Avastin®

Bevacizumab

Antineoplastic agent

Composition

Active substances
Bevacizumab (manufactured by recombinant DNA technology using CHO [Chinese hamster ovary] cells).

Excipients
α,α-Trehalose dihydrate, sodium dihydrogen phosphate monohydrate, anhydrous disodium phosphate, polysorbate 20, water for injection.

1 ml of concentrate contains 1.35 mg sodium, i.e. 5.42 mg or 21.67 mg per vial.Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion.

Clear to slightly opalescent, colourless to pale brown sterile fluid for intravenous infusion.

Each 4 ml vial contains 100 mg bevacizumab.

Each 16 ml vial contains 400 mg bevacizumab.

Indications/Uses

Metastatic colorectal cancer
Avastin (bevacizumab) is indicated for first-line treatment of patients with metastatic carcinoma of the colon or rectum in combination with the following chemotherapies:

- 5-fluorouracil/folinic acid
- 5-fluorouracil/folinic acid/irinotecan
- capecitabine/oxaliplatin (XELOX)

Avastin is indicated as second-line therapy in combination with an irinotecan- or oxaliplatin-based chemotherapy regimen in patients with metastatic colorectal cancer with prior oxaliplatin- or irinotecan-based chemotherapy with or without Avastin.

Metastatic breast cancer
Avastin (bevacizumab) is indicated in combination with paclitaxel for first-line treatment of patients with HER2-negative, metastatic breast cancer.

Advanced, metastatic or recurrent non-small cell lung cancer (NSCLC)
First-line therapy in combination with cisplatin- and gemcitabine-containing chemotherapy in unresectable, advanced, metastatic or recurrent, non-squamous non-small cell lung cancer (NSCLC).

Advanced and/or metastatic renal cell cancer

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

Glioblastoma (WHO Grade IV)

Avastin is indicated as a single agent for the treatment of patients with relapsed glioblastoma (WHO Grade IV) after prior therapy with temozolomide.

Ovarian cancer

Previously untreated patients

Avastin is indicated in combination with carboplatin and paclitaxel for the treatment of previously untreated patients with ovarian cancer (FIGO stages III and IV) in whom complete tumour resection was not possible and who are unlikely to benefit from further surgery after chemotherapy (second-look surgery with interval debulking).

Relapsing platinum-sensitive patients

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

Relapsing platinum-resistant patients

Avastin is indicated in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin for the treatment of patients with recurrent, platinum-resistant epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer who have been treated with up to two prior chemotherapy regimens and have not been previously treated with bevacizumab or other VEGF inhibitors.

Cervical cancer

Avastin is indicated in combination with chemotherapy (see “Properties/Effects: Cervical cancer”) for the treatment of patients with persistent, recurrent or metastatic cervical cancer.

Dosage/Administration

The initial dose of Avastin should be administered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion can be infused over 60 minutes. If the infusion administered over 60 minutes is well tolerated, an infusion duration of 30 minutes is sufficient for all subsequent infusions.

Do not administer as an intravenous bolus injection.

Avastin infusions must not be administered or mixed with glucose solutions.

To ensure the traceability of biological medicinal products, it is recommended that the trade name and batch number be documented with every treatment.

Usual dosage

Metastatic colorectal cancer

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

First-line treatment: 5 mg/kg body weight once every 2 weeks or 7.5 mg/kg body weight once every 3 weeks.

Second-line treatment: 5 mg/kg or 10 mg/kg body weight once every 2 weeks or 7.5 mg/kg or 15 mg/kg body weight once every 3 weeks.

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

Metastatic breast cancer

The recommended dose of Avastin is 10 mg/kg body weight given once every 2 weeks or 15 mg/kg body weight given once every 3 weeks as an intravenous infusion. It is recommended that Avastin treatment be continued until progression of the malignant disease.

Advanced, metastatic or recurrent non-small cell lung cancer (NSCLC)

Avastin is administered in conjunction with cisplatin- and gemcitabine-containing chemotherapy for up to 6 treatment cycles. It is then continued as monotherapy until disease progression.

The recommended dosage of Avastin in combination with cisplatin- and gemcitabine-containing chemotherapy is 7.5 mg/kg body weight once every 3 weeks as an intravenous infusion.

Advanced and/or metastatic renal cell cancer

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

It is recommended that Avastin treatment be continued until progression of the disease. The 5 mg/kg body weight dose has not been studied.

