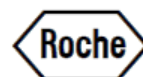


Avastin®



BEVACIZUMAB

Concentrate for solution for intravenous infusion

1. NAME OF THE MEDICINAL PRODUCT

Avastin 25 mg/ml concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 25 mg of bevacizumab*.

Each 4 ml vial contains 100 mg of bevacizumab.

Each 16 ml vial contains 400 mg of bevacizumab.

For dilution and other handling recommendations, see section 6.6.

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

Excipient with known effect

Each 4 ml vial contains 1.6 mg of polysorbate 20.

Each 16 ml vial contains 6.4 mg of polysorbate 20.

For the 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 human epidermal growth factor receptor 2 (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 erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations (see section 5.1).

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

Avastin, as a single agent, is indicated for the treatment of glioblastoma in patients with progressive disease following prior therapy.

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 in patients who are at high risk for recurrence (residual disease after debulking).

Avastin, in combination with carboplatin and gemcitabine, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.

Bevacizumab in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents (see section 5.1).

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

Bevacizumab, in combination with atezolizumab, is indicated for the treatment of patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy. Refer to the Prescribing Information for medicines administered in combination with bevacizumab for further information.

4.2 Posology and method of administration

Do not shake the vial.

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

Posology

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)

First-line treatment of non-squamous NSCLC in combination with platinum-based chemotherapy

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 (see section 5.1).

It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

First-line treatment of non-squamous NSCLC with EGFR activating mutations in combination with erlotinib

EGFR mutation testing should be performed prior to initiation of treatment with the combination of Avastin and erlotinib. It is important that a well-validated and robust methodology is chosen to avoid false negative or false positive determinations.

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

It is recommended that the treatment with Avastin in addition to erlotinib is continued until disease progression.

For the posology and method of administration of erlotinib, please refer to the full erlotinib prescribing information.

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.

Malignant Glioma (WHO Grade IV)- Glioblastoma

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

Epithelial ovarian, fallopian tube and primary peritoneal cancer

Front-line treatment: 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.

Treatment of platinum-sensitive recurrent disease: Avastin is 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. The recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

Treatment of platinum-resistant recurrent disease: Avastin is administered in combination with one of the following agents – paclitaxel, topotecan (given weekly) or pegylated liposomal doxorubicin. The recommended dose of Avastin is 10 mg/kg of body weight given once every 2 weeks as an intravenous infusion. When Avastin is administered in combination with topotecan (given on days 1-5, every 3 weeks), 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 treatment be continued until disease progression or unacceptable toxicity (see section 5.1, study MO22224).

Cervical cancer

Avastin is administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin or paclitaxel and topotecan.

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 treatment be continued until progression of the underlying disease or until unacceptable toxicity (see section 5.1).

Special populations

Elderly patients: No dose adjustment is required in the patients ≥ 65 years of age.

Patients with renal impairment: The safety and efficacy have not been studied in patients with renal impairment (see section 5.2).

Patients with hepatic impairment: The safety and efficacy have not been studied in patients with hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of bevacizumab in children aged less than 18 years old have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

There is no relevant use of bevacizumab in the paediatric population in the indications for treatment of cancers of the colon, rectum, breast, lung, ovarian, fallopian tube, peritoneum, cervix and kidney.

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.

It should not be administered as an intravenous push or bolus.

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

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 listed in section 6.1.
- 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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Gastrointestinal (GI) perforations and Fistulae (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. Prior radiation is a risk factor for GI perforation in patients treated for persistent, recurrent or metastatic cervical cancer with Avastin and all patients with GI perforation had a history of prior radiation. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.

GI-vaginal Fistulae in study GOG-0240

Patients treated for persistent, recurrent, or metastatic cervical cancer with Avastin are at increased risk of fistulae between the vagina and any part of the GI tract (Gastrointestinal-vaginal fistulae). Prior radiation is a major risk factor for the development of GI-vaginal fistulae and all patients with GI-vaginal fistulae had a history of prior radiation. Recurrence of cancer within the field of prior radiation is an additional important risk factor for the development of GI-vaginal fistulae.

