

Avastin

Summary of Product Characteristics (SmPC)

MEDICINAL PRODUCT

Avastin 25mg/mL concentrate for solution for infusion

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Avastin 25 mg/ml concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 25 mg of bevacizumab.

Each vial contains 100 mg of bevacizumab in 4 ml and 400 mg in 16 ml respectively, corresponding to 1.4 to 16.5 mg/ml when diluted as recommended.

Bevacizumab is a recombinant humanised monoclonal antibody produced by DNA technology in Chinese Hamster ovary cells.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to slightly opalescent, colourless to pale brown liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Avastin in combination with paclitaxel is indicated for first-line treatment of patients with metastatic breast cancer. For further information as to HER2 status, please refer to section 5.1.

Avastin in combination with capecitabine is indicated for first-line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Avastin in combination with capecitabine. For further information as to HER2 status, please refer to section 5.1.

Avastin, in addition to platinum-based chemotherapy, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology.

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

Avastin, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.

4.2 Posology and method of administration

Avastin must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products.

Dose reduction for adverse events is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended as described in section 4.4.

Metastatic carcinoma of the colon or rectum (mCRC)

The recommended dose of Avastin, administered as an intravenous infusion, is either 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 treatment be continued until progression of the underlying disease or until unacceptable toxicity.

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 treatment be continued until progression of the underlying disease or until unacceptable toxicity.

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 is 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

Clinical benefit in NSCLC patients has been demonstrated with both 7.5 mg/kg and 15 mg/kg doses. For details refer to section 5.1 *Pharmacodynamic Properties, Non-small cell lung cancer (NSCLC)*. It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

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 treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

Avastin is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Avastin as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier.

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

Special populations

Elderly: No dose adjustment is required in the elderly.

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

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

Paediatric population

The safety and efficacy of bevacizumab in children and adolescents have not been established. There is no relevant use of bevacizumab in the paediatric population in the granted indications. Currently available data are described in section 5.2 and section 5.3 but no recommendation on a posology can be made.

Method of administration

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

Do not administer as an intravenous push or bolus.

Precautions to be taken before handling or administering the medicinal product

For instructions on dilution of the medicinal product before administration, see section 6.6. Avastin infusions should not be administered or mixed with glucose solutions. This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Hypersensitivity to Chinese hamster ovary (CHO) cell products or other recombinant human or humanised antibodies.
- Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Gastrointestinal perforations (see section 4.8)

Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation when treated with Avastin. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.

Fistulae (see section 4.8)

Patients may be at increased risk for the development of fistulae when treated with Avastin. Permanently discontinue Avastin in patients with TE (tracheoesophageal) 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.

Wound healing complications (see section 4.8)

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

Hypertension (see section 4.8)

An increased incidence of hypertension was observed in Avastin-treated patients. 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 therapy. Monitoring of blood pressure is generally recommended during therapy.

In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. The use of diuretics to manage hypertension is not advised in patients who receive a cisplatin-based chemotherapy regimen. 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.

Reversible posterior leukoencephalopathy syndrome (RPLS) (see section 4.8)

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

Proteinuria (see section 4.8)

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 all Grade [US National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 3.0] proteinuria may be related to the dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Therapy should be permanently discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome).

Arterial thromboembolism (see section 4.8)

In clinical trials, the incidence of arterial thromboembolic events including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs) was higher in patients receiving Avastin in combination with chemotherapy compared to those who received chemotherapy alone.

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

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

Venous thromboembolism (see section 4.8)

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

Haemorrhage

Patients treated with Avastin have an increased risk of haemorrhage, especially tumour-associated haemorrhage. Avastin should be discontinued permanently in patients who experience Grade 3 or 4 bleeding during Avastin therapy (see section 4.8).

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 patients has not been prospectively evaluated in randomised clinical trials (see section 4.8). 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 therapy in these patients. However,

patients who developed venous thrombosis while receiving therapy did not appear to have an increased rate of grade 3 or above bleeding when treated with a full dose of warfarin and Avastin concomitantly.

Pulmonary haemorrhage/haemoptysis

Patients with non-small cell lung cancer treated with Avastin may be at risk of serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis. Patients with recent pulmonary haemorrhage/haemoptysis (> 2.5 ml of red blood) should not be treated with Avastin.

Congestive heart failure (CHF) (see section 4.8)

Events consistent with 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. 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 4.8).

Neutropenia and infections (see section 4.8)

Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus Avastin in comparison to chemotherapy alone. This has mainly been seen in combination with platinum- or taxane-based therapies in the treatment of NSCLC and mBC.

Hypersensitivity reactions/infusion reactions (see section 4.8)

Patients may be at risk of developing infusion/hypersensitivity reaction. 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.

Osteonecrosis of the jaw (see section 4.8)

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. Caution should be exercised when Avastin and i.v. bisphosphonates are administered simultaneously or sequentially.

Invasive dental procedures are also an identified 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.

Eye disorders

Adverse reactions have been reported from unapproved intravitreal use. These reactions included infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these appeared as serious adverse reactions.

Ovarian failure/fertility

Avastin may impair female fertility (see sections 4.6 and 4.8). Therefore fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with Avastin.

4.5 Interaction 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 alfa-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 dedicated drug-drug interaction trial demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan and its active metabolite SN38.

Results from one trial in metastatic colorectal cancer patients demonstrated no significant effect of bevacizumab on the pharmacokinetics of capecitabine and its metabolites, and on the pharmacokinetics of oxaliplatin, as determined by measurement of free and total platinum.

Results from one trial in renal cancer patients demonstrated no significant effect of bevacizumab on the pharmacokinetics of interferon alfa-2a.

The potential effect of bevacizumab on the pharmacokinetics of cisplatin and gemcitabine was investigated in non-squamous NSCLC patients. Trial results demonstrated no significant effect of bevacizumab on the pharmacokinetics of cisplatin. Due to high inter-patient variability and limited sampling, the results from that trial do not allow firm conclusions to be drawn on the impact of bevacizumab on gemcitabine pharmacokinetics.

