines and who had not received anthracyclines before, no increased incidence of all grade CHF was observed in the anthracycline + bevacizumab group compared to the treatment with anthracyclines only. In both AVF3694g and AVF3693g, CHF grade 3 or higher events were somewhat more frequent among patients receiving bevacizumab in combination with chemotherapy than in patients receiving chemotherapy alone. This is consistent with results in patients in other studies of metastatic breast cancer who did not receive concurrent anthracycline treatment (*see section 2.6.1*).

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.

Wound Healing

Avastin may adversely affect the wound healing process. Serious wound healing complications with a fatal outcome have been reported.

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 treatment, Avastin should be withheld until the wound is fully healed. Avastin therapy should be withheld for elective surgery (*see section 2.6.1 Undesirable Effects, Clinical Trials*).

Necrotising fasciitis including fatal cases, has rarely been reported in patients treated with Avastin; usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Avastin therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated (*see section 2.6.2 Undesirable Effects, Post Marketing*).

Proteinuria (see section 2.6 Undesirable Effects)

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.

Hypersensitivity reactions, infusion reactions (see section 2.6 Undesirable Effects, Clinical Trials and Post Marketing)

Patients may be at risk of developing infusion / hypersensitivity reactions. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanized monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

Immunogenicity

Patients from two phase III studies on the adjuvant treatment of colon cancer were screened for Avastin antibodies by immunoassay. Avastin antibodies were detected in 14 out of the 2233 patients (0.6%), including neutralising antibodies in three of these antibody-positive patients.

The clinical significance of an immune reaction to Avastin is unknown. However, none of the adverse events in patients developing Avastin antibodies showed any relationship to type I hypersensitivity or to a type III immune complex-mediated reaction.

Immunogenicity data are highly dependent on the sensitivity and specificity of the tests used and may be influenced by several factors, including sample handling, timing of sample collection, drug interactions, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of Avastin antibodies between different indications or with the incidence of antibodies to other therapeutic proteins may be misleading.

Osteonecrosis of the jaw (ONJ)

Cases of ONJ have been reported in cancer patients treated with Avastin, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates, for which ONJ is an identified risk.

Particular caution is therefore required when Avastin and i.v. bisphosphonates are administered simultaneously or sequentially.

Invasive dental procedures are also an additional risk factor.

A dental examination and appropriate preventive dentistry should be considered prior to starting the treatment with Avastin. In patients who have previously received or are receiving i.v. bisphosphonates, invasive dental procedures should be avoided if possible.

Systemic effects following intravitreal use

A reduction of circulating VEGF concentration has been demonstrated following intravitreal anti-VEGF therapy. Systemic adverse reactions including non-ocular hemorrhages and arterial thromboembolic reactions have been reported following intravitreal injection of VEGF inhibitors, and there is a theoretical risk that these may relate to VEGF inhibition.

Ovarian Failure / Fertility (see section 2.5.1 Use in Special Populations, Pregnancy and 2.6.1 Undesirable Effects, Clinical Trials)

Avastin may impair female fertility. Therefore fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with Avastin.

1.9.2 ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machine 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.

1.9.3 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Effect of antineoplastic agents on bevacizumab pharmacokinetics

No clinically relevant pharmacokinetic interaction of co-administered chemotherapy on Avastin pharmacokinetics has been observed based on the results of a population PK analysis. There was neither statistical significance nor clinically relevant difference in clearance of Avastin in patients receiving Avastin monotherapy compared to patients receiving Avastin in combination with Interferon alpha 2a or other chemotherapies (IFL, 5-FU/LV, carboplatin/paclitaxel, capecitabine, doxorubicin or cisplatin/gemcitabine).

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

Results from BO17704 demonstrated no significant effect of bevacizumab on the pharmacokinetics of cisplatin. Due to high inter-patient variability and limited sampling, the results from BO17704 do not allow firm conclusions on the impact of bevacizumab on gemcitabine pharmacokinetics to be drawn.

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 Hypertension, Proteinuria, PRES in section 2.4.1 Warnings and Precautions, General*)

Radiotherapy

There is evidence that infection rates are increased when Avastin is added to radiotherapy (a use unapproved for any disease; see Undesirable effects).

1.10 USE IN SPECIAL POPULATIONS

1.10.1 PREGNANCY

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.

There are no adequate and well-controlled studies in pregnant women (*see section 3.3.4 Teratogenicity*). IgGs are known to cross the placental barrier, and Avastin may inhibit angiogenesis in the foetus. In the post-marketing setting, cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic

chemotherapeutics have been observed (*see section 2.6.2 Undesirable Effects, Post Marketing*).

Therefore, Avastin should not be used during pregnancy. In women with childbearing potential, appropriate contraceptive measures should be used during Avastin therapy. Based on pharmacokinetic considerations, contraceptive measures should be used for at least 6 months following the last dose of Avastin.

Fertility (see section 2.4.1 Warnings and Precautions, General and section 2.6.1 Undesirable Effects, Clinical Trials)

Repeat dose safety studies in animals have shown that bevacizumab may have an adverse effect on female fertility (*see section 3.3 Preclinical Safety*). A substudy with 295 premenopausal women has shown a higher incidence of new cases of ovarian failure in the bevacizumab group compared to the control group. After discontinuation of bevacizumab treatment, ovarian function recovered in the majority of patients. Long term effects of the treatment with bevacizumab on fertility are unknown.

1.10.2 NURSING MOTHERS

It is not known whether bevacizumab is excreted in human milk. As maternal IgG is excreted in milk and Avastin could harm infant growth and development, women should be advised to discontinue nursing during Avastin therapy and not to breast feed for at least 6 months following the last dose of Avastin.

1.10.3 PAEDIATRIC USE

The safety and efficacy of Avastin in children and adolescents has not been established. Avastin is not approved for use in patients under the age of 18 years. In published reports, cases of osteonecrosis at sites other than the jaw have been observed in patients under the age of 18 years exposed to Avastin (*see section 3.3.5 Preclinical Safety, Other (Physeal Development)*).

1.10.4 GERIATRIC USE

Refer to section 2.4.1 under the sub-heading *Arterial Thromboembolism*.

1.10.5 RENAL IMPAIRMENT

The safety and efficacy of Avastin has not been studied in patients with renal impairment.

1.10.6 HEPATIC IMPAIRMENT

The safety and efficacy of Avastin has not been studied in patients with hepatic impairment.

1.11 UNDESIRABLE EFFECTS

1.11.1 CLINICAL TRIALS

Clinical trials have been conducted in patients with various malignancies treated with Avastin, predominantly in combination with chemotherapy. The safety profile from a clinical trial population of approximately 5,200 patients is presented in this section. For post marketing experience see section 2.6.2 Post Marketing below. See section 3.1.2 Clinical/Efficacy Studies for details of major studies, including study designs and major efficacy results.

The most serious adverse drug reactions were

- § Gastrointestinal Perforations (*see section 2.4.1 Warning and Precautions, General*)
- § Haemorrhage including pulmonary haemorrhage/haemoptysis, which is more common in NSCLC patients (*see section 2.4.1 Warning and Precautions, General*)
- § Arterial Thromboembolism (*see section 2.4.1 Warning and Precautions, General*)

Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with Avastin therapy are likely to be dose-dependent.

The most frequently observed adverse drug reactions across clinical trials in patients receiving Avastin were hypertension, fatigue or asthenia, diarrhoea and abdominal pain.

Table 1 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 this table fall into the following categories (Very Common ($\geq 10\%$) and Common ($\geq 1\% - < 10\%$)). Adverse drug reactions are added to the appropriate category in the table below 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, however, Avastin may exacerbate these reactions when combined with chemotherapeutic agents. Examples include palmar-plantar erythrodysesthesia syndrome with pegylated liposomal doxorubicin or capecitabine, peripheral sensory neuropathy with paclitaxel or oxaliplatin, and nail disorders or alopecia with paclitaxel.

Table 1: Very Common and Common Adverse Drug Reactions

System Organ Class (SOC)	NCI-CTC Grade 3-5 Reactions ($\geq 2\%$ difference between the study arms in at least one clinical trial)	All Grade Reactions ($\geq 10\%$ difference between the study arms in at least one clinical trial)

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	<i>Very common</i>	<i>Common</i>	<i>Very Common</i>
<i>Infections and infestations</i>		Sepsis Abscess Cellulitis Infection	
<i>Blood and the lymphatic systems disorders</i>	Febrile neutropenia Leucopenia Neutropenia Thrombocytopenia	Anaemia Lymphopenia	
<i>Metabolism and nutrition disorders</i>		Dehydration	Anorexia
<i>Nervous system disorders</i>	Peripheral sensory neuropathy	Cerebrovascular accident Syncope Somnolence Headache	Dysgeusia Headache Dysarthria
<i>Eye disorders</i>			Eye disorder Lacrimation increased
<i>Cardiac disorders</i>		Cardiac failure congestive Supraventricular tachycardia	
<i>Vascular disorders</i>	Hypertension	Thromboembolism (arterial) Deep vein thrombosis Haemorrhage	Hypertension
<i>Respiratory, thoracic and mediastinal disorders</i>		Pulmonary embolism Dyspnoea Hypoxia Epistaxis	Dyspnoea Epistaxis Rhinitis
<i>Gastrointestinal disorders</i>	Diarrhoea Nausea Vomiting Abdominal pain	Intestinal Perforation Ileus Intestinal obstruction Recto-vaginal fistulae ** Gastrointestinal disorder Stomatitis Proctalgia	Constipation Stomatitis Rectal haemorrhage Diarrhoea
<i>Endocrine disorders</i>			Ovarian failure*
<i>Skin and subcutaneous tissue disorders</i>		Palmar-plantar erythrodysesthesia syndrome	Exfoliative dermatitis Dry skin Skin discolouration
<i>Musculoskeletal, connective tissue and bone disorders</i>		Muscular weakness Myalgia Arthralgia Back pain	Arthralgia

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Renal and urinary disorders		Urinary Tract Infection	Proteinuria
General disorders and administration site conditions	Asthenia Fatigue	Pain Lethargy Mucosal inflammation	Pyrexia Asthenia Pain Mucosal inflammation
Reproductive System and Breast Investigations		Pelvic pain	
			Weight decreased

*Based on a substudy from AVF3077s (NSABP C-08) with 295 patients

** Recto-vaginal fistulae are the most common fistulae in the GI-vaginal fistula category

Further information on selected, serious adverse drug reactions:

The following adverse drug reactions, reported using NCI-CTC (common toxicity criteria) for assessment of toxicity, have been observed in patients treated with Avastin.