Non-GI 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 tracheoesophageal (TE) fistula or any Grade 4 fistula [US National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE v.3)]. Limited information is available on the continued use of Avastin in patients with other fistulae.

In cases of internal fistula not arising in the gastrointestinal tract, discontinuation of Avastin should be considered.

Wound healing complications (see section 4.8)

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

Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with Avastin. This condition is 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.

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.

Posterior Reversible Encephalopathy Syndrome (PRES) (see section 4.8)

There have been rare reports of Avastin-treated patients developing signs and symptoms that are consistent with PRES, 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 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.

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 Terminology Criteria for Adverse Events [NCI-CTCAE v.3]) proteinuria may be related to the dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with Avastin. Therapy should be permanently discontinued in patients who develop nephrotic syndrome (NCI-CTCAE v.3).

Arterial thromboembolism (see section 4.8)

In clinical trials, the incidence of arterial thromboembolic reactions 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, diabetes or age greater than 65 years have an increased risk of developing arterial thromboembolic reactions during therapy. Caution should be taken when treating these patients with Avastin.

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

Venous thromboembolism (see section 4.8)

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

Patients treated for persistent, recurrent, or metastatic cervical cancer with Avastin in combination with paclitaxel and cisplatin may be at increased risk of venous thromboembolic events.

Avastin should be discontinued in patients with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism (NCI-CTCAE v.3). Patients with thromboembolic reactions ≤ Grade 3 need to be closely monitored (NCI-CTCAE v.3).

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 (NCI-CTCAE v.3) (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 (NCI-CTCAE v.3).

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.

Aneurysms and artery dissections

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating Avastin, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Congestive heart failure (CHF) (see section 4.8)

Reactions 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 reactions 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 (NCI-CTCAE v.3) (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, mBC, and in combination with paclitaxel and topotecan in persistent, recurrent, or metastatic cervical cancer.

Hypersensitivity reactions (including anaphylactic shock) /infusion reactions (see section 4.8)

Patients may be at risk of developing infusion/hypersensitivity reactions (including anaphylactic shock). Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanised 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 (ONJ) (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 intravenous bisphosphonates, for which ONJ is an identified risk. Caution should be exercised when Avastin and intravenous 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 intravenous bisphosphonates invasive dental procedures should be avoided, if possible.

Intravitreal use

Avastin is not formulated for intravitreal use.

Eye disorders

Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intravitreal use of Avastin compounded from vials approved for intravenous administration in cancer patients. 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 reactions have resulted in various degrees of visual loss, including permanent blindness.

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 haemorrhages and arterial thromboembolic reactions have been reported following intravitreal injection of VEGF inhibitors.

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.

Excipients

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

This medicine contains 1.6 mg of polysorbate 20 in each 100 mg/4 ml vial and 6.4 mg in each 400 mg/16 ml vial which is equivalent to 0.4 mg/ml. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of antineoplastic agents on bevacizumab pharmacokinetics

No clinically relevant interaction of co-administered chemotherapy on bevacizumab pharmacokinetics was observed based on the results of population pharmacokinetic analyses. There were neither statistically significant nor clinically relevant differences in bevacizumab clearance in patients receiving Avastin monotherapy compared to patients receiving Avastin in combination with interferon alfa-2a, erlotinib or chemotherapies (IFL, 5-FU/LV, carboplatin/paclitaxel, capecitabine, doxorubicin or cisplatin/gemcitabine).

Effect of bevacizumab on the pharmacokinetics of other antineoplastic agents

No clinically relevant interaction of bevacizumab was observed on the pharmacokinetics of co-administered interferon alfa 2a, erlotinib (and its active metabolite OSI-420), or the chemotherapies irinotecan (and its active metabolite SN38), capecitabine, oxaliplatin (as determined by measurement of free and total platinum), and cisplatin. Conclusions on the impact of bevacizumab on gemcitabine pharmacokinetics cannot be drawn.

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*, *PRES* 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.