Combination of bevacizumab and sunitinib malate

In two clinical trials 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, RPLS* in section 4.4).

Combination with platinum- or taxane-based therapies (see sections 4.4 and 4.8)

Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed mainly in patients treated with platinum- or taxane-based therapies in the treatment of NSCLC and mBC.

Radiotherapy

The safety and efficacy of concomitant administration of radiotherapy and Avastin has not been established.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential have to use effective contraception during (and up to 6 months after) treatment.

Pregnancy

There are no data on the use of Avastin in pregnant women. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). IgGs are known to cross the placenta, and Avastin is anticipated to inhibit angiogenesis in the foetus, and thus is suspected to cause serious birth defects when administered during pregnancy. Avastin is contraindicated in pregnancy (see section 4.3).

Breastfeeding

It is not known whether bevacizumab is excreted in human milk. As maternal IgG is excreted in milk and bevacizumab could harm infant growth and development (see section 5.3), women must discontinue breast-feeding during therapy and not breast-feed for at least six months following the last dose of Avastin.

Fertility

Repeat dose toxicity studies in animals have shown that bevacizumab may have an adverse effect on female fertility (see section 5.3). In a phase III trial in the adjuvant treatment of patients with colon cancer, a substudy with 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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The overall safety profile of Avastin is based on data from over 3,500 patients with various malignancies, predominantly treated with Avastin in combination with chemotherapy in clinical trials.

The most serious adverse reactions were:

- Gastrointestinal perforations (see section 4.4).
- Haemorrhage, including pulmonary haemorrhage/haemoptysis, which is more common in non-small cell lung cancer patients (see section 4.4).
- Arterial thromboembolism (see section 4.4).

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

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

Table 1 lists adverse 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 reactions listed in this table fall into the following categories: Very Common ($\geq 1/10$) and Common ($\geq 1/100 - < 1/10$). Adverse 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 reactions are presented in the order of decreasing seriousness. Some of the adverse reactions are reactions commonly seen with chemotherapy, (e.g. palmar-plantar erythrodysesthesia syndrome with capecitabine and peripheral sensory neuropathy with paclitaxel or oxaliplatin); however, an exacerbation by Avastin therapy can not be excluded.

Table 1 Very common and common adverse reactions

<i>System organ class (SOC)</i>	<i>NCI-CTC grade 3-5 reactions ($\geq 2\%$ difference between the trial arms in at least one clinical trial)</i>		<i>All grade reactions ($\geq 10\%$ difference between the trial arms in at least one clinical trial)</i>
	<i>Very common</i>	<i>Common</i>	<i>Very common</i>
<i>Infections and infestations</i>		Sepsis Abscess Infection	
<i>Blood and the lymphatic systems disorders</i>	Febrile neutropenia Leucopenia Thrombocytopenia Neutropenia	Anaemia	
<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	Intestinal Perforation Ileus Intestinal obstruction Abdominal pain Gastrointestinal disorder Stomatitis	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>System organ class (SOC)</i>	<i>NCI-CTC grade 3-5 reactions (≥2% difference between the trial arms in at least one clinical trial)</i>		<i>All grade reactions (≥10% difference between the trial arms in at least one clinical trial)</i>
	<i>Very common</i>	<i>Common</i>	<i>Very common</i>
<i>Musculoskeletal, connective tissue and bone disorders</i>		Muscular weakness Myalgia Arthralgia	Arthralgia
<i>Renal and urinary disorders</i>		Proteinuria Urinary Tract Infection	Proteinuria
<i>General disorders and administration site conditions</i>	Asthenia Fatigue	Pain Lethargy Mucosal inflammation	Pyrexia Asthenia Pain Mucosal inflammation

* Pooled arterial thromboembolic events including cerebrovascular accident, myocardial infarction, transient ischaemic attack and other arterial thromboembolic events.

Data are unadjusted for the differential time on treatment.

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

Further information on selected serious adverse reactions

Gastrointestinal perforations (see section 4.4)

Avastin has been associated with serious cases of gastrointestinal perforation.

Gastrointestinal perforations have been reported in clinical trials with an incidence of less than 1% in patients with metastatic breast cancer or non-squamous non-small cell lung cancer, and up to 2.0% in metastatic colorectal cancer patients or in patients with ovarian cancer receiving front-line treatment. Fatal outcome was reported in approximately a third of serious cases of gastrointestinal perforations, which represents between 0.2%-1% of all Avastin treated patients.

The presentation of these events varied in type and severity, ranging from free air seen on the plain abdominal X-ray, which resolved without treatment, to intestinal perforation with abdominal abscess and fatal outcome. In some cases underlying intra-abdominal inflammation was present, either from gastric ulcer disease, tumour necrosis, diverticulitis, or chemotherapy-associated colitis.

Fistulae (see section 4.4)

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

In clinical trials, gastrointestinal fistulae have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer, but were also reported less commonly in patients with other types of cancers. Uncommon (≥ 0.1% to < 1%) reports of other types of fistulae that involve areas of the body other than the gastrointestinal tract (e.g. bronchopleural, urogenital and 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.

Wound healing (see section 4.4)

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

In clinical trials of metastatic carcinoma of the colon or rectum, there was no increased risk of post-operative bleeding or wound healing complications observed in patients who underwent major surgery 28-60 days prior to starting Avastin. An increased incidence of post-operative bleeding or wound

healing complication occurring within 60 days of major surgery was observed if the patient was being treated with Avastin at the time of surgery. The incidence varied between 10% (4/40) and 20% (3/15).

In locally recurrent and metastatic breast cancer 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 clinical trials of ovarian cancer, grade 3-5 wound healing complications were observed in up to 1.2% of patients in the bevacizumab arm versus 0.1% in the control arm.

Hypertension (see section 4.4)

An increased incidence of hypertension (all grades) of up to 34% has been observed in Avastin-treated patients in clinical trials compared with up to 14% in those treated with comparator. Grade 3 and 4 hypertension (requiring oral anti-hypertensive medicines) 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 and chemotherapy compared to up to 0.2% of 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.