Gastrointestinal Perforation and Fistulae (see section 2.4.1 Warnings and Precautions, General)

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, up to 2% in patients with metastatic renal cell cancer, or ovarian cancer receiving front-line treatment, and up to 2.7% (including gastrointestinal fistula and abscess) in patients with metastatic colorectal cancer. Cases of GI perforations have also been observed in patients with relapsed glioblastoma.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), GI perforations (all grade) were reported in 3.2% of patients, all of whom had a history of prior pelvic radiation.

The occurrence of those 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.

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.

In Avastin clinical trials, gastrointestinal fistulae (all grade) have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer and ovarian cancer, but were also reported less commonly in patients with other types of cancer.

In a trial of patients with persistent, recurrent or metastatic cervical cancer, the incidence of GI-vaginal fistulae was 8.3% in Avastin-treated patients and 0.9% in control patients, all of whom had a history of prior pelvic radiation. Patients who develop GI-vaginal fistulae may also have bowel obstructions and require surgical intervention as well as diverting ostomies.

Non-GI Fistulae (see section 2.4.1 Warnings and Precautions, General)

Avastin use has been associated with serious cases of fistulae including events resulting in death.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (GOG-240), 1.8% of Avastin-treated patients and 1.4% of control patients were reported to have had non-gastrointestinal vaginal, vesical, or female genital tract fistulae.

Uncommon ($\geq 0.1\%$ to $< 1\%$) reports of fistulae that involve areas of the body other than the gastrointestinal tract (e.g. bronchopleural, 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.

Haemorrhage

In clinical trials across all indications the overall incidence of NCI-CTC Grade 3-5 bleeding events ranged from 0.4% to 6.9% in Avastin-treated patients, compared to 0 to 4.5% of patients in the chemotherapy control group. The haemorrhagic events that have been observed in Avastin clinical studies were predominantly tumour-associated haemorrhage (see below) and minor mucocutaneous haemorrhage (e.g. epistaxis).

- 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 (see 2.4.1 General (Warnings and Precautions)).

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

Tumour-associated haemorrhages were also seen rarely in other tumour types and locations and included cases of central nervous system (CNS) bleeding in patients with CNS metastases and in patients with glioblastoma.

The incidence of CNS bleeding in patients with untreated CNS metastases receiving bevacizumab has not been prospectively 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 bevacizumab, compared to 1 case (Grade 5) out of 96 patients (1%) that were not exposed to bevacizumab. In two subsequent studies in patients with treated brain metastases (which included around 800 patients), one case of Grade 2 CNS haemorrhage was reported

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

Across all Avastin clinical trials, *mucocutaneous haemorrhages* were seen in up to 50% of patients treated with Avastin. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any change in the Avastin treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous haemorrhage (e.g. epistaxis) may be dose-dependent.

There have also been less common events of minor mucocutaneous haemorrhage in other locations, such as gingival bleeding or vaginal bleeding.

Hypertension (see section 2.4.1 Warnings and Precautions, General)

An increased incidence of hypertension (all grades) of up to 42.1% 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 NCI-CTC Grade 3 and 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 adequately controlled 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 section 2.4.1, Warnings and Precautions, General*). The risk of Avastin-associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy.

Posterior Reversible Encephalopathy Syndrome (see section 2.4.1 Warnings and Precautions, General)

Two confirmed cases (0.8%) of PRES have been reported in one clinical study. Symptoms usually resolve or improve within days, although some patients have experienced neurologic sequelae.

Thromboembolism

- Arterial thromboembolism

An increased incidence of arterial thromboembolic events was observed in patients treated with Avastin across indications including cerebrovascular accidents, myocardial infarction, transient ischemic attacks, and other arterial thromboembolic events.

In clinical trials, the overall incidence ranged up to 5.9% in the Avastin containing arms compared 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 ischemic 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.

In one clinical trial, AVF2192g, patients with metastatic colorectal cancer who were not candidates for treatment with irinotecan were included. In this trial arterial thromboembolic events were observed in 11% (11/100) of Avastin patients compared to 5.8% (6/104) in the chemotherapy control group. In an uncontrolled clinical trial, AVF3708g, in patients with relapsed glioblastoma, arterial thromboembolic events were observed in 6.3% (5/79) of patients who received Avastin in combination with irinotecan compared to 4.8% (4/84) of patients who received Avastin alone.

Venous thromboembolism (see section 2.4.1 Warnings and Precautions, General)

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.

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 chemotherapy 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 chemotherapy alone.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), grade 3-5 venous thromboembolic events have been reported in up to 10.6% of patients treated with chemotherapy and bevacizumab compared with up to 5.4% in patients with chemotherapy alone.

Congestive Heart Failure

In clinical trials with Avastin, congestive heart failure (CHF) was observed in all cancer indications studied to date, but occurred predominantly in patients with metastatic breast cancer. In five phase III studies (AVF2119g, E2100, BO17708, AVF3694g and AVF3693g) in patients with metastatic breast cancer CHF Grade 3 or higher was reported in up to 3.5% of patients treated with Avastin in combination with chemotherapy compared with up to 0.9% in the control arms. For patients in study AVF3694g who received anthracyclines concomitantly with bevacizumab, the incidences of grade 3 or higher CHF for the respective bevacizumab and control arms were similar to those in the other studies in metastatic breast cancer: 2.9% in the anthracycline + bevacizumab arm and 0% in the anthracycline + placebo arm. In addition, in study AVF3694g the incidences of all grade CHF were similar between the anthracycline + Avastin (6.2%) and the anthracycline + placebo arms (6.0%).

Most patients who developed CHF during mBC trials 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 (*see section 2.4.1 Warnings and Precautions, General*).

An increased incidence of CHF has been observed in a clinical trial of patients with diffuse large B-cell lymphoma when receiving bevacizumab with a cumulative doxorubicin dose greater than 300 mg/m²[89]. This phase III clinical trial compared rituximab/cyclophosphamide/doxorubicin/vincristine/ prednisone (R-CHOP) plus bevacizumab to R-CHOP without bevacizumab. While the incidence of CHF was, in both arms, above that previously observed for doxorubicin therapy [90, 91], the rate was higher in the R-CHOP plus bevacizumab arm.

Wound Healing (see section 2.4.1 Warnings and Precautions, General)

As Avastin may adversely impact wound healing, patients who had major surgery within the last 28 days prior to starting Avastin treatment were excluded from participation in phase III trials.

Across mCRC 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).

Cases of serious wound healing complications have been reported during Avastin use, some of which had a fatal outcome (*see section 2.4.1 Warnings and Precautions, General*).

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In locally recurrent and metastatic breast cancer trials, Grade 3-5 wound healing complications were observed in up to 1.1% of patients receiving Avastin compared with up to 0.9% of patients in the control arms.

In a study of patients with relapsed glioblastoma (study AVF3708g), the incidence of post-operative wound healing complications (including 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 plus irinotecan.

Proteinuria (see section 2.4.1 Warnings and Precautions, General)

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 up to 8.1% of treated 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.

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 related to Avastin dose. Testing for proteinuria is recommended prior to start of Avastin therapy. In most clinical studies urine protein levels of $\geq 2\text{g} / 24\text{ hrs}$ led to the holding of Avastin until recovery to $< 2\text{g} / 24\text{ hrs}$.

Hypersensitivity, infusion reactions (see section 2.4.1 Warnings and Precautions, General and section 2.6.2 Undesirable Effects, Post Marketing)

In some clinical trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving Avastin in combination with chemotherapies than with chemotherapy alone. The incidence of these reactions in some clinical trials of Avastin is common (up to 5% in bevacizumab-treated patients).

Ovarian Failure / Fertility (see section 2.4.1 Warnings and Precautions, General and section 2.5.1 Use in Special Populations, Pregnancy)

The incidence of new cases of ovarian failure, defined as amenorrhoea lasting 3 or more months, FSH level $\geq 30\text{ mIU/mL}$ and a negative serum $\beta\text{-HCG}$ pregnancy test, has been evaluated. New cases of ovarian failure were reported more frequently in patients receiving bevacizumab. After discontinuation of bevacizumab treatment, ovarian function recovered in a majority of women. Long term effects of the treatment with bevacizumab on fertility are unknown.

Infections (see section 2.4.1 Warnings and Precautions, General)

A randomised, double-blind, placebo-controlled study of Avastin combined with chemotherapy plus radiotherapy (a use unapproved for any disease) showed that adding Avastin increased the rate of any-grade and Grade 3–5 infection compared to chemotherapy or radiotherapy alone.

Elderly Patients

In randomised clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic events including cerebrovascular accidents, transient ischemic attacks and myocardial infarction as compared to those aged ≤65 years when treated with Avastin (see sections 2.4.1 Warnings and Precautions, General and 2.6.1 Undesirable Effects, Clinical Trials, Thromboembolism). Other reactions with a higher frequency seen in patients over 65 were Grade 3-4 leucopenia, thrombocytopenia; and all Grade neutropenia, diarrhoea, nausea, headache and fatigue.