EGFR monoclonal antibodies in combination with bevacizumab chemotherapy regimens

No interaction studies have been performed. EGFR monoclonal antibodies should not be administered for the treatment of mCRC in combination with bevacizumab-containing chemotherapy. Results from the randomised phase III studies, PACCE and CAIRO-2, in patients with mCRC suggest that the use of anti-EGFR monoclonal antibodies panitumumab and cetuximab, respectively, in combination with bevacizumab plus chemotherapy, is associated with decreased PFS and/or OS, and with increased toxicity compared with bevacizumab plus chemotherapy alone.

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 clinical trial 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. 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 4.8). Avastin is contraindicated in pregnancy (see section 4.3).

Breast-feeding

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

Avastin has no or negligible influence on the ability to drive and use machines. However, somnolence and syncope have been reported with Avastin use (see table 1 in section 4.8). If

patients are experiencing symptoms that affect their vision or concentration, or their ability to react, they should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of Avastin is based on data from over 5,700 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.

Tabulated list of adverse reactions

The adverse reactions listed in this section fall into the following frequency categories: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

Tables 1 and 2 list adverse reactions associated with the use of Avastin in combination with different chemotherapy regimens in multiple indications, by MedDRA system organ class.

Table 1 provides all adverse reactions by frequency that were determined to have a causal relationship with Avastin through:

- comparative incidences noted between clinical trial treatment arms (with at least a 10% difference compared to the control arm for NCI-CTCAE Grade 1-5 reactions or at least a 2% difference compared to the control arm for NCI-CTCAE Grade 3-5 reactions,
- post-authorisation safety studies,
- spontaneous reporting,
- epidemiological studies/non-interventional or observational studies,
- or through an evaluation of individual case reports.

Table 2 provides the frequency of severe adverse reactions. Severe reactions are defined as adverse events with at least a 2% difference compared to the control arm in clinical studies for NCI-CTCAE Grade 3-5 reactions. Table 2 also includes adverse reactions which are considered by the MAH to be clinically significant or severe.

Post-marketing adverse reactions are included in both Tables 1 and 2, where applicable. Detailed information about these post-marketing reactions are provided in Table 3.

Adverse reactions are added to the appropriate frequency category in the tables below according to the highest incidence seen in any indication.

Within each frequency category, adverse reactions are presented in the 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, nail disorders or alopecia with paclitaxel, and paronychia with erlotinib.

Table 1: Adverse reactions by frequency

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Infections and infestations		Sepsis, Abscess ^{b,d} , Cellulitis, Infection, Urinary tract infection		Necrotising fasciitis ^a		
Blood and lymphatic system disorders	Febrile neutropenia, Leucopenia, Neutropenia ^b , Thrombocytopenia	Anaemia, Lymphopenia				
Immune system disorders		Hypersensitivity, infusion reactions ^{a,b,d}		Anaphylactic shock		
Metabolism and nutrition disorders	Anorexia, Hypomagnesaemia ^a , Hyponatraemia	Dehydration				
Nervous system disorders	Peripheral sensory neuropathy ^b , Dysarthria, Headache, Dysguesia	Cerebrovascular accident, Syncope, Somnolence		Posterior reversible encephalopathy syndrome ^{a,b,d}	Hypertensive encephalopathy ^a	
Eye disorders	Eye disorder, Lacrimation increased					
Cardiac disorders		Congestive heart failure ^{b,d} , Supraventricular tachycardia				
Vascular disorders	Hypertension ^{b,d} , Thromboembolism (venous) ^{b,d}	Thromboembolism (arterial) ^{b,d} , Haemorrhage ^{b,d} , Deep vein thrombosis				Renal thrombotic micro-angiopathy ^{a,b} , Hyaline occlusive glomerular microangiopathy ^a , Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders	Dyspnoea, Rhinitis, Epistaxis, Cough	Pulmonary haemorrhage/ Haemoptysis ^{b,d} , Pulmonary embolism, Hypoxia, Dysphonia ^a				Pulmonary hypertension ^a , Nasal septum perforation ^a
Gastrointestinal disorders	Rectal haemorrhage, Stomatitis, Constipation, Diarrhoea, Nausea, Vomiting, Abdominal pain	Gastrointestinal perforation ^{b,d} , Intestinal perforation, Ileus, Intestinal obstruction, Recto-vaginal fistulae ^{d,e}				Gastrointestinal ulcer ^a