The risk of Avastin-associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy.

Proteinuria (see section 4.4)

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, with the great majority as Grade 1 proteinuria. Grade 3 proteinuria was reported in < 3% of treated patients: however, in patients treated for advanced and/or metastatic renal cell carcinoma this was up to 7% in patients having minimal to no proteinuria at baseline. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of treated patients. The proteinuria seen in clinical trials was not associated with renal dysfunction and rarely required permanent discontinuation of therapy. Testing for proteinuria is recommended prior to start of Avastin therapy. In most clinical trials urine protein levels of $\geq 2\text{g}/24\text{ hrs}$ led to the holding of Avastin until recovery to $< 2\text{g}/24\text{ hrs}$.

Haemorrhage (see section 4.4)

In clinical trials across all indications the overall incidence of NCI-CTC Grade 3-5 bleeding events ranged from 0.4% to 5% in Avastin treated patients, compared with up to 2.9% of patients in the chemotherapy control group.

The haemorrhagic events that have been observed in clinical trials were predominantly tumour-associated haemorrhage (see below) and minor mucocutaneous haemorrhage (e.g. epistaxis).

Tumour-associated haemorrhage (see section 4.4)

Major or massive pulmonary haemorrhage/haemoptysis has been observed primarily in trials in patients with non-small cell lung cancer (NSCLC). Possible risk factors include squamous cell histology, treatment with antirheumatic/anti-inflammatory substances, 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 phase III trials, 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.

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

Tumour-associated haemorrhage was also seen rarely in other tumour types and locations, including cases of central nervous system (CNS) bleeding in patients with CNS metastases (see section 4.4).

The incidence of CNS bleeding in patients with untreated CNS metastases receiving bevacizumab has not been prospectively evaluated in randomised clinical trials. 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 in 83 subjects treated with bevacizumab (1.2%) at the time of interim safety analysis.

Across all clinical trials, mucocutaneous haemorrhage has been seen in up to 50% of Avastin-treated patients. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in 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.

Thromboembolism (see section 4.4)

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 of arterial thromboembolic events ranged up to 3.8% in the Avastin containing arms compared with up to 1.7% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving Avastin compared to 0.5% in patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischemic attacks) were reported in up to 2.3% of patients treated with Avastin in combination with chemotherapy compared to 0.5% of patients treated with chemotherapy alone. Myocardial infarction was reported in 1.4% of patients treated with Avastin in combination with chemotherapy compared to 0.7% of patients treated with chemotherapy alone.

In one clinical trial evaluating Avastin in combination with 5-fluorouracil/folinic acid, 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 patients compared to 5.8% (6/104) in the chemotherapy control group.

Venous thromboembolism: The incidence of venous thromboembolic events in clinical trials was similar in patients receiving Avastin in combination with chemotherapy compared to those receiving

the control chemotherapy alone. Venous thromboembolic events include deep venous thrombosis, pulmonary embolism and thrombophlebitis.

In clinical trials across indications, the overall incidence of venous thromboembolic events ranged from 2.8% to 17.3% of Avastin-treated patients compared with 3.2% to 15.6% in the control arms.

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 treated 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.

Congestive heart failure (CHF)

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 four phase III trials (AVF2119g, E2100, BO17708 and AVF3694g) 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 (New York Heart Association) 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.

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. 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, the rate was higher in the R-CHOP plus bevacizumab arm. These results suggest that close clinical observation with appropriate cardiac assessments should be considered for patients exposed to cumulative doxorubicin doses greater than 300 mg/m² when combined with bevacizumab.

Hypersensitivity reactions/infusion reactions (see section 4.4 and Post-marketing experience below)

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

Elderly patients

In randomised clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic events, including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs). Other reactions with a higher frequency seen in patients over 65 were grade 3-4 leucopenia and thrombocytopenia; and all grade neutropenia,

diarrhoea, nausea, headache and fatigue as compared to those aged ≤ 65 years when treated with Avastin (see sections 4.4 and 4.8 under *Thromboembolism*).

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

Paediatric population

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

Ovarian failure/fertility (see sections 4.4 and 4.6)

In NSABP C-08, a phase III trial of Avastin in adjuvant treatment of patients with colon cancer, the incidence of new cases of ovarian failure, defined as amenorrhoea lasting 3 or more months, FSH level ≥ 30 mIU/mL and a negative serum β -HCG pregnancy test, has been evaluated in 295 premenopausal women. New cases of ovarian failure were reported in 2.6% patients in the mFOLFOX-6 group compared to 39% in the mFOLFOX-6 + bevacizumab group. After discontinuation of bevacizumab treatment, ovarian function recovered in 86.2% of these evaluable women. Long term effects of the treatment with bevacizumab on fertility are unknown.

Laboratory abnormalities

Decreased neutrophil count, decreased white blood cell count and presence of urine protein may be associated with Avastin treatment.

Across clinical trials, the following Grade 3 and 4 laboratory abnormalities occurred in patients treated with Avastin with at least a 2% difference compared to the corresponding control groups: hyperglycaemia, decreased haemoglobin, hypokalaemia, hyponatraemia, decreased white blood cell count, increased international normalised ratio (INR).

Post-marketing experience

Table 2 Adverse reactions reported in post-marketing setting

<i>System organ class (SOC)</i>	<i>Reactions (frequency*)</i>
<i>Nervous system disorders</i>	Hypertensive encephalopathy (very rare) (see also section 4.4 and <i>Hypertension</i> in section 4.8) Reversible posterior leukoencephalopathy syndrome (rare) (see also section 4.4)
<i>Vascular disorders</i>	Renal thrombotic microangiopathy, clinically manifested as proteinuria (not known). For further information on proteinuria see section 4.4 and <i>Proteinuria</i> in section 4.8.
<i>Respiratory, thoracic and mediastinal disorders</i>	Nasal septum perforation (not known) Pulmonary hypertension (not known) Dysphonia (common)
<i>Gastrointestinal disorders</i>	Gastrointestinal ulcer (not known)
<i>Hepatobiliary disorders</i>	Gall bladder perforation (not known)
<i>Immune system disorders</i>	Hypersensitivity reactions and infusion reactions (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 (see also section 4.4 and <i>Hypersensitivity reactions/infusion reactions</i> above)
<i>Musculoskeletal and connective tissue disorders</i>	Cases of osteonecrosis of the jaw (ONJ) have been reported in patients treated with Avastin, most of which occurred in patients who had identified risk factors for ONJ, in particular exposure to i.v. bisphosphonates and/or a history of dental disease requiring invasive dental procedures (see also section 4.4)

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: monoclonal antibody, ATC code: L01X C07

Mechanism of action

Bevacizumab binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and

KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.