From a clinical trial in patients with metastatic colorectal cancer (study AVF2107), no increase in the incidences of other reactions, including gastrointestinal perforation, wound healing complications, congestive heart failure and haemorrhage, was observed in elderly patients (> 65 years) receiving Avastin as compared to those aged ≤ 65 years treated with Avastin.

Osteonecrosis of the jaw (see Warnings and precautions)

Cases of osteonecrosis of the jaw have been reported in patients treated with Avastin. Most of these cases occurred in patients with known risk factors for developing osteonecrosis of the jaw, including in particular a history of intravenous bisphosphonate use and/or dental disease requiring invasive dental procedures.

1.11.1.1 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 PT (prothrombin time), normalised ratio.

1.11.2 POST MARKETING

Table 2: Adverse reactions reported in post-marketing setting

System Organ Class (SOC)	Reactions (frequency*)
Congenital, familial and genetic disorders	Cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see section 2.5.1 Use in Special Populations, Pregnancy).

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Nervous system disorders	Hypertensive encephalopathy (very rare**) (see section 2.4 Warnings and Precautions, and section 2.6.1 Undesirable Effects, Clinical Trials) Posterior Reversible Encephalopathy Syndrome (PRES), (rare***) (see section 2.4 Warnings and Precautions)
Vascular Disorders	Renal Thrombotic Microangiopathy, clinically manifested as proteinuria (frequency not known). For further information on proteinuria see section 2.4 Warnings and Precautions, and Proteinuria in section 2.6.1 Undesirable Effects, Clinical Trials.
Respiratory, thoracic and mediastinal disorders	Nasal septum perforation (frequency not known) Pulmonary hypertension (frequency not known) Dysphonia (common****)
Gastrointestinal disorders	Gastrointestinal ulcer (frequency not known)
Hepatobiliary disorders	Gallbladder perforation (frequency not known)
Immune system disorders	Hypersensitivity, infusion reactions (frequency not known); with the following possible co-manifestations: dyspnoea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting.
Eye disorders (reported from unapproved intravitreal use)	Infectious endophthalmitis ⁴ (some cases leading to permanent blindness) (frequency not known); Intraocular inflammation ^{1,5} (some cases leading to permanent blindness) such as sterile endophthalmitis, uveitis, and vitritis; Retinal detachment (frequency not known); Retinal pigment epithelial tear (frequency not known); Intraocular pressure increased (frequency not known); Intraocular hemorrhage such as vitreous hemorrhage or retinal hemorrhage (frequency not known); Conjunctival hemorrhage (frequency not known). An observational claims database ¹ study comparing unapproved intravitreal Avastin to an approved treatment in patients treated for wet age-related macular degeneration has reported an increased risk of intraocular inflammation for Avastin (adjusted HR: 1.82; 99% CI: 1.20, 2.76) (Incidence 0.46 events per 100 patients per year; comparator 0.26 events per 100 patients per year) as well as an increased risk for cataract surgery (adjusted HR: 1.11; 99% CI: 1.01, 1.23) (Incidence 6.33 events per 100 patients per year; comparator 5.64 events per 100 patients per year). Following variable and non-validated methods in compounding ⁵ , storage, and handling of Avastin, serious ocular adverse events (including infectious endophthalmitis and other ocular inflammatory conditions) affecting multiple patients have been reported.

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<p>Systemic Events (reported from unapproved intravitreal use)</p>	<p>An observational claims database¹ study comparing unapproved intravitreal Avastin to an approved treatment in patients treated for wet age-related macular degeneration has reported an increased risk of hemorrhagic stroke for Avastin (adjusted HR: 1.57; 99% CI: 1.04, 2.37) (Incidence 0.41 events per 100 patients per year; comparator 0.26 events per 100 patients per year) as well as an increased risk for overall mortality (adjusted HR: 1.11; 99% CI: 1.01, 1.23) (Incidence 6.03 events per 100 patients per year; comparator 5.51 events per 100 patients per year). A second observational study found similar results for all-cause mortality². A randomized controlled clinical trial comparing unapproved Avastin to an approved treatment for patients with wet age-related macular degeneration³ has reported an increased risk of serious systemic adverse events for Avastin, most of which resulted in hospitalization (adjusted risk ratio 1.29; 95% CI: 1.01, 1.66) (Incidence 24.1%; comparator 19.0%).</p>
<p>Musculoskeletal and Connective Tissue disorders</p>	<p>Cases of Osteonecrosis of the Jaw (ONJ) have been observed in Avastin treated patients mainly in association with prior or concomitant use of bisphosphonates.</p> <p><i>Cases of osteonecrosis at sites other than the jaw, have been observed in Avastin treated paediatric patients (see section 2.5.4 Use in special populations, paediatric use)</i>⁶.</p>
<p>Infections and Infestations</p>	<p>Necrotising fasciitis, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation (rare) (see section 2.4.1 Warnings and Precautions, General).</p>

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

¹ Gower et al. Adverse Event Rates Following Intravitreal Injection of Avastin or Lucentis for Treating Age-Related Macular Degeneration ARVO 2011, Poster 6644, Data on file

² Curtis LH, et al. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration. Arch Ophthalmol. 2010;128(10):1273-1279

³ CATT Research Group, Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration. 10.1056/NEJMoa1102673

⁴ One case reported extraocular extension of infection resulting in meningoencephalitis [103]

⁵ Including a cluster of serious eye inflammation leading to blindness after compounding an anticancer chemotherapy product for iv administration [103]

⁶ Osteonecrosis observed in pediatric population in non-company clinical trials was identified through post-marketing surveillance and has therefore been added to the post-marketing section as neither CTC grade nor reporting rate were available from published data.

** very rare (<1/10,000)

*** rare (≥1/10,000 to <1/1,000)

**** common (≥1/100 to <1/10)

1.12 OVERDOSE

The highest dose tested in humans (20 mg/kg of body weight every 2 weeks, intravenous) was associated with severe migraine in several patients.

2. PHARMACOLOGICAL PROPERTIES AND EFFECTS

2.1 PHARMACODYNAMIC PROPERTIES

2.1.1 MECHANISM OF ACTION

Avastin (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. Bevacizumab consists of 214 amino acids and has a molecular weight of approximately 149,000 daltons.

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.

2.1.2 CLINICAL / EFFICACY STUDIES

Metastatic Colorectal Cancer (mCRC)

The safety and efficacy of the recommended dose of Avastin (5 mg/kg of body weight every two weeks) in metastatic carcinoma of the colon or rectum were studied in three randomised, active-controlled clinical trials in combination with fluoropyrimidine-based first-line chemotherapy. Avastin was combined with two chemotherapy regimens:

- § **AVF2107g:** A weekly schedule of irinotecan/bolus 5-fluorouracil/leucovorin (IFL regimen) for a total of 4 weeks of each 6 week cycle.
- § **AVF0780g:** In combination with bolus 5-fluorouracil/leucovorin (5-FU/LV) for a total of 6 weeks of each 8 week cycle (Roswell Park regimen).
- § **AVF2192g:** In combination with bolus 5-fluorouracil/leucovorin (5-FU/LV) for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen) in patients who were not optimal candidates for first-line irinotecan treatment.

Three additional studies with Avastin have been conducted in mCRC patients: first-line (NO16966), second-line with no previous Avastin treatment (E3200), and second-line with previous Avastin treatment following disease progression in first-line (ML18147). In these studies, Avastin was administered at the following dosing regimens, in combination with FOLFOX-4 (5FU/LV/oxaliplatin), XELOX (capecitabine/oxaliplatin), and fluoropyrimidine/irinotecan and fluoropyrimidine/oxaliplatin:

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- § **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 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4).
- § **E3200:** Avastin 10 mg/kg of body weight every 2 weeks in combination with leucovorin and 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4) in Avastin naïve patients.
- § **ML18147:** Avastin 5.0 mg/kg of body weight every 2 weeks or Avastin 7.5 mg/kg of body weight every 3 weeks in combination with fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin in patients with disease progression following first-line treatment with Avastin. Use of irinotecan- or oxaliplatin-containing regimen was switched depending on first-line usage of either oxaliplatin or irinotecan.

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 carcinoma of the colon or rectum [3, 7]. Eight hundred and thirteen patients were randomised to receive IFL + placebo (Arm 1) or IFL+Avastin (5 mg/kg every 2 weeks, Arm 2). A third group of 110 patients received bolus 5-FU/LV+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 primary efficacy parameter of the trial was overall survival. The addition of Avastin to IFL resulted in statistically significant increases in overall survival, progression-free survival and overall response rate (see Table 3 for details). The clinical benefit of Avastin, as measured by survival, was seen in all pre-specified patient subgroups, including those defined by age, sex, performance status, location of primary tumour, number of organs involved, and duration of metastatic disease.

Table 3 Efficacy Results for Study AVF2107g

	AVF2107g	
	Arm 1 IFL + Placebo	Arm 2 IFL + Avastin ^a
Number of Patients	411	402
<u>Overall Survival</u>		
Median (months)	15.6	20.3
95% confidence interval	14.29 – 16.99	18.46 – 24.18
Hazard ratio ^b	0.660 (p-value = 0.00004)	
<u>Secondary endpoint: Progression-Free Survival</u>		
Median (months)	6.2	10.6

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Hazard ratio	0.54 (p-value < 0.00001)	
Overall Response Rate	34.8%	44.8%
	(p-value = 0.0036)	

^a 5 mg/kg every 2 weeks

^b Relative to control arm

Among the 110 patients randomised to Arm 3 (5-FU/LV + Avastin) prior to discontinuation of this arm, the median overall survival was 18.3 months, and the median progression free survival was 8.8 months.