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
		Gastrointestinal disorder, Proctalgia				
Hepatobiliary disorders						Gallbladder perforation ^{a,b}
Skin and subcutaneous tissue disorders	Wound healing complications ^{b,d} Exfoliative dermatitis, Dry skin, Skin discolouration	Palmar-plantar erythro-dysaesthesia syndrome				
Musculoskeletal and connective tissue disorders	Arthralgia, Myalgia	Fistula ^{b,d} , Muscular weakness, Back pain				Osteonecrosis of the jaw ^{a,b} Non - mandibular osteonecrosis ^{a,f}
Renal and urinary disorders	Proteinuria ^{b,d}					
Reproductive system and breast disorders	Ovarian failure ^{b,c,d}	Pelvic pain				
Congenital, familial, and genetic disorder						<u>Foetal abnormalities</u> ^{a,b}
General disorders and administration site conditions	Asthenia, Fatigue, Pyrexia, Pain, Mucosal inflammation	Lethargy				
Investigations	Weight decreased					

When events were noted as both all grade and grade 3-5 adverse drug reactions in clinical trials, the highest frequency observed in patients has been reported. Data are unadjusted for the differential time on treatment.

^a For further information please refer to Table 3 'Adverse reactions reported in post-marketing setting.'

^b Terms represent a group of events that describe a medical concept rather than a single condition or MedDRA (Medical Dictionary for Regulatory Activities) preferred term. This group of medical terms may involve the same underlying pathophysiology (e.g. arterial thromboembolic reactions include cerebrovascular accident, myocardial infarction, transient ischaemic attack and other arterial thromboembolic reactions).

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

^d For additional information refer below within section "Further information on selected serious adverse reactions."

^e Recto-vaginal fistulae are the most common fistulae in the GI-vaginal fistula category.

^f Observed in paediatric population only

Table 2: Severe adverse reactions by frequency

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Infections and infestations		Sepsis, Cellulitis, Abscess ^{a,b} , Infection, Urinary tract infection				Necrotising fasciitis ^c
Blood and lymphatic system disorders	Febrile neutropenia, Leucopenia, Neutropenia ^a , Thrombocytopenia	Anaemia, Lymphopenia				

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Immune system disorders		Hypersensitivity, infusion reactions ^{a,b,c}		Anaphylactic shock		
Metabolism and nutrition disorders		Dehydration, Hyponatraemia				
Nervous system disorders	Peripheral sensory neuropathy ^a	Cerebrovascular accident, Syncope, Somnolence, Headache				Posterior reversible encephalopathy syndrome ^{a,b,c} , Hypertensive encephalopathy ^c
Cardiac disorders		Congestive heart failure ^{a,b} , Supraventricular tachycardia				
Vascular disorders	Hypertension ^{a,b}	Thromboembolism arterial ^{a,b} , Haemorrhage ^{a,b} , Thromboembolism (venous) ^{a,b} , Deep vein thrombosis				Renal thrombotic microangiopathy ^{b,c} , Hyaline occlusive glomerular microangiopathy ^c , Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders		Pulmonary haemorrhage/ Haemoptysis ^{a,b} , Pulmonary embolism, Epistaxis, Dyspnoea, Hypoxia				Pulmonary hypertension ^c , Nasal septum perforation ^c
Gastrointestinal disorders	Diarrhoea, Nausea, Vomiting, Abdominal pain	Intestinal perforation, Ileus, Intestinal obstruction, Recto-vaginal fistulae ^{c,d} , Gastrointestinal disorder, Stomatitis, Proctalgia				Gastrointestinal perforation ^{a,b} , Gastrointestinal ulcer ^c , Rectal haemorrhage
Hepatobiliary disorders						Gallbladder perforation ^{b,c}
Skin and subcutaneous tissue disorders		Wound healing complications ^{a,b} , Palmar-plantar erythrodysesthesia syndrome				
Musculoskeletal and connective tissue disorders		Fistula ^{a,b} , Myalgia, Arthralgia, Muscular weakness, Back pain				Osteonecrosis of the jaw ^{b,c}
Renal and urinary disorders		Proteinuria ^{a,b}				
Reproductive system and breast disorders		Pelvic pain				Ovarian failure ^{a,b}
Congenital, familial, and genetic disorder						Foetal abnormalities ^{a,c}