Pharmacodynamic effects

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.

Clinical efficacy

Metastatic carcinoma of the colon or rectum (mCRC)

The safety and efficacy of the recommended dose (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/folinic acid (IFL) for a total of 4 weeks of each 6 week-cycle (Saltz regimen).
- **AVF0780g:** In combination with bolus 5-fluorouracil/ folinic acid (5-FU/FA) for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen).
- **AVF2192g:** In combination with bolus 5-FU/FA 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.

Two additional trials were conducted in first (NO16966) and second line (E3200) treatment of metastatic carcinoma of the colon or rectum, with Avastin administered in the following dosing regimens, in combination with FOLFOX-4 (5FU/LV/Oxaliplatin) and XELOX (Capecitabine/Oxaliplatin):

- **NO16966:** Avastin 7.5 mg/kg of body weight every 3 weeks in combination with oral capecitabine and intravenous oxaliplatin (XELOX) or Avastin 5 mg/kg every 2 weeks in combination with leucovorin plus 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).

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. 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/FA+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. All treatments were continued until disease progression. The overall mean age was 59.4 years; 56.6% of patients had an ECOG performance status of 0, 43% had a value of 1 and 0.4% had a value of 2. 15.5% had received prior radiotherapy and 28.4% prior chemotherapy.

The primary efficacy variable 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). The clinical benefit, as measured by overall 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.

The efficacy results of Avastin in combination with IFL-chemotherapy are displayed in Table 3.

Table 3 Efficacy results for trial AVF2107g

	AVF2107g	
	Arm 1 IFL + placebo	Arm 2 IFL + Avastin^a
Number of patients	411	402
Overall survival		
Median time (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)	
Progression-free survival		
Median time (months)	6.2	10.6
Hazard ratio	0.54 (p-value < 0.0001)	
Overall response rate		
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/FA + 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 evaluating the efficacy and safety of Avastin in combination with 5-FU/FA 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/FA + placebo arm and 104 patients to 5-FU/FA + Avastin (5 mg/kg every 2 weeks) arm. All treatments were continued until disease progression. The addition of Avastin 5 mg/kg every two weeks to 5-FU/FA resulted in higher objective response rates, significantly longer progression-free survival, and a trend in longer survival as compared to 5-FU/FA chemotherapy alone.

AVF0780g

This was a phase II randomised, active-controlled, open-labelled clinical trial investigating Avastin in combination with 5-FU/FA as first-line treatment of metastatic colorectal cancer. The median age was 64 years. 19% of the patients had received prior chemotherapy and 14% prior radiotherapy. Seventy-one patients were randomised to receive bolus 5-FU/FA or 5-FU/FA + Avastin (5 mg/kg every 2 weeks). A third group of 33 patients received bolus 5-FU/FA + Avastin (10 mg/kg every 2 weeks). Patients were treated until disease progression. The primary endpoints of the trial were objective response rate and progression-free survival. The addition of Avastin 5 mg/kg every two weeks to 5-FU/FA resulted in higher objective response rates, longer progression-free survival, and a trend in longer survival, compared with 5-FU/FA chemotherapy alone (see Table 4). These efficacy data are consistent with the results from trial AVF2107g.

The efficacy data from trials AVF0780g and AVF2192g investigating Avastin in combination with 5-FU/FA-chemotherapy are summarised in Table 4.

Table 4 Efficacy results for trials AVF0780g and AVF2192g

	AVF0780g			AVF2192g	
	5-FU/FA	5-FU/FA + Avastin ^a	5-FU/FA + Avastin ^b	5-FU/FA + placebo	5-FU/FA + Avastin
Number of patients	36	35	33	105	104
Overall survival					
Median time (months)	13.6	17.7	15.2	12.9	16.6
95% Confidence interval				10.35 - 16.95	13.63 - 19.32
Hazard ratio ^c	-	0.52	1.01		0.79
p-value		0.073	0.978		0.16
Progression-free survival					
Median time (months)	5.2	9.0	7.2	5.5	9.2
Hazard ratio		0.44	0.69		0.5
p-value	-	0.0049	0.217		0.0002
Overall response rate					
Rate (percent)	16.7	40.0	24.2	15.2	26
95% CI	7.0 – 33.5	24.4 – 57.8	11.7 – 42.6	9.2 - 23.9	18.1 - 35.6
p-value		0.029	0.43		0.055
Duration of response					
Median time (months)	NR	9.3	5.0	6.8	9.2
25–75 percentile (months)	5.5 – NR	6.1 – NR	3.8 – 7.8	5.59 - 9.17	5.88 - 13.01

^a 5 mg/kg every 2 weeks.

^b 10 mg/kg every 2 weeks.

^c Relative to control arm.

NR = not reached.

NO16966

This was a phase III randomised, double-blind (for bevacizumab), clinical trial investigating Avastin 7.5 mg/kg in combination with oral capecitabine and IV oxaliplatin (XELOX), administered on a 3-weekly schedule; or Avastin 5 mg/kg in combination with leucovorin with 5-fluorouracil bolus, followed by 5-fluorouracil infusional, with IV oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule. The trial 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 trial arms in the Part II of the trial.

Table 5 Treatment regimens in trial 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 trial, 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:

- 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.
- 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 6).