AVF2192g

This was a phase II randomised, double-blind, active-controlled clinical trial investigating Avastin in combination with 5-FU/leucovorin as first-line treatment for metastatic colorectal cancer in patients who were not optimal candidates for first-line irinotecan treatment. One hundred and five patients were randomised to 5-FU/LV+placebo arm and 104 patients randomised to 5-FU/LV+Avastin (5 mg/kg every 2 weeks). All treatments were continued until disease progression.

The addition of Avastin 5 mg/kg every two weeks to 5-FU/LV resulted in higher objective response rates, significantly longer progression-free survival, and a trend in longer survival as, compared with 5-FU/LV chemotherapy alone.

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 i.v. oxaliplatin (XELOX), administered on a 3-weekly schedule; or Avastin 5 mg/kg in combination with leucovorin with 5-fluorouracil bolus, followed by 5-fluorouracil infusional, with i.v. oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule. The study contained two parts: 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 4 study arms in the Part II of the trial.

Table 4 Treatment Regimens in Study N016966 (mCRC)

	Treatment	Starting Dose	Schedule
FOLFOX-4 or FOLFOX-4 + Avastin	Oxaliplatin	85 mg/m ² IV 2 h	Oxaliplatin on Day 1
	Leucovorin	200 mg/m ² IV 2 h	Leucovorin on Day 1 and 2
	5-Fluorouracil	400 mg/m ² IV bolus, 600 mg/ m ² IV 22 h	5-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	130 mg/m ² IV 2 h	Oxaliplatin on Day 1
	Capecitabine	1000 mg/m ² oral bid	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
5-Fluorouracil: IV bolus injection immediately after leucovorin			

The primary efficacy parameter of the trial was the duration of progression-free survival. 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:

- i) Non-inferiority of the XELOX-containing arms compared with the FOLFOX-4-containing arms in the overall comparison was demonstrated in terms of progression-free survival and overall survival in the eligible per-protocol population.
- ii) 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 (Table 5).

Secondary PFS analyses, based on Independent Review Committee (IRC)- and ‘on-treatment’-based response assessments, confirmed the significantly superior clinical benefit for patients treated with Avastin (subgroup analyses shown in Table 5), consistent with the statistically significant benefit observed in the pooled analysis.

**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)**	7.9	10.4	<0.0001
Hazard ratio (97.5% CI)	0.63 (0.52-0.75)		
Median PFS (Indep. review)**	8.5	11.0	<0.0001
Hazard ratio (97.5% CI)	0.70 (0.58-0.83)		
Overall response rate (Invest. Assessment)**	49.2%,	46.5%	
Overall response rate (Indep. Review)**	37.5%	37.5%	
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

ECOG E3200

This was a phase III randomised, active-controlled, open-label study investigating Avastin 10 mg/kg in combination with leucovorin with 5-fluorouracil bolus and then 5-fluorouracil infusional, with iv 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 randomization 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
<u>Overall Survival</u>		
Median (months)	10.8	13.0
95% confidence interval	10.12 – 11.86	12.09 – 14.03
Hazard ratio ^b	0.751 (p-value = 0.0012)	
<u>Progression-Free Survival</u>		
Median (months)	4.5	7.5
Hazard ratio	0.518 (p-value < 0.0001)	
<u>Objective Response Rate</u>		
Rate	8.6 %	22.2 % (p-value < 0.0001)

^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.

ML18147

This was a Phase III randomized, controlled, open-label trial investigating Avastin 5.0 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks in combination with fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone in patients with metastatic colorectal cancer who have progressed on a first-line Avastin-containing regimen.

Patients with histologically confirmed mCRC and disease progression were randomized 1:1 within 3 months after discontinuation of Avastin first-line therapy to receive fluoropyrimidine/oxaliplatin or fluoropyrimidine/irinotecan-based chemotherapy (chemotherapy switched depending on first-line chemotherapy) with or without Avastin. Treatment was given until progressive disease or unacceptable toxicity. The primary outcome measure was overall survival (OS) defined as the time from randomization until death from any cause.

A total of 820 patients were randomized. The addition of Avastin to fluoropyrimidine-based chemotherapy resulted in a statistically significant prolongation of survival in patients with metastatic colorectal cancer who have progressed on a first-line Avastin-containing regimen (ITT = 819) (see Table 7).

Table 7 Efficacy Results for Study ML18147

	ML18147	
	fluoropyrimidine/irinotecan or fluoropyrimidine/oxaplatin based chemotherapy	fluoropyrimidine/irinotecan or fluoropyrimidine/oxaplatin based chemotherapy+ Avastin ^a
Number of Patients	410	409
Overall Survival		
Median (months)	9.8	11.2
95% confidence interval	9-11	10-12
Hazard ratio	0.81 (p-value = 0.0062)	
Progression-Free Survival		
Median (months)	4.1	5.7
Hazard ratio	0.68 (p-value < 0.0001)	
Objective Response Rate (ORR)		
Rate	3.9%	5.4%
	(p-value = 0.3113)	

^a 2.5 mg/kg/week

Statistically significant improvements in progression-free survival were also observed. Objective response rate was low in both treatment arms and did not meet statistical significance.

Adjuvant Colon Cancer (aCC)

BO17920

This was a phase III randomized open-label, 3-arm study evaluating the efficacy and safety 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 versus FOLFOX4 alone as adjuvant chemotherapy in 3451 patients with high-risk stage II and stage III colon carcinoma.

More relapses and deaths due to disease progression were observed in both Avastin arms compared to the control arm. The primary objective of prolonging disease free survival (DFS) in patients with stage III colon cancer (n = 2867) by adding Avastin to either chemotherapy regimen was not met. The hazard ratios for DFS were 1.17 (95% CI: 0.98-1.39) for the FOLFOX4 + Avastin arm and 1.07 (95% CI: 0.90-1.28) for the XELOX + Avastin arm.

Locally recurrent or metastatic Breast Cancer (mBC)

ECOG E2100

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.

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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 8.

Table 8 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=273)	Paclitaxel/Avastin (n=252)	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

Overall Survival		
	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	

BO17708

BO17708 was a randomised, double-blind, placebo-controlled, multicentre (phase III) trial to evaluate the efficacy and safety of Avastin in combination with docetaxel compared with docetaxel plus placebo, as first-line treatment for patients with HER2-negative metastatic or locally recurrent breast cancer who have not received prior chemotherapy for their metastatic disease.

Patients were randomised in a 1:1:1 ratio to treatment with either

- placebo + docetaxel 100 mg/m² every 3 weeks
- Avastin 7.5 mg/kg + docetaxel 100 mg/m² every 3 weeks
- Avastin 15 mg/kg + docetaxel 100 mg/m² every 3 weeks.

Docetaxel treatment was limited to a maximum of 9 cycles, while Avastin or placebo was continued until disease progression/death or unacceptable toxicity. The patient and disease characteristics were similar across the three arms.

On documented disease progression, patients from all three treatment arms could enter into a post-study treatment phase during which they received open-label Avastin together with a wide-range of second line therapies.

The primary endpoint was progression free survival (PFS), as assessed by investigators. For the efficacy endpoints two comparisons were performed:

- Avastin 7.5 mg/kg + docetaxel 100 mg/m² every 3 weeks versus placebo + docetaxel 100 mg/m² every 3 weeks
- Avastin 15 mg/kg + docetaxel 100 mg/m² every 3 weeks vs placebo + docetaxel 100 mg/m² every 3 weeks.

The results of this study are presented in Table 9. For progression free survival and response rates this includes results from the pre-specified final analysis and results from an exploratory (updated) analysis carried out at the same time as the pre-specified final OS analysis which included an additional 18 months of follow up. Overall survival results presented are those from the pre-specified final analysis for OS. At this point approximately 45% of patients across all treatment arms had died.

The updated analysis shows:

- Avastin 15 mg/kg q 3weeks + Docetaxel is consistently associated with better primary and secondary efficacy outcomes with similar safety compared with Avastin 7.5 mg/kg q 3weeks + Docetaxel
- Avastin 7.5 mg/kg q 3weeks + Docetaxel is not superior to control for PFS and response rates.

Therefore the 15 mg/kg q 3weeks dose is recommended for treatment in patients with mBC (*see section 2.2 Dosage and Administration*).