Glioblastoma (WHO Grade IV)

The recommended dose of Avastin is 10 mg/kg body weight every 2 weeks as an intravenous infusion. It is recommended that Avastin treatment be continued until progression of the disease. The dosage of 15 mg/kg every 3 weeks is not supported by the submitted data.

Ovarian cancer

Previously untreated patients:

Avastin is administered in combination with carboplatin and paclitaxel for up to 6 treatment cycles. Avastin is then administered for 15 months or until disease progression, should this occur earlier. The recommended dose of Avastin is 7.5 mg/kg body weight given once every 3 weeks as an intravenous infusion.

Relapsing platinum-sensitive patients:

Avastin is administered in combination with carboplatin and gemcitabine for 6 to 10 treatment cycles or in combination with carboplatin and paclitaxel for 6 to 8 treatment cycles. Avastin is then administered until disease progression. The recommended dose of Avastin is 15 mg/kg body weight given once every 3 weeks as an intravenous infusion.

Relapsing platinum-resistant patients:

In combination with paclitaxel, topotecan (administered weekly) or pegylated liposomal doxorubicin, the recommended dose of Avastin is 10 mg/kg body weight given once every 2 weeks as an intravenous infusion. In combination with topotecan, administered on days 1-5, the recommended dose of Avastin is 15 mg/kg body weight given once every 3 weeks as an intravenous infusion.

Cervical cancer

Avastin is administered in combination with paclitaxel and cisplatin or paclitaxel and topotecan.

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

Dose adjustment following undesirable effects/interactions

Reducing the dose of Avastin because of adverse events is not recommended. If necessary, Avastin should be withdrawn permanently or temporarily (see "Warnings and precautions").

Special dosage instructions

Patients with hepatic impairment

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

Patients with renal impairment

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

Elderly patients

No dose adjustment is required in patients ≥65 years of age (see "Warnings and precautions" and "Undesirable effects").

Children and adolescents

Avastin is not approved for children and adolescents under 18 years of age. The safety and efficacy of Avastin in this population have not been established (see end of "Properties/Effects" and "Pharmacokinetics" sections).

Attention should be paid to reports of non-mandibular osteonecrosis occurring in patients under 18 years of age. Attention is also drawn to the epiphyseal dysplasia findings in animal studies (see "Preclinical data").

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed under "Composition".

Hypersensitivity to CHO (Chinese hamster ovary) cell products or other recombinant human or humanised antibodies.

Pregnancy.

Warnings and precautions

Gastrointestinal perforation and fistula

Patients may be at increased risk of developing gastrointestinal perforation and gall bladder perforation if treated with Avastin (see "Undesirable effects"). Avastin must be permanently discontinued in patients developing gastrointestinal perforation.

Patients with persistent, recurrent or metastatic cervical cancer treated with Avastin may be at increased risk of developing fistulae between the vagina and gastrointestinal tract (gastrointestinal-vaginal fistulae; see "Undesirable effects").

Non-gastrointestinal fistulae

Patients may be at increased risk of developing a fistula when treated with Avastin (see "Undesirable effects").

Avastin should be permanently discontinued in patients with a tracheo-oesophageal fistula (TOF) or other Grade 4 fistula. Only limited information is available on the continued use of Avastin in patients with other types of fistula. In cases of internal fistula not arising in the GI tract, discontinuation of Avastin should be considered.

Haemorrhage

Patients treated with Avastin have an increased risk of haemorrhage, especially tumour-associated haemorrhage (see "Undesirable effects", "Haemorrhage"). Avastin should be permanently withdrawn in patients developing Grade 3 or 4 bleeding on Avastin therapy.

Patients with untreated CNS metastases have been routinely excluded from clinical trials with Avastin, based on imaging procedures or signs and symptoms. For this reason the risk of CNS haemorrhage in such patients has not been prospectively evaluated in randomised clinical studies (see "Pulmonary haemorrhage and haemoptysis"). Patients should be monitored for signs and symptoms of CNS bleeding, and Avastin treatment discontinued in case of intracranial bleeding.

Since daily use of non-steroidal anti-inflammatory drugs (NSAIDs: acetylsalicylic acid at doses >325 mg/day and other NSAIDs) was excluded in the clinical studies, no experience is available on Avastin in combination with these substances.

No information is available on the safety profile of Avastin in patients with congenital blood disorders or acquired coagulopathy, or in those receiving anticoagulants at full dose for the treatment of thromboembolism before starting Avastin therapy, since such patients were excluded from the clinical studies. For this reason caution is advised before starting Avastin therapy in such patients.