Secondary PFS analyses, based on ‘on-treatment’-based response assessments, confirmed the significantly superior clinical benefit for patients treated with Avastin (analyses shown in Table 6), consistent with the statistically significant benefit observed in the pooled analysis.

Table 6 Key efficacy results for the superiority analysis (ITT population, trial 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)		
Overall response rate (invest. assessment)**	49.2%,	46.5%	
Median overall survival*	19.9	21.2	0.0769
Hazard ratio (97.5% CI)	0.89 (0.76-1.03)		

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

** Primary analysis at clinical cut-off 31 January 2006

^a relative to control arm

In the FOLFOX treatment subgroup, the median PFS was 8.6 months in placebo and 9.4 months in bevacizumab treated patients, HR = 0.89, 97.5% CI = [0.73 ; 1.08]; p-value = 0.1871, the corresponding results in the XELOX treatment subgroup being 7.4 vs. 9.3 months, HR = 0.77, 97.5% CI = [0.63 ; 0.94]; p-value = 0.0026.

The median overall survival was 20.3 months in placebo and 21.2 months in bevacizumab treated patients in the FOLFOX treatment subgroup, HR=0.94, 97.5% CI = [0.75 ; 1.16]; p-value = 0.4937, the corresponding results in the XELOX, treatment subgroup being 19.2 vs. 21.4 months, HR = 0.84, 97.5% CI = [0.68 ; 1.04]; p-value = 0.0698.

ECOG E3200

This was a phase III randomised, active-controlled, open-label trial 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 5 for trial 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 7).

Table 7 Efficacy results for trial E3200

	E3200	
	FOLFOX-4	FOLFOX-4 + Avastin ^a
Number of patients	292	293
Overall survival		
Median (months)	10.8	13.0
95% confidence interval	10.12 – 11.86	12.09 – 14.03
Hazard ratio ^b	0.751 (p-value = 0.0012)	
Progression-free survival		
Median (months)	4.5	7.5
Hazard ratio	0.518 (p-value < 0.0001)	
Objective response rate		
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.

The benefit of Avastin re-treatment in metastatic colorectal cancer patients who were exposed to Avastin in previous therapies has not been addressed in randomized clinical trials.

Metastatic breast cancer (mBC)

Two large Phase III trials were designed to investigate the treatment effect of Avastin in combination with two individual chemotherapy agents, as measured by the primary endpoint of PFS. A clinically meaningful and statistically significant improvement in PFS was observed in both trials.

Summarised below are PFS results for the individual chemotherapy agents included in the indication:

- Study E2100 (paclitaxel)
 - Median PFS increase 5.6 months, HR 0.421 (p <0.0001, 95% CI 0.343 ; 0.516)
- Study AVF3694g (capecitabine)
 - Median PFS increase 2.9 months, HR 0.69 (p = 0.0002, 95% CI 0.56 ; 0.84)

Further details of each study and the results are provided below.

ECOG E2100

Trial 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. 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). Prior hormonal therapy for the treatment of metastatic disease was allowed. Adjuvant taxane therapy was allowed only if it was completed at least 12 months prior to trial entry. Of the 722 patients in the trial, the majority of

patients had HER2-negative disease (90%), with a small number of patients with unknown (8%) or confirmed HER2-positive status (2%), who had previously been treated with or were considered unsuitable for trastuzumab therapy. Furthermore, 65% of patients had received adjuvant chemotherapy including 19% prior taxanes and 49% prior anthracyclines. Patients with central nervous system metastasis, including previously treated or resected brain lesions, were excluded.

In trial E2100, patients were treated until disease progression. In situations where early discontinuation of chemotherapy was required, treatment with Avastin as a single agent continued until disease progression. The patient characteristics were similar across the trial arms. The primary endpoint of this trial was progression free survival (PFS), based on trial investigators' assessment of disease progression. In addition, an independent review of the primary endpoint was also conducted. The results of this trial are presented in Table 8.

Table 8 Trial E2100 efficacy results

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	

The clinical benefit of Avastin as measured by PFS was seen in all pre-specified subgroups tested (including disease-free interval, number of metastatic sites, prior receipt of adjuvant chemotherapy and estrogen receptor (ER) status).

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 plus Avastin or chemotherapy plus placebo. The choices of chemotherapy included capecitabine, taxane (protein-bound paclitaxel, docetaxel), and anthracycline-based agents (doxorubicin/ cyclophosphamide, epirubicin/ cyclophosphamide, 5-fluorouracil/ doxorubicin/ cyclophosphamide, 5-fluorouracil/epirubicin/cyclophosphamide) 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.

Statistical analyses were performed independently for 1) patients who received capecitabine in combination with Avastin or placebo; 2) patients who received taxane-based or anthracycline-based chemotherapy in combination with Avastin or placebo. The primary endpoint of the study was PFS by investigator assessment. In addition, the primary endpoint was also assessed by an independent review committee (IRC).

The results of this study from the final protocol defined analyses for progression free survival and response rates for the independently powered capecitabine cohort of Study AVF3694g are presented in Table 9. Results from an exploratory overall survival analysis which include an additional 7 months of follow-up (approximately 46% of patients had died) are also presented. The percentage of patients who received Avastin in the open-label phase was 62.1% in the capecitabine + placebo arm and 49.9% in the capecitabine + Avastin arm.

Table 9 Efficacy results for study AVF3694g: – Capecitabine^a and Avastin/Placebo (Cap + Avastin/PI)

Progression-free survival ^b				
	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) ^b				
	Cap + PI (n= 161)		Cap + Avastin (n=325)	
% pts with objective response	23.6		35.4	
p-value	0.0097			
Overall survival ^b				
HR (95% CI)	0.88 (0.69, 1.13)			
p-value (exploratory)	0.33			

^a1000 mg/m² oral twice daily for 14 days administered every 3 weeks

^bStratified 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.

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.