Table 9 Efficacy results for study BO17708

Progression-free survival			
	Docetaxel + Placebo q 3 weeks (n=241)	Docetaxel + Avastin 7.5 mg/kg q 3 weeks (n=248)	Docetaxel + Avastin 15 mg/kg q 3 weeks (n=247)
Median PFS (months)	8.0	8.7	8.8
[updated analysis]	[8.2]	[9.0]	[10.1]
Hazard ratio vs placebo arm (95% CI)		0.79 (0.63–0.98)	0.72 (0.57–0.90)
[updated analysis]		[0.86] [0.72;1.04]	[0.77] [0.64;0.93]
P value (log rank test) vs placebo arm [exploratory p value from updated analysis]		0.0318 [0.1163]	0.0099 [0.0061]
Progression-free survival (sensitivity analysis) *			
	Docetaxel + Placebo q 3 weeks (n=241)	Docetaxel + Avastin 7.5 mg/kg q 3 weeks (n=248)	Docetaxel + Avastin 15 mg/kg q 3 weeks (n=247)
Median PFS (months)	8.0	8.7	8.8
[updated analysis]	[8.1]	[9.0]	[10.0]
Hazard ratio vs placebo arm (95% CI)		0.69 (0.54–0.89)	0.61 (0.48–0.78)
[updated analysis]		[0.80] [0.65; 1.00]	[0.67] [0.54; 0.83]
P value (log rank test) vs placebo arm [exploratory p value from updated analysis]		0.0035 [0.0450]	0.0001 [0.0002]
Response rates (for patients with measurable disease)			
	Docetaxel + Placebo q 3 weeks (n=207)	Docetaxel + Avastin 7.5 mg/kg q 3 weeks (n=201)	Docetaxel + Avastin 15 mg/kg q 3 weeks (n=206)
% pts with objective response	44.4	55.2	63.1
[updated analysis]	[46.4]	[55.2]	[64.1]
p-value vs placebo arm [exploratory p value from updated analysis]		0.0295 [0.0739]	0.0001 [0.0003]
Overall Survival			
	Docetaxel + Placebo q 3 weeks (n=241)	Docetaxel + Avastin 7.5 mg/kg q 3 weeks (n=248)	Docetaxel + Avastin 15 mg/kg q 3 weeks (n=247)
Median OS (months)	31.9	30.8	30.2

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HR (95% CI)		1.05 (0.81;1.36)	1.03 (0.79;1.33)
p-value		0.7198	0.8528

* Stratified analysis which included all progression and death events except those where non-protocol therapy (NPT) was initiated prior to documented progression - those patients were censored at the last tumor assessment prior to the start of NPT.

AVF3694g

Study AVF3694g was a Phase III, multicentre, randomised, placebo-controlled trial designed to evaluate the efficacy and safety of Avastin in combination with chemotherapy compared to chemotherapy plus placebo as first-line treatment for patients with HER2-negative metastatic or locally recurrent breast cancer.

Chemotherapy was chosen at the investigator's discretion prior to randomization in a 2:1 ratio to receive either chemotherapy + Avastin or chemotherapy + placebo. The choices of chemotherapy included taxane (protein-bound paclitaxel, docetaxel), anthracycline-based agents (doxorubicin/ cyclophosphamide, epirubicin/ cyclophosphamide, 5-fluorouracil/ doxorubicin/ cyclophosphamide, 5-fluorouracil/ epirubicin/ cyclophosphamide) or capecitabine given every three weeks (q3w). Avastin or placebo was administered at a dose of 15 mg/kg q3w.

This study included a blinded treatment phase, an optional open-label post-progression phase, and a survival follow-up phase. During the blinded treatment phase, patients received chemotherapy and study drug (Avastin or placebo) every 3 weeks until disease progression, treatment-limiting toxicity, or death.

On documented disease progression, patients who entered the optional open label phase could receive open label Avastin together with a wide-range of second line therapies. The percentage of patients in each arm who received open-label Avastin were: Taxane/Anth + Placebo: 43.0 %, Taxane/Anth + Avastin: 29.6% and Cap + Placebo: 51.9%, Cap + Avastin 34.7%.

Patients were analyzed in the two cohorts depending on the treatment they received as follows:

- Patients receiving taxane/anthracycline + Avastin/placebo (Taxane/Anth + Avastin/PI) – Cohort 1
- Patients receiving capecitabine + Avastin/placebo (Cap + Avastin/PI) – Cohort 2

The primary endpoint was progression free survival (PFS) based on investigator assessment for 1) patients receiving either taxane therapy or anthracycline-based therapy (Cohort 1); and 2) patients receiving capecitabine therapy (Cohort 2). Each cohort was independently powered. In addition, an independent review of the primary endpoint was also conducted.

The results of this study from the final protocol defined analyses for progression free survival and response rates are presented in Table 10 (Cohort 1) and Table 11 (Cohort 2). Results from an exploratory overall survival analysis which include an additional 7 months of follow-up are also presented for both cohorts. At this point approximately 45% of patients across all treatment arms had died.

**Table 10 Efficacy results for study AVF3694g: Cohort 1 –Taxane/
 Anthracycline and Avastin/Placebo (Taxane/Anth + Avastin/PI)**

Progression-free survival*				
	Investigator Assessment		IRC Assessment	
	Taxane/Anth + PI (n= 207)	Taxane/Anth + Avastin (n=415)	Taxane/Anth + PI (n= 207)	Taxane/Anth + Avastin (n=415)
Median PFS (months)	8.0	9.2	8.3	10.7
Hazard ratio vs placebo arm (95% CI)	0.64 (0.52; 0.80)		0.77 (0.60; 0.99)	
p-value	<0.0001		0.040	
Response rate (for patients with measurable disease)*				
	Taxane/Anth + PI (n= 177)		Taxane/Anth + Avastin (n=345)	
% pts with objective response	37.9		51.3	
p-value	0.0054			
Overall survival*				
Median OS (months)	NR**		27.5	
HR (95% CI)	1.11 (0.86, 1.43)			
p-value (exploratory)	0.44			

*Stratified analysis included all progression and death events except those where non-protocol therapy (NPT) was initiated prior to documented progression; data from those patients were censored at the last tumor assessment prior to starting NPT.

** Not reached

**Table 11 Efficacy results for study AVF3694g: Cohort 2 –
 Capecitabine and Avastin/Placebo (Cap+ Avastin/PI)**

Progression-free survival*				
	Investigator Assessment		IRC Assessment	
	Cap + PI (n= 206)	Cap + Avastin (n=409)	Cap + PI (n= 206)	Cap + Avastin (n=409)
Median PFS (months)	5.7	8.6	6.2	9.8
Hazard ratio vs placebo arm (95% CI)	0.69 (0.56; 0.84)		0.68 (0.54; 0.86)	
p-value	0.0002		0.0011	
Response rate (for patients with measurable disease)*				
	Cap + PI (n= 161)		Cap + Avastin (n=325)	
% pts with objective response	23.6		35.4	
p-value	0.0097			
Overall survival*				
Median OS (months)	22.8		25.7	

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HR (95% CI)	0.88 (0.69, 1.13)
p-value (exploratory)	0.33

*Stratified analysis included all progression and death events except those where non-protocol therapy (NPT) was initiated prior to documented progression; data from those patients were censored at the last tumor assessment prior to starting NPT.

For both cohorts, an unstratified analysis of PFS (investigator assessed) was performed that did not censor for non-protocol therapy prior to disease progression. The results of these analyses were very similar to the primary PFS results.

AVF3693g

Study AVF3693g was a Phase III, multicentre, randomised, placebo-controlled double-blinded trial designed to evaluate the efficacy and safety of Avastin in combination with chemotherapy compared with chemotherapy plus placebo for treatment of patients with metastatic breast cancer who have failed first-line chemotherapy. The choices of chemotherapy included taxane (paclitaxel, protein-bound paclitaxel, docetaxel), gemcitabine, capecitabine or vinorelbine. Chemotherapy was chosen at the investigator's discretion prior to randomisation 2:1 to receive either chemotherapy + Avastin or chemotherapy + placebo. The dose of Avastin/placebo administered in this study was 15 mg/kg intravenously every 3 weeks (q3w) or 10 mg/kg every 2 weeks (q2w), depending on the schedule of chemotherapy chosen:

- Taxane
 - Paclitaxel: 90 mg/m² IV every week for 3 weeks followed by 1 week of rest
 - Paclitaxel: 175 mg/m² IV every 3 weeks
 - Paclitaxel protein-bound particles: 260 mg/m² IV every 3 weeks
 - Docetaxel: 75–100 mg/m² IV every 3 weeks
- Gemcitabine: 1250 mg/m² IV on Days 1 and 8 of each 3-week cycle
- Capecitabine: 1000 mg/m² orally twice daily on Days 1–14 of each 3-week cycle
- Vinorelbine: 30 mg/m² IV every week

The study included a blinded treatment phase, an optional open-label extended treatment phase, and a survival follow-up phase. During the blinded treatment phase, patients received chemotherapy and study drug (Avastin or placebo) until disease progression, treatment-limiting toxicity, discontinuation per investigator decision, or death due to any cause.

The primary endpoint was PFS, as assessed by investigators, pooled across all chemotherapy cohorts. The results of the key endpoints in this study are summarized in Table 12. An unstratified analysis of PFS was performed; results of this analysis was similar to those of the primary PFS analysis.

The results based on the interim analysis (57% of events) of overall survival is summarized in Table 12. This interim analysis was performed at the same time as the primary analysis of PFS.

Table 12 Efficacy results for study AVF3693g:

Progression-free survival*		
	Chemo + Placebo (n = 225)	Chemo + Avastin (n = 459)
Median PFS (months)	5.1	7.2
Hazard ratio relative to placebo (95% CI)	0.78 (0.64, 0.93)	
p-value	0.0072	
Response rate (for patients with measurable disease)*		
	Chemo + Placebo (n = 179)	Chemo + Avastin (n = 362)
% pts with objective response	29.6	39.5
p-value	0.0193**	
Interim Overall survival*		
Median OS (months)	16.4	18.0
Hazard ratio (95% CI)	0.90 (0.71, 1.14)	
p-value	0.3741	

* Stratified analysis

** Based on alpha = 0.01

The study was not powered for individual chemotherapy cohorts however progression-free-survival by chemotherapy cohorts was a pre-specified secondary endpoint. All the chemotherapy cohorts were consistent with the primary results except for the smallest chemotherapy cohort of vinorelbine (n=76).

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

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 platinum-based chemotherapy in studies E4599 and BO17704.

E4599

E4599 was an open-label, randomised, active-controlled, multicentre clinical trial evaluating Avastin as first-line treatment of patients with locally advanced, metastatic or recurrent NSCLC other than predominantly squamous cell histology.

Patients were randomised to platinum-based chemotherapy (paclitaxel 200 mg/m² 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. 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. 878 patients were randomised to the two arms.

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 duration of survival. Results are presented in Table 13.