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
General disorders and administration site conditions	Asthenia, Fatigue,	Pain, Lethargy, Mucosal inflammation				

Table 2 provides the frequency of severe adverse reactions. Severe reactions are defined as adverse events with at least a 2% difference compared to the control arm in clinical studies for NCI-CTCAE Grade 3-5 reactions. Table 2 also includes adverse reactions which are considered by the MAH to be clinically significant or severe. These clinically significant adverse reactions were reported in clinical trials but the grade 3-5 reactions did not meet the threshold of at least a 2% difference compared to the control arm. Table 2 also includes clinically significant adverse reactions that were observed only in the postmarketing setting, therefore, the frequency and NCI-CTCAE grade is not known. These clinically significant reactions have therefore been included in Table 2 within the column entitled "Frequency Not Known."

^a Terms represent a group of events that describe a medical concept rather than a single condition or MedDRA (Medical Dictionary for Regulatory Activities) preferred term. This group of medical terms may involve the same underlying pathophysiology (e.g. arterial thromboembolic reactions include cerebrovascular accident, myocardial infarction, transient ischaemic attack and other arterial thromboembolic reactions).

^b For additional information refer below within section "Further information on selected serious adverse reactions"

^c For further information please refer to Table 3 'Adverse reactions reported in post-marketing setting'.

^d Recto-vaginal fistulae are the most common fistulae in the GI-vaginal fistula category.

Description of selected serious adverse reactions

Gastrointestinal (GI) perforations and Fistulae (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 non-squamous non-small cell lung cancer, up to 1.3% in patients with metastatic breast cancer, up to 2.0% in patients with metastatic renal cell cancer or in patients with ovarian cancer, 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.

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.

GI-vaginal Fistulae in study GOG-0240

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. The frequency of GI-vaginal fistulae in the group treated with Avastin + chemotherapy was higher in patients with recurrence within the field of prior radiation (16.7%) compared with patients with no prior radiation and/ or no recurrence inside the field of prior radiation (3.6%). The corresponding frequencies in the control group receiving chemotherapy alone were 1.1% vs. 0.8%, respectively. 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 4.4)

Avastin use has been associated with serious cases of fistulae including reactions 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 and biliary fistulae) were observed across various indications. Fistulae have also been reported in post-marketing experience.

Reactions were reported at various time points during treatment ranging from one week to greater than 1 year from initiation of Avastin, with most reactions 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 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.

Serious wound healing complications, including anastomotic complications, have been reported, some of which had a fatal outcome.

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 (NCI-CTCAE v.3).

In clinical trials of ovarian cancer, Grade 3-5 wound healing complications were observed in up to 1.8% of patients in the bevacizumab arm versus 0.1% in the control arm (NCI-CTCAE v.3).

Hypertension (see section 4.4)

In clinical trials, with the exception of study JO25567, the overall incidence of hypertension (all grades) ranged up to 42.1% in the Avastin containing arms compared with up to 14% in the control arms. 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 and chemotherapy compared to up to 0.2% of patients treated with the same chemotherapy alone.

In study JO25567, all grade hypertension was observed in 77.3% of the patients who received Avastin in combination with erlotinib as first-line treatment for non-squamous NSCLC with EGFR activating mutations, compared to 14.3% of patients treated with erlotinib alone. Grade 3 hypertension was 60.0% in patients treated with Avastin in combination with erlotinib compared to 11.7% in patients treated with erlotinib alone. There were no grade 4 or 5 hypertension events.