Non-small cell lung cancer (NSCLC)

The safety and efficacy of Avastin, in addition to platinum-based chemotherapy, in the first-line treatment of patients with non-squamous non-small cell lung cancer (NSCLC), was investigated in trials E4599 and BO17704. An overall survival benefit has been demonstrated in trial E4599 with a 15 mg/kg/q3wk dose of bevacizumab. Trial BO17704 has demonstrated that both 7.5 mg/kg/q3wk and 15 mg/kg/q3wk bevacizumab doses increase progression free survival and response rate.

E4599

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

Patients were randomized 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 trial, 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 10.

Table 10 Efficacy results for trial E4599

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

In an exploratory analysis, the extent of Avastin benefit on overall survival was less pronounced in the subgroup of patients who did not have adenocarcinoma histology.

BO17704

Trial BO17704 was a randomised, double-blind phase III trial of Avastin in addition to cisplatin and gemcitabine versus placebo, cisplatin and gemcitabine in patients with locally advanced (stage IIIb with supraclavicular lymph node metastases or with malignant pleural or pericardial effusion), metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy. The primary endpoint was progression free survival, secondary endpoints for the trial 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. Trial 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 11.

Table 11 Efficacy results for trial BO17704

	Cisplatin/Gemcitabine + placebo	Cisplatin/Gemcitabine + Avastin 7.5 mg/kg q 3 weeks	Cisplatin/Gemcitabine + Avastin 15 mg/kg q 3 weeks
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]
Best overall response rate ^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)

Avastin in Combination with Interferon alfa-2a for the First-Line Treatment of Advance and/or Metastatic Renal Cell Cancer (BO17705)

This was a phase III randomised double-blind 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 randomized patients (641 treated) had Karnofsky Performance Status (KPS) of $\geq 70\%$, no CNS metastases and adequate organ function. Patients were nephrectomised for primary renal cell carcinoma. Avastin 10 mg/kg was given every 2 weeks until disease progression. IFN alfa-2a was given up to 52 weeks or until disease progression at a recommend starting dose of 9 MIU three times a week, allowing a dose reduction to 3 MIU three times a week in 2 steps. 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 trial including progression-free survival. The addition of Avastin to IFN-alpha-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-trial anti-cancer therapies, including antineoplastic agents, which may have impacted the analysis of overall survival.

The efficacy results are presented in Table 12.

Table 12 Efficacy results for trial BO17705

	BO17705	
	Placebo+ IFN ^a	Bv ^b + IFN ^a
Number of patients	322	327
Progression-free survival		
Median (months)	5.4	10.2
Hazard ratio	0.63	
95% CI	0.52, 0.75	
	(p-value < 0.0001)	
Objective response rate (%) in Patients with measurable disease		
N	289	306
Response rate	12.8%	31.4%
	(p-value < 0.0001)	

^a Interferon alfa-2a 9 MIU 3x/week

^b Bevacizumab 10 mg/kg q 2 wk

Overall survival		
Median (months)	21.3	23.3
Hazard ratio	0.91	
95% CI	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 trial 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 trial, 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 trial 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 trial, 53 to Avastin 10 mg/kg every 2 weeks plus placebo and 51 to Avastin 10 mg/kg every 2 weeks plus erlotinib 150 mg daily. The analysis of the primary endpoint showed no difference between the Avastin + Placebo arm and the Avastin + Erlotinib arm (median PFS 8.5 versus 9.9 months). Seven patients in each arm had an objective response. The addition of erlotinib to bevacizumab did not result in an improvement in OS (HR = 1.764; p=0.1789), duration of objective response (6.7 vs 9.1 months) or time to symptom progression (HR = 1.172; p = 0.5076).

AVF0890

This was a randomised phase II trial conducted to compare the efficacy and safety of bevacizumab versus placebo. A total of 116 patients were randomized to receive bevacizumab 3 mg/kg every 2 weeks (n=39), 10 mg/kg every 2 weeks; (n=37), or placebo (n=40). An interim analysis showed there was a significant prolongation of the time to progression of disease in the 10 mg/kg group as compared with the placebo group (hazard ratio, 2.55; p<0.001). There was a small difference, of borderline significance, between the time to progression of disease in the 3 mg/kg group and that in the placebo group (hazard ratio, 1.26; p=0.053). Four patients had objective (partial) response, and all of these had received the 10 mg/kg dose bevacizumab; the ORR for the 10 mg/kg dose was 10%.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal 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 evaluated 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 advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer.

Patients who had received prior therapy with bevacizumab or prior systemic anticancer therapy for ovarian cancer (e.g. chemotherapy, monoclonal antibody therapy, tyrosine kinase inhibitor therapy, or hormonal therapy) or previous radiotherapy to the abdomen or pelvis were excluded from the study.

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

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

The majority of patients included in the study were White (87% in all three arms); the median age was 60 years in CPP and CPB15 arms and 59 years in CPB15+ arm; and 29% of patients in CPP or CPB15 and 26% in CPB15+ were over 65 years of age. Overall approximately 50% of patients had a GOG PS of 0 at baseline, 43% a GOG PS score of 1, and 7% a GOG PS score of 2. Most patients had EOC (82% in CPP and CPB15, 85% in CPB15+) followed by PPC (16% in CPP, 15% in CPB15, 13% in CPB15+) and FTC (1% in CPP, 3% in CPB15, 2% in CPB15+). The majority of patients had serous adenocarcinoma histologic type (85% in CPP and CPB15, 86% in CPB15+). Overall approximately 34% of patients were FIGO Stage III optimally debulked with gross residual disease, 40% Stage III sub-optimally debulked, and 26% were Stage IV patients.

The primary endpoint was PFS based on investigator's assessment of disease progression based on radiological scans or CA 125 levels, or symptomatic deterioration per protocol. In addition, a prespecified analysis of the data censoring for CA-125 progression events was conducted, as well as an independent review of PFS as determined by radiological scans.

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

bevacizumab alone (CPB15+), had a clinically meaningful and statistically significant improvement in PFS.

In patients who only received bevacizumab in combination with chemotherapy and did not continue to receive bevacizumab alone (CPB15), no clinically meaningful benefit in PFS was observed.

The results of this study are summarized in Table 13.