Table 13 Efficacy results for study E4599

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

BO17704

Study BO17704 was a randomised, double-blind phase III study of Avastin in addition to cisplatin and gemcitabine versus placebo, cisplatin and gemcitabine in patients with locally advanced, metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy. The primary endpoint was progression free survival, secondary endpoints for the study included the duration of overall survival.

Patients were randomised to platinum-based chemotherapy, cisplatin 80 mg/m² i.v. infusion on day 1 and gemcitabine 1250 mg/m² i.v. infusion on days 1 and 8 of every 3-week cycle for up to 6 cycles (CG) with placebo or CG with Avastin at a dose of 7.5 or 15 mg/kg IV infusion day 1 of every 3-week cycle. In the Avastin-containing arms, patients could receive Avastin as a single-agent every 3 weeks until disease progression or unacceptable toxicity.

Study results show that 94% (277/296) of eligible patients went on to receive single agent bevacizumab at cycle 7. A high proportion of patients (approximately 62%) went on to receive a variety of non-protocol specified anti-cancer therapies, which may have impacted the analysis of overall survival.

The efficacy results are presented in Table 14.

Table 14 Efficacy results for study BO17704

	Cisplatin/Gemcitabine + placebo	Cisplatin/Gemcitabine + Avastin 7.5 mg/kg q 3 weeks	Cisplatin/Gemcitabine + Avastin 15 mg/kg q 3 weeks

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Number of Patients	347	345	351
Progression-Free Survival			
Median (months)	6.1	6.7 (p = 0.0026)	6.5 (p = 0.0301)
Hazard ratio		0.75 [0.62;0.91]	0.82 [0.68;0.98]
<u>Best Overall Response Rate</u> ^a	20.1%	34.1% (p< 0.0001)	30.4% (p=0.0023)

a patients with measurable disease at baseline

Overall Survival			
Median (months)	13.1	13.6 (p = 0.4203)	13.4 (p = 0.7613)
Hazard ratio		0.93 [0.78; 1.11]	1.03 [0.86, 1.23]

Advanced and/or metastatic Renal Cell Cancer (mRCC)

BO17705

Study 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 mRCC. The 649 randomised patients (641 treated) had clear cell mRCC, Karnofsky Performance Status (KPS) of $\geq 70\%$, 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. Patients were stratified according to country and Motzer score and the treatment arms were shown to be well balanced for the prognostic factors.

The primary endpoint was overall survival, with secondary endpoints for the study including progression-free survival. The addition of Avastin to IFN-alfa-2a significantly increased PFS and objective tumour response rate. These results have been confirmed through an independent radiological review. However, the increase in the primary endpoint of overall survival by 2 months was not significant (HR= 0.91). A high proportion of patients (approximately 63% IFN/placebo; 55% Avastin/IFN) received a variety of non-specified, post-protocol anti-cancer therapies, including antineoplastic agents, which may have impacted the analysis of overall survival.

The efficacy results are presented in Table 15.

Table 15 Efficacy Results for Study BO17705

	BO17705	
	IFN + Placebo	IFN + Avastin
Number of Patients	322	327

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Progression-Free Survival		
Median (months)	5.4	10.2
Hazard ratio [95% CI]	0.63 [0.52; 0.75] (p-value < 0.0001)	
<u>Objective Response Rate (%) in Patients with Measurable Disease</u>		
N	289	306
Response rate	12.8 %	31.4 %
	(p-value < 0.0001)	
Overall Survival		
Median (months)	21.3	23.3
Hazard ratio [95% CI]	0.91 [0.76; 1.10] (p-value 0.3360)	

An exploratory multivariate Cox regression model using backward selection indicated, that the following baseline prognostic factors were strongly associated with survival independent of treatment: gender, white blood cell count, platelets, body weight loss in the 6 months prior to study entry, number of metastatic sites, sum of longest diameter of target lesions, Motzer score. Adjustment for these baseline factors resulted in a treatment hazard ratio of 0.78 (95% CI [0.63;0.96], p = 0.0219), indicating a 22% reduction in the risk of death for patients in the Avastin+ IFN alfa-2a arm compared to IFN alfa-2a arm.

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. Dose-reduction of IFN alfa-2a did not appear to affect the efficacy of the combination of Avastin and IFN alfa-2a, based on PFS event free rates over time, as shown by a sub-group analysis. The 131 patients in the Avastin + IFN alfa-2a arm who reduced and maintained the IFN alfa-2a dose at 6 or 3 MIU during the study, exhibited at 6, 12 and 18 months, PFS event free rates of 73, 52 and 21% respectively, as compared to 61, 43 and 17% in the total population of patients receiving Avastin + IFN alfa-2a.

AVF2938

This was a randomised, double-blind, phase II clinical study investigating Avastin 10 mg/kg in a 2 weekly schedule with the same dose of Avastin in combination with 150 mg daily erlotinib, in patients with metastatic clear cell RCC. A total of 104 patients were randomised to treatment in this study, 53 to Avastin 10 mg/kg q2w plus placebo and 51 to Avastin 10 mg/kg q2w plus erlotinib 150 mg daily. The analysis of the primary endpoint showed no difference between the Avastin + Pl arm and the Avastin + Erl arm (median PFS 8.5 versus 9.9 months). Seven patients in each arm had an objective response.

Malignant Glioma (WHO Grade IV) - Glioblastoma

AVF3708g

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

Glioblastoma 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/m² IV or 340 mg/m² 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 (IRF). Other outcome measures were duration of PFS, duration of response and overall survival.

Results of the study are summarised in Table 16.

Table 16 Efficacy Results from Study AVF3708g

	Avastin		Avastin + Irinotecan	
Number of patients	85		82	
	Inv	IRF	Inv	IRF
Primary endpoints				
6-month progression-free survival	43.6%	42.6%	57.9%	50.3%
95% CI (Inv)	(33.0, 54.3)	-	(46.6, 69.2)	-
97.5% CI (IRF)	-	(29.6, 55.5)	-	(36.8, 63.9)
Objective Response Rate	41.2%	28.2%	51.2%	37.8%
95% CI (Inv)	(30.6, 52.3)	-	(39.9, 62.4)	-
97.5% CI (IRF)	-	(18.5, 40.3)	-	(26.5, 50.8)
Secondary endpoints				
Progression-free survival (months)				
Median	4.2	4.2	6.8	5.6
(95% CI)	(3.0, 6.9)	(2.9, 5.8)	(5.0, 8.2)	(4.4, 6.2)
Duration of objective response (months)				
Median	8.1	5.6	8.3	4.3
(95% CI)	(5.5, *)	(3.0, 5.8)	(5.5, *)	(4.2, *)
Overall survival (months)				
Median	9.3		8.8	
(95% CI)	(8.2, *)		(7.8, *)	

ORR was determined using modified McDonald criteria; Inv = Investigator's assessment; IRF = Independent Review Facility

* Upper limit of the confidence interval could not be obtained

In study AVF3708g, six-month PFS based on IRF assessments was significantly higher ($p < 0.0001$) compared with historical controls for both treatment arms: 42.6% in the Avastin arm and 50.3% in the Avastin plus irinotecan arm (investigator assessment: 43.6% in the Avastin arm and 57.9% in the Avastin plus irinotecan arm). Objective response rates were also significantly higher ($p < 0.0001$) compared with historical controls for both treatment

arms: 28.2% in the Avastin arm and 37.8% in the Avastin plus irinotecan arm (investigator assessment: 41.2% in the Avastin arm and 51.2% in the Avastin plus irinotecan arm).

The majority of patients who were receiving steroids at baseline, including responders and non-responders, were able to reduce their steroid utilization over time while receiving bevacizumab treatment. The majority of patients experiencing an objective response or prolonged PFS (at week 24) were able to maintain or improve their neurocognitive functions while on study treatment 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.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

Front-line Ovarian Cancer

The safety and efficacy of Avastin in the front-line treatment of patients with epithelial ovarian, fallopian tube or primary peritoneal cancer were studied in two phase III trials (GOG-0218 and BO17707) that compared the effect of the addition of Avastin to carboplatin and paclitaxel compared to the chemotherapy regimen alone.

GOG-0218

The GOG-0218 study was a Phase III multicenter, randomized, double-blind, placebo controlled, three arm study evaluating the effect of adding Avastin to an approved chemotherapy regimen (carboplatin and paclitaxel) in patients with optimally or sub-optimally debulked stage III or stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer.

A total of 1873 patients were randomized in equal proportions to the following three arms:

- CPP arm: Placebo in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m²) for 6 cycles followed by placebo alone, for a total of up to 15 months of therapy
- CPB15 arm: Five cycles of Avastin (15 mg/kg q3w) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m²) for 6 cycles (Avastin commenced at cycle 2 of chemotherapy) followed by placebo alone, for a total of up to 15 months of therapy
- CPB15+ arm: Five cycles of Avastin (15 mg/kg q3w) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m²) for 6 cycles (Avastin commenced at cycle 2 of chemotherapy) followed by continued use of Avastin (15 mg/kg q3w) as single agent for a total of up to 15 months of therapy.

The primary endpoint was Progression Free Survival (PFS) based on investigator's assessment of radiological scans. In addition, an independent review of the primary endpoint was also conducted.

The results of this study are summarized in Table 18.