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.

Posterior Reversible Encephalopathy Syndrome (see section 4.4)

There have been rare reports of Avastin-treated patients developing signs and symptoms that are consistent with PRES, a rare neurological disorder. Presentation may include seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. The clinical presentation of PRES is often nonspecific, and therefore the diagnosis of PRES requires confirmation by brain imaging, preferably MRI.

In patients developing PRES, early recognition of symptoms with prompt treatment of specific symptoms including control of hypertension (if associated with severe uncontrolled hypertension) is recommended in addition to discontinuation of bevacizumab therapy. Symptoms usually resolve or improve within days after treatment discontinuation, although some patients have experienced some neurologic sequelae. The safety of reinitiating Avastin therapy in patients previously experiencing PRES is not known.

Across clinical trials, 8 cases of PRES have been reported. Two of the eight cases did not have radiological confirmation via MRI.

Proteinuria (see section 4.4)

In clinical trials, proteinuria has been reported within the range of 0.7% to 54.7% 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 (NCI-CTCAE v.3). Grade 3 proteinuria was reported in up to 10.9% of treated patients. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of treated patients. 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-CTCAE v.3 Grade 3-5 bleeding reactions ranged from 0.4% to 6.9% in Avastin treated patients, compared with up to 4.5% of patients in the chemotherapy control group.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), grade 3-5 bleeding reactions have been reported in up to 8.3% of patients treated with Avastin in combination with paclitaxel and topotecan compared with up to 4.6% of patients treated with paclitaxel and topotecan.

The haemorrhagic reactions 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

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 reactions were observed in 11% (11/100) of 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 up to 6.3% (5/79) of patients who received Avastin in combination with irinotecan compared to up to 4.8% (4/84) of patients who received Avastin alone.

Venous thromboembolism:

The incidence of venous thromboembolic reactions in clinical trials was similar in patients receiving Avastin in combination with chemotherapy compared to those receiving the control chemotherapy alone. Venous thromboembolic reactions include deep venous thrombosis, pulmonary embolism and thrombophlebitis.

In clinical trials across indications, the overall incidence of venous thromboembolic reactions 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 (NCI-CTCAE v.3) venous thromboembolic reactions 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 (across indications, excluding persistent, recurrent, or metastatic cervical cancer).

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 15.6% of patients treated with Avastin in combination with paclitaxel and cisplatin compared with up to 7.0% of patients treated with paclitaxel and cisplatin.

Patients who have experienced a venous thromboembolic reaction 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 (NCI-CTCAE v.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

*Clinical efficacy and safety**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.

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

Table 4 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% CI	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 5). 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 5.

Table 5 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% CI				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 intravenous 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 intravenous 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 6 Treatment regimens in trial NO16966 (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	Oxaliplatin	130 mg/m ² IV 2 h	Oxaliplatin on day 1

	Treatment	Starting dose	Schedule
or XELOX + Avastin	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 7).

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 7), consistent with the statistically significant benefit observed in the pooled analysis.

Table 7 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 intravenous oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule in previously-treated patients (second line) with advanced colorectal cancer. In the chemotherapy arms, the FOLFOX-4 regimen used the same doses and schedule as shown in Table 6 for trial NO16966.

The primary efficacy parameter of the trial was overall survival, defined as the time from randomisation to death from any cause. Eight hundred and twenty-nine patients were randomised (292 FOLFOX-4, 293 Avastin + FOLFOX-4 and 244 Avastin monotherapy). The addition of Avastin to FOLFOX-4 resulted in a statistically significant prolongation of survival. Statistically significant improvements in progression-free survival and objective response rate were also observed (see Table 8).

Table 8 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% CI	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.

ML18147

This was a phase III randomised, 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 mCRC who have progressed on a first-line bevacizumab-containing regimen.

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

A total of 820 patients were randomised. The addition of bevacizumab to fluoropyrimidine-based chemotherapy resulted in a statistically significant prolongation of survival in patients with