Table 13 Efficacy Results from Study GOG-0218

Progression-free survival¹			
	CPP (n = 625)	CPB15 (n = 625)	CPB15+ (n = 623)
Median PFS (months)	10.6	11.6	14.7
Hazard ratio (95% CI)²		0.89 (0.78, 1.02)	0.70 (0.61, 0.81)
p-value^{3,4}		0.0437	< 0.0001
Objective response Rate⁵			
	CPP (n = 396)	CPB15 (n = 393)	CPB15+ (n = 403)
% pts with objective response	63.4	66.2	66.0
p-value		0.2341	0.2041
Overall survival⁶			
	CPP (n = 625)	CPB15 (n = 625)	CPB15+ (n = 623)
Median OS (months)	39.4	37.9	43.4
Hazard Ratio (95% CI)²		1.14 (0.95, 1.37)	0.90 (0.74, 1.08)
p-value³		0.0809	0.1253

¹ Investigator assessed GOG protocol-specified PFS analysis (neither censored for CA-125 progressions nor censored for NPT prior to disease progression) with data cut-off date of 25 February, 2010.

² Relative to the control arm; stratified hazard ratio.

³ One-sided log-rank p-value

⁴ Subject to a p-value boundary of 0.0116.

⁵ Patients with measurable disease at baseline.

⁶ Overall survival analysis performed when approximately 36% of the patients had died.

Prespecified PFS analyses were conducted, all with a cut-off date of 29 September 2009. The results of these prespecified analyses are as follows:

- The protocol specified analysis of investigator-assessed PFS (without censoring for CA-125 progression or non-protocol therapy [NPT]) shows a stratified hazard ratio of 0.71 (95% CI: 0.61-0.83, 1-sided logrank p-value < 0.0001) when CPB15+ is compared with CPP, with a median PFS of 10.4 months in the CPP arm and 14.1 months in the CPB15+ arm.
- The primary analysis of investigator-assessed PFS (censoring for CA-125 progressions and NPT) shows a stratified hazard ratio of 0.62 (95% CI: 0.52-0.75, 1-sided log-rank p-value < 0.0001) when CPB15+ is compared with CPP, with a median PFS of 12.0 months in the CPP arm and 18.2 months in the CPB15+ arm.
- The analysis of PFS as determined by the independent review committee (censoring for NPT) shows a stratified hazard ratio of 0.62 (95% CI: 0.50-0.77, 1-sided logrank p-value < 0.0001) when CPB15+ is compared with CPP, with a median PFS of 13.1 in the CPP arm and 19.1 months in the CPB15+ arm.

PFS subgroup analyses by disease stage and debulking status are summarized in Table 14. These results demonstrate robustness of the analysis of PFS as shown in Table 13.

Table 14 PFS¹ Results by Disease Stage and Debulking Status from Study GOG-0218

Randomized patients stage III optimally debulked disease^{2,3}			
	CPP (n = 219)	CPB15 (n = 204)	CPB15+ (n = 216)
Median PFS (months)	12.4	14.3	17.5
Hazard ratio (95% CI) ⁴		0.81 (0.62, 1.05)	0.66 (0.50, 0.86)
Randomized patients with stage III suboptimally debulked disease³			
	CPP (n = 253)	CPB15 (n = 256)	CPB15+ (n = 242)
Median PFS (months)	10.1	10.9	13.9
Hazard ratio (95% CI) ⁴		0.93 (0.77, 1.14)	0.78 (0.63, 0.96)
Randomized patients with stage IV disease			
	CPP (n = 153)	CPB15 (n = 165)	CPB15+ (n = 165)
Median PFS (months)	9.5	10.4	12.8
Hazard Ratio (95% CI) ⁴		0.90 (0.70, 1.16)	0.64 (0.49, 0.82)

¹ Investigator assessed GOG protocol-specified PFS analysis (neither censored for CA-125 progressions nor censored for NPT prior to disease progression) with data cut-off date of 25 February, 2010

² With gross residual disease.

³ 3.7% of the overall randomized patient population had Stage IIIB disease. Relative to the control arm.

BO17707 (ICON7)

BO17707 was a Phase III, two arm, multicenter, randomized, controlled, open-label study comparing the effect of adding Avastin to carboplatin plus paclitaxel in patients with FIGO Stage I or IIA (Grade 3 or clear cell histology only; n = 142), or FIGO Stage IIB - IV (all grades and all histological types, n = 1386) epithelial ovarian, fallopian tube or primary peritoneal cancer following surgery.

Patients who had received prior therapy with bevacizumab or prior systemic anticancer therapy for ovarian cancer (e.g. chemotherapy, monoclonal antibody therapy, tyrosine kinase inhibitor therapy, or hormonal therapy) or previous radiotherapy to the abdomen or pelvis were excluded from the study.

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 of 3 weeks duration
- CPB7.5+ arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m²) for 6 cycles of 3 weeks plus Avastin (7.5 mg/kg q3w) for up to 12 months (Avastin was started at cycle 2 of chemotherapy if treatment was initiated within 4 weeks of surgery or at cycle 1 if treatment was initiated more than 4 weeks after surgery).

The majority of patients included in the study were White (96%), the median age was 57 years in both treatment arms, 25% of patients in each treatment arm were 65 years of age or over, and approximately 50% of patients had an ECOG PS of 1; 7% of patients in each treatment arm had an ECOG PS of 2. The majority of patients had EOC (87.7%) followed by PPC (6.9%) and FTC (3.7%) or a mixture of the three origins (1.7%). Most patients were FIGO Stage III (both 68%) followed by FIGO Stage IV (13% and 14%), FIGO Stage II (10% and 11%) and FIGO Stage I (9% and 7%). The majority of the patients in each treatment arm (74% and 71%) had poorly differentiated (Grade 3) primary tumors at baseline. The incidence of each histologic sub-type of EOC was similar between the treatment arms; 69% of patients in each treatment arm had serous adenocarcinoma histologic type.

The primary endpoint was PFS as assessed by the investigator using RECIST criteria.