Table 18 Efficacy Results from Study GOG-0218

Progression-free survival						
	Investigator Assessment ¹			IRC Assessment		
	CPP (n= 625)	CPB15 (n= 1248) ²	CPB15+ (n=1248) ²	CPP (n= 625)	CPB15 (n= 1248) ²	CPB15+ (n=1248) ²
Median PFS (months)	12.0	12.7	18.2	13.1	13.2	19.1
Hazard ratio (95% CI) ³		0.842 [0.714, 0.993]	0.644 [0.541, 0.766]		0.941 [0.779, 1.138]	0.630 (0.513, 0.773)
p –value ⁴		0.0204 ⁵	< 0.0001 ⁵		0.2663	< 0.0001
Objective response Rate⁶						
	Investigator Assessment			IRC Assessment		
	CPP (n= 396)	CPB15 (n= 393)	CPB15+ (n=403)	CPP (n= 474)	CPB15 (n=460)	CPB15+ (n=499)
% pts with objective response	63.4	66.2	66.0	68.8	75.4	77.4
p –value ⁴		0.2341	0.2041		0.0106	0.0012
Overall survival⁷						
	CPP (n= 625)		CPB15 (n= 625) ²	CPB15+ (n= 623) ²		
Median OS (months)	40.6		38.8	43.8		
Hazard Ratio (95% CI) ³			1.065 (0.908, 1.249)	0.879 (0.745, 1.038)		
p-value ⁴			0.2197	0.0641		

¹ Primary PFS analysis

² Events prior to Cycle 7 from the CPB15 and CPB15+ arms were pooled for the analyses

³ Relative to the control arm; stratified hazard ratio

⁴ One-sided log-rank p-value

⁵ Subject to a p-value boundary of 0.0116

⁶ Patients with measurable disease at baseline

⁷ Final overall survival analysis

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (carboplatin and paclitaxel) alone, patients who received front-line bevacizumab at a dose of 15 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab alone, had a clinically meaningful and statistically significant improvement in PFS.

Although there was an improvement in PFS for patients who received front-line bevacizumab in combination with chemotherapy and did not continue to receive bevacizumab alone, the improvement was neither clinically meaningful nor statistically significant compared to patients who received chemotherapy alone.

BO17707 (ICON7)

BO17707 was a Phase III, two arm, multicenter, randomized, controlled, open-label study comparing the effects of adding Avastin to carboplatin plus paclitaxel in patients with FIGO stage I or IIA (Grade 3 or clear cell histology only), or FIGO stage IIB - IV (all grades and all histological types) epithelial ovarian, fallopian tube or primary peritoneal cancer following surgery, and in whom no further surgery was planned before progression.

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A total of 1528 patients were randomized in equal proportions to the following two arms:

- CP arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m²) for 6 cycles
- CPB7.5+ arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m²) for 6 cycles plus Avastin (7.5 mg/kg q3w) for up to 18 cycles.

The primary endpoint was Progression Free Survival (PFS) as assessed by the investigator.

The results of this study are summarized in Table 19.

Table 19 Efficacy Results from Study BO17707 (ICON7)

Progression-free survival		
	CP (n= 764)	CPB7.5+ (n=764)
Median PFS (months)	16.0	18.3
Hazard ratio [95% CI]	0.79 [0.68; 0.91] (p-value = 0.0010)	
Objective Response Rate¹		
	CP (n=277)	CPB7.5+ (n=272)
Response rate	41.9 %	61.8 %
	(p-value <0.0001)	
Overall Survival²		
	CP (n= 764)	CPB7.5+ (n=764)
Median (months)	58.0	57.4
Hazard ratio [95% CI]	0.99 [0.85; 1.15]	

¹ in patients with measurable disease at baseline

² Final OS analysis when 46.7% of patients died

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (carboplatin and paclitaxel) alone, patients who received bevacizumab at a dose of 7.5 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab for up to 18 cycles had a statistically significant improvement in PFS.

Recurrent Ovarian Cancer

AVF4095g

The safety and efficacy of Avastin 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, was studied in a phase III trial randomized, double-blind, placebo-controlled trial (AVF4095g). The study compared the effect of adding Avastin to carboplatin and gemcitabine chemotherapy and continuing Avastin as a single agent to progression to carboplatin and gemcitabine alone.

A total of 484 patients with measurable disease were randomized in equal portions to either:

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- Carboplatin (AUC₄, Day 1) and gemcitabine (1000 mg/m² on Days 1 and 8) and concurrent placebo every 3 weeks for 6 and up to 10 cycles followed by placebo alone until disease progression or unacceptable toxicity
- Carboplatin (AUC₄, Day 1) and gemcitabine (1000 mg/m² on Days 1 and 8) and concurrent Avastin (15 mg/kg Day 1) every 3 weeks for 6 and up to 10 cycles followed by Avastin (15 mg/kg every 3 weeks) alone until disease progression or unacceptable toxicity

The primary endpoint was progression-free survival based on investigator assessment using RECIST criteria. Additional endpoints included objective response, duration of response, safety and overall survival. An independent review of the primary endpoint was also conducted.

The results of this study are summarized in Table 20.

Table 20 Efficacy Results from Study AVF4095g

Progression-free survival				
	Investigator Assessment*		IRC Assessment	
	Placebo+ C/G (n = 242)	Avastin + C/G (n = 242)	Placebo+ C/G (n = 242)	Avastin + C/G (n = 242)
Median PFS (months)	8.4	12.4	8.6	12.3
Hazard ratio (95% CI)	0.484 [0.388, 0.605]		0.451 [0.351, 0.580]	
p –value	<0.0001		<0.0001	
Objective response rate				
	Investigator Assessment		IRC Assessment	
	Placebo+ C/G (n = 242)	Avastin + C/G (n = 242)	Placebo+ C/G (n = 242)	Avastin + C/G (n = 242)
% pts with objective response	57.4 %	78.5%	53.7 %	74.8%
p –value	<0.0001		<0.0001	
Overall survival**				
	Placebo + C/G (n = 242)		Avastin + C/G (n = 242)	
Median OS (months)	32.9		33.6	
Hazard Ratio (95% CI)	0.952 [0.771; 1.176]			
p-value	0.6479			

* Primary analysis

** Final overall survival analysis performed when approximately 73% of the patients had died

MO22224 (AURELIA)

Study MO22224 evaluated the efficacy and safety of bevacizumab in combination with chemotherapy for platinum-resistant recurrent ovarian cancer. This study was designed as an open-label, randomized, two-arm Phase III evaluation of bevacizumab plus chemotherapy (CT+BV) versus chemotherapy alone (CT).

A total of 361 patients were enrolled into this study and administered either chemotherapy (paclitaxel, topotecan, or PLD) alone or in combination with bevacizumab:

- CT Arm (chemotherapy alone):
 - Paclitaxel 80 mg/m² as a 1-hour IV infusion on Days 1, 8, 15, and 22 every 4 weeks.
 - Topotecan 4 mg/m² as a 30 minute IV infusion on Days 1, 8, and 15 every 4 weeks. Alternatively, a 1.25 mg/m² dose could be administered over 30 minutes on Days 1–5 every 3 weeks.
 - PLD 40 mg/m² as a 1 mg/min IV infusion on Day 1 only every 4 weeks. After Cycle 1, the drug could be delivered as a 1 hour infusion.
- CT+BV Arm (chemotherapy plus bevacizumab):

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- The chosen chemotherapy was combined with bevacizumab 10 mg/kg IV every 2 weeks (or bevacizumab 15 mg/kg every 3 weeks if used in combination with topotecan 1.25 mg/m² on Days 1–5 on a every 3 weeks schedule).

Eligible patients had ovarian cancer that progressed within 6 months of previous platinum therapy. If a patient had been previously included in a blinded trial with an anti-angiogenic agent, the patient was enrolled in the same stratum as those patients who were known to have previously received an anti-angiogenic agent.

The primary endpoint was progression-free-survival, with secondary endpoints including objective response rate and overall survival. Results are presented in Table 21.

Table 21 Efficacy Results from Study MO22224 (AURELIA)

Primary Endpoint		
Progression-Free Survival		
	CT (n=182)	CT+BV (n=179)
Median (months)	3.4	6.7
Hazard ratio (95% CI)	0.379 [0.296, 0.485]	
p-value	<0.0001	
Secondary Endpoints		
Objective Response Rate*		
	CT (n=144)	CT+BV (N=142)
% pts with objective response	18 (12.5%)	40 (28.2%)
p –value	0.0007	
Overall Survival (final analysis)**		
	CT (n=182)	CT+BV (n=-179)
Median OS (months)	13.3	16.6
Hazard Ratio (95% CI)	0.870 (0.678, 1.116)	
p-value	0.2711	

All analyses presented in this table are stratified analyses

*Randomized Patients with Measurable Disease at Baseline

** At the time of the final OS analysis (25 January 2013),

266 patients (73.7%) had died across the two treatment arms.

Cervical Cancer

GOG-0240

The efficacy and safety of bevacizumab in combination with chemotherapy (paclitaxel and cisplatin or paclitaxel and topotecan) as a treatment for patients with persistent, recurrent, or metastatic carcinoma of the cervix was evaluated in study GOG-0240, a randomized, four-arm, multi-centre phase III trial.

A total of 452 patients were randomized to receive either:

- Paclitaxel 135 mg/m² IV over 24 hours on Day 1 and cisplatin 50 mg/m² IV on Day 2, every 3 weeks (q3w); or paclitaxel 175 mg/m² IV over 3 hours on Day 1 and cisplatin 50 mg/m² IV on Day 2 (q3w); or paclitaxel 175 mg/m² IV over 3 hours on Day 1 and cisplatin 50 mg/m² IV on Day 1 (q3w)
- Paclitaxel 135 mg/m² IV over 24 hours on Day 1 and cisplatin 50 mg/m² IV on Day 2 plus bevacizumab 15 mg/kg IV on Day 2 (q3w); or paclitaxel 175 mg/m² IV over 3 hours on Day 1 and cisplatin 50 mg/m² IV on Day 2 plus bevacizumab 15 mg/kg IV on Day 2 (q3w); or paclitaxel 175 mg/m² IV over 3 hours on Day 1 and cisplatin 50 mg/m² IV on Day 1 and bevacizumab 15 mg/kg IV on Day 1 (q3w)
- Paclitaxel 175 mg/m² over 3 hours on Day 1 and topotecan 0.75 mg/m² over 30 minutes on days 1-3 (q3w)
- Paclitaxel 175 mg/m² over 3 hours on Day 1 and topotecan 0.75 mg/m² over 30 minutes on Days 1-3 plus bevacizumab 15 mg/kg IV on Day 1 (q3w)

Eligible patients had persistent, recurrent, or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which was not amenable to curative treatment with surgery and/or radiation therapy.