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (carboplatin and paclitaxel) alone in the front-line setting, 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

The results of this study are summarized in Table 15.

Table 15 Efficacy Results from Study BO17707 (ICON7)

Progression-free survival		
	CP (n = 764)	CPB7.5+ (n = 764)
Median PFS (months) ²	16.9	19.3
Hazard ratio [95% CI] ²	0.86 [0.75; 0.98] (p-value = 0.0185)	
Objective Response Rate¹		
	CP (n = 277)	CPB7.5+ (n = 272)
Response rate	54.9%	64.7%
	(p-value = 0.0188)	
Overall Survival³		
	CP (n = 764)	CPB7.5+ (n = 764)
Median (months)	Not reached	Not reached
Hazard ratio [95% CI]	0.85 [0.70; 1.04] (p-value = 0.1167)	

¹ In patients with measurable disease at baseline.

² Investigator assessed PFS analysis with data cut-off date of 30 November 2010.

³ Exploratory OS analysis when approximately 25% of patients died.

The primary analysis of investigator-assessed PFS with a data cut-off date of 28 February 2010 shows an unstratified hazard ratio of 0.79 (95% CI: 0.68-0.91, 2-sided log-rank p-value 0.0010) with a median PFS of 16.0 months in the CP arm and 18.3 months in the CPB7.5+ arm.

PFS subgroup analyses by disease stage and debulking status are summarized in Table 16. These results demonstrate robustness of the primary analysis of PFS as shown in Table 15.

Table 16 PFS¹ Results by Disease Stage and Debulking Status from Study BO17707 (ICON7)

Randomized patients stage III optimally debulked disease^{2,3}		
	CP (n = 368)	CPB7.5+ (n = 383)
Median PFS (months)	17.7	19.3
Hazard ratio (95% CI) ⁴		0.89 (0.74, 1.07)
Randomized patients with stage III suboptimally debulked disease³		
	CP (n = 154)	CPB7.5+ (n = 140)
Median PFS (months)	10.1	16.9
Hazard ratio (95% CI) ⁴		0.67 (0.52, 0.87)
Randomized patients with stage IV disease		
	CP (n = 97)	CPB7.5+ (n = 104)
Median PFS (months)	10.1	13.5
Hazard Ratio (95% CI) ⁴		0.74 (0.55, 1.01)

¹ Investigator assessed PFS analysis with data cut-off date of 30 November 2010.

² With or without gross residual disease.

³ 5.8% of the overall randomized patient population had Stage IIIB disease.

⁴ Relative to the control arm.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies, in all subsets of the paediatric population, in breast carcinoma, adenocarcinoma of the colon and rectum, lung carcinoma (small cell and non-small cell carcinoma) kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney), ovarian carcinoma (excluding rhabdomyosarcoma and germ cell tumours), fallopian tube carcinoma (excluding rhabdomyosarcoma and germ cell tumours) and peritoneal carcinoma (excluding blastomas and sarcomas).

5.2 Pharmacokinetic properties

The pharmacokinetic data for bevacizumab are available from ten clinical trials in patients with solid tumours. In all clinical trials, bevacizumab was administered as an IV infusion. The rate of infusion was based on tolerability, with an initial infusion duration of 90 minutes. The pharmacokinetics of bevacizumab was linear at doses ranging from 1 to 10 mg/kg.

Distribution

The typical value for central volume (V_c) was 2.73 L and 3.28 L for female and male patients 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 patients had a larger V_c (+ 20%) than female patients.

Metabolism

Assessment of bevacizumab metabolism in rabbits following a single IV dose of ¹²⁵I-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.

Elimination

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.

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.

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.

Renal impairment: No trials 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 trials 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.

Paediatric population

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.

5.3 Preclinical safety data

In studies of up to 26 weeks duration in cynomolgus monkeys, physal dysplasia was observed in young animals with open growth plates, at bevacizumab average serum concentrations below the expected human therapeutic average serum concentrations. In rabbits, bevacizumab was shown to inhibit wound healing at doses below the proposed clinical dose. Effects on wound healing were shown to be fully reversible.

Studies to evaluate the mutagenic and carcinogenic potential of bevacizumab have not been performed.

No specific studies in animals have been conducted to evaluate the effect on fertility. An adverse effect on female fertility can however be expected as repeat dose toxicity studies in animals have shown inhibition of the maturation of ovarian follicles and a decrease/absence of corpora lutea and associated decrease in ovarian and uterus weight as well as a decrease in the number of menstrual cycles.

Bevacizumab 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 malformations. Adverse foetal outcomes were observed at all tested doses, of which the lowest dose resulted in average serum concentrations approximately 3 times larger than in humans receiving 5 mg/kg every 2 weeks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trehalose dihydrate
Sodium phosphate
Polysorbate 20
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

A concentration dependent degradation profile of bevacizumab was observed when diluted with glucose solutions (5%).

6.3 Shelf life

2 years.

Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C to 30°C in sodium chloride 9 mg/ml (0.9%) solution for injection. 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.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

4 ml solution in a vial (Type I glass) with a stopper (butyl rubber) containing 100 mg of bevacizumab.
16 ml solution in a vial (Type I glass) with a stopper (butyl rubber) containing 400 mg of bevacizumab.

Pack of 1 vial.

6.6 Special precautions for disposal and other handling

Avastin should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared solution.

The necessary amount of bevacizumab should be withdrawn and diluted to the required administration volume with sodium chloride 9 mg/ml (0.9%) solution for injection. The concentration of the final bevacizumab solution should be kept within the range of 1.4-16.5 mg/ml.

Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration.

Avastin is for single-use only, as the product contains no preservatives. Any unused product or waste material should be disposed of in accordance with local requirements.

No incompatibilities between Avastin and polyvinyl chloride or polyolefine bags or infusion sets have been observed.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited
6 Falcon Way
Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/300/001 – 100 mg/4 ml vial
EU/1/04/300/002 – 400 mg/16 ml vial

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 January 2005
Date of latest renewal: 14 January 2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMA): <http://www.ema.europa.eu>