The primary efficacy endpoint was overall survival (OS). Secondary efficacy endpoints included progression-free survival (PFS) and objective response rate (ORR). Results are presented in Table 22.

Table 22 Overall Efficacy by Bevacizumab Treatment (ITT Population) from study GOG-0240

	Chemotherapy (n=225)	Chemotherapy + BV (n=227)
<u>Primary Endpoint</u>		
Overall Survival		
Median (months) ¹	12.9	16.8
Hazard ratio [95% CI]	0.74 [0.58;0.94] (p-value ⁵ = 0.0132)	
<u>Secondary Endpoints</u>		
Progression-free survival		
Median PFS (months) ¹	6.0	8.3
Hazard ratio [95% CI]	0.66 [0.54;0.81] (p-value ⁵ = <0.0001)	
Best Overall Response		
Response rate ²	76 (33.8 %)	103 (45.4 %)
95% CI for Response Rates ³	[27.6; 40.4]	[38.8; 52.1]
Difference in Response Rates	11.60	
95% CI for Difference in Response Rates ⁴	[2.4; 20.8]	
p-Value (Chi-squared Test)	0.0117	

¹ Kaplan-Meier estimates

² Patients with best overall response of confirmed CR or PR

³ 95% CI for one sample binomial using Pearson-Clopper method

⁴ Approximate 95% CI for difference of two rates using Hauck-Anderson method

⁵ log-rank test (stratified)

2.2 PHARMACOKINETIC PROPERTIES

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 characterized by a low clearance, a limited volume of the central compartment (V_c), and a long elimination half-life. This enables target therapeutic bevacizumab serum 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 patient age [the median age was 59 year with 5th and 95th percentiles of 37 and 76 year]).

Low albumin and high tumour burden are generally indicative of disease severity. Bevacizumab clearance was approximately 30% faster in patients with low levels of serum albumin and 7% faster in subjects with higher tumour burden when compared with a typical patient with median values of albumin and tumour burden.

2.2.1 ABSORPTION

Not applicable.

2.2.2 DISTRIBUTION

The typical value for central volume (V_c) was 2.73 L and 3.28 L for female and male subjects respectively, which is in the range that has been described for IgGs and other monoclonal antibodies. The typical value for peripheral volume (V_p) was 1.69 L and 2.35 L for female and male patients respectively, when bevacizumab is coadministered with anti-neoplastic agents. After correcting for body weight, male subjects had a larger V_c (+ 20%) than females.

2.2.3 METABOLISM

Assessment of bevacizumab metabolism in rabbits following a single IV dose of ^{125}I -bevacizumab indicated that its metabolic profile was similar to that expected for a native IgG molecule which does not bind VEGF. The metabolism and elimination of bevacizumab is similar to endogenous IgG i.e. primarily via proteolytic catabolism throughout the body, including endothelial cells, and does not rely primarily on elimination through the kidneys and liver. Binding of the IgG to the FcRn receptor result in protection from cellular metabolism and the long terminal half-life.

2.2.4 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 0.188 and 0.220 L/day for female and male patients, respectively. After correcting for body weight, male patients had a higher bevacizumab clearance (+ 17%) than females. According to the two-compartmental model, the elimination half-life is 18 days for a typical female patient and 20 days for a typical male patient.

2.2.5 PHARMACOKINETICS IN SPECIAL POPULATIONS

The population pharmacokinetics 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 studies have been conducted to investigate the pharmacokinetics of bevacizumab in renally impaired patients since the kidneys are not a major organ for bevacizumab metabolism or excretion.

Hepatic impairment: No studies have been conducted to investigate the pharmacokinetics of bevacizumab in patients with hepatic impairment since the liver is not a major organ for bevacizumab metabolism or excretion.

2.3 PRECLINICAL SAFETY

2.3.1 CARCINOGENICITY

Studies have not been performed to evaluate the carcinogenic potential of Avastin.

2.3.2 MUTAGENICITY

Studies have not been performed to evaluate the mutagenic potential of Avastin.

2.3.3 IMPAIRMENT OF FERTILITY

No specific studies in animals have been performed to evaluate the effect of Avastin on fertility. No adverse effect on male reproductive organs was observed in repeat dose toxicity studies in cynomolgus monkeys.

Inhibition of ovarian function 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 for 13 or 26 weeks. The doses associated with this effect were ≥ 4 times the human therapeutic dose or ³ 2-fold above the expected human exposure based on average serum concentrations in female monkeys. In rabbits, administration of 50 mg/kg of Avastin resulted in a significant decrease in ovarian weight and number of corpora lutea. The results in both monkeys and rabbits were reversible upon cessation of treatment. The inhibition of angiogenesis following administration of Avastin is likely to result in an adverse effect on female fertility.

2.3.4 TERATOGENICITY

Avastin has been shown to be embryotoxic and teratogenic when administered to rabbits. Observed effects included decreases in maternal and 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 of 10-100 mg/kg. Information on foetal malformations observed in the post marketing setting are provided in *section 2.5.1 Use in Special Populations, Pregnancy and 2.6.2 Undesirable Effects, Post Marketing.*

2.3.5 OTHER

Physéal Development:

In studies of up to 26 weeks duration in cynomolgus monkeys, Avastin was associated with physéal dysplasia. Physéal dysplasia was characterised primarily by thickened growth plate cartilage, subchondral bony plate formation and inhibition of vascular invasion of the growth plate. This effect occurred at doses ≥ 0.8 times the human therapeutic dose and exposure levels slightly below the expected human clinical exposure, based on average serum concentrations. It should be noted, however, that physéal dysplasia occurred only in actively growing animals with open growth plates.

Wound Healing:

In rabbits, the effects of Avastin on circular wound healing were studied. Wound re-epithelialisation was delayed in rabbits following five doses of Avastin, ranging from 2-50mg/kg, over a 2-week period. A trend toward a dose-dependent relationship was observed. The magnitude of effect on wound healing was similar to that observed with corticosteroid administration. Upon treatment cessation with either 2 or 10 mg/kg Avastin, the wounds closed completely. The lower dose of 2 mg/kg was approximately equivalent to the proposed clinical dose. A more sensitive linear wound healing model was also studied in rabbits. Three doses of Avastin ranging from 0.5-2 mg/kg dose-dependently and significantly decreased the tensile strength of the wounds, consistently with delayed wound healing. The low dose of 0.5 mg/kg was 5-fold below the proposed clinical dose.

As effects on wound healing were observed in rabbits at doses below the proposed clinical dose, the capacity for Avastin to adversely impact wound healing in human should be considered.

In cynomolgus monkeys, the effects of Avastin on the healing of a linear incision were highly variable and no dose-response relationship was evident.

Renal Function:

In normal cynomolgus monkeys, Avastin had no measurable effect on renal function treated once or twice weekly for up to 26 weeks, and did not accumulate in the kidney of rabbits following two doses up to 100 mg/kg (approximately 80-folds the proposed clinical dose).

Investigative toxicity studies in rabbits, using models of renal dysfunction, showed that Avastin did not exacerbate renal glomerular injury induced by bovine serum albumin or renal tubular damage induced by cisplatin.

Albumin:

In male cynomolgus monkeys, Avastin administered at doses of 10 mg/kg twice weekly or 50 mg/kg once weekly for 26 weeks was associated with a statistically significant decrease in albumin and albumin to globulin ratio and increase in globulin. These effects were reversible upon cessation of exposure. As the parameters remained within the normal reference range of values for these endpoints, these changes were not considered as clinically significant.

Hypertension:

At doses up to 50 mg/kg twice weekly in cynomolgus monkeys, Avastin showed no effects on blood pressure.

Haemostasis:

Non-clinical toxicology studies of up to 26 weeks duration in cynomolgus monkeys did not find changes in haematology or coagulation parameters including platelet counts, prothrombin and activated partial thromboplastin time. A model of haemostasis in rabbits, used to investigate the effect of Avastin on thrombus formation, did not show alteration in the rate of clot formation or any other haematological parameters compared to treatment with Avastin vehicle.

3. PHARMACEUTICAL PARTICULARS

3.1 STORAGE

Avastin should not be used after the expiry date (EXP) shown on the pack.

Store vials in a refrigerator at 2°C-8°C.

Keep vial in the outer carton in order to protect from light.

DO NOT FREEZE. DO NOT SHAKE.

Avastin does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution.

Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C-30°C in 0.9% sodium chloride solution. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

3.2 SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

Avastin infusions should not be administered or mixed with dextrose or glucose solutions [4 (see “Incompatibilities” below)].

Do not administer as an intravenous push or bolus.

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.

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Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Avastin is not formulated for intravitreal use.

Incompatibilities [1]

No incompatibilities between Avastin and polyvinyl chloride or polyolefin bags have been observed. A concentration-dependent degradation profile of Avastin was observed when diluted with dextrose solutions (5%).

Packs

Vials 400 mg/16 ml	1
Vials 100 mg/4 ml	1

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

This is a medicament

A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor’s prescription, the method of use and the instructions of the pharmacist who sold the medicament.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed for you.

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

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