Only limited data are available on patients receiving prophylactic anticoagulants. However, in these patients the rate of Grade 3 or higher bleeding did not appear to be increased. The same also applies to patients developing venous thrombosis during Avastin therapy who were treated concomitantly with warfarin at full dose and Avastin.

No experience is available on acenocoumarol or phenprocoumon in combination with Avastin.

Pulmonary haemorrhage and haemoptysis

Patients with non-small cell lung cancer (NSCLC) treated with Avastin may be at risk of serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis (see "Undesirable effects", "Tumour-associated haemorrhage"). Patients with recent pulmonary haemorrhage/haemoptysis (>½ teaspoon of blood per event) must not be treated with Avastin.

Hypertension

An increased incidence of hypertension has been observed in patients treated with Avastin. Clinical safety data indicate that the incidence of hypertension is dose-dependent. Pre-existing hypertension should be adequately controlled before starting Avastin treatment. No data are available on the effect of Avastin in patients with untreated hypertension on starting Avastin therapy. Blood pressure monitoring is recommended during Avastin therapy (see "Undesirable effects").

In most cases hypertension was adequately controlled with standard antihypertensive therapy tailored to the individual patient. Avastin should be permanently discontinued if clinically significant hypertension cannot be adequately controlled by antihypertensive treatment or if the patient develops a hypertensive crisis or hypertensive encephalopathy (see also further below and "Undesirable effects").

Encephalopathy

Hypertensive encephalopathy

Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal. The symptoms of hypertensive encephalopathy include headache, decreased attention, confusion or stupor, with or without convulsions (see "Undesirable effects" and "Hypertension").

Posterior reversible leukoencephalopathy syndrome (PRLS)

There have been rare reports of Avastin-treated patients developing signs and symptoms consistent with posterior reversible leukoencephalopathy syndrome (PRLS), a rare neurological disorder that can present with the following signs and symptoms, among others: seizures, headache, altered mental status, and visual disturbance or cortical blindness, with or without associated hypertension. The diagnosis of PRLS must be confirmed by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRLS, treatment of specific symptoms including hypertension is recommended along with discontinuation of Avastin. The safety of reinitiating Avastin therapy in patients previously experiencing PRLS is not known (see "Undesirable effects").

Differential diagnosis between hypertensive encephalopathy and posterior reversible leukoencephalopathy syndrome can be difficult and mixed forms are also possible.

Arterial thromboembolism

In clinical studies the incidence of arterial thromboembolism including stroke, transient ischaemic attack (TIA) and myocardial infarction in patients receiving Avastin in combination with chemotherapy was higher than in those receiving chemotherapy alone (see "Undesirable effects").

Avastin should be permanently withdrawn in patients developing arterial thromboembolism.

Patients with a history of arterial thromboembolism, diabetes or age over 65 years receiving Avastin in combination with chemotherapy have an increased risk of arterial thromboembolism during treatment with Avastin. For this reason caution is advised in the treatment of such patients with Avastin.

Venous thromboembolism

Patients may be at risk of developing venous thromboembolic events, including pulmonary embolism, under Avastin treatment (see "Undesirable effects").

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

Congestive heart failure

Events consistent with congestive heart failure (CHF) were reported in clinical trials. Symptoms ranged from an asymptomatic decrease in left ventricular ejection fraction (LVEF) to symptomatic CHF requiring treatment or hospitalisation.

Most of the patients with CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or had other risk factors for CHF, such as pre-existing coronary heart disease or concomitant cardiotoxic therapy (see "Undesirable effects"). Caution is advised when treating patients with clinically relevant cardiovascular disease or pre-existing CHF with Avastin.

Neutropenia

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

Wound healing

Avastin may adversely affect the wound healing process (see "Preclinical data" and "Undesirable effects"). Serious wound healing complications with fatal outcome have been reported.

Avastin therapy should not be initiated for at least 28 days following major surgery or until wound healing is complete. In patients developing wound healing complications during Avastin therapy, Avastin must be withdrawn until the wound has completely healed. Avastin therapy should be suspended for elective surgery.

Rare cases of necrotising fasciitis, including some with fatal outcome, have been reported in association with the use of Avastin. Most of these cases occurred in patients with risk factors such as immunosuppression, wound healing complications, gastrointestinal perforation or fistula formation. Avastin therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated (see "Undesirable effects").

Proteinuria

In clinical studies the frequency of proteinuria in patients on Avastin in combination with chemotherapy was higher than in patients on chemotherapy alone. Grade 4 proteinuria (nephrotic syndrome) occurred in up to 1.4% of patients treated with Avastin (see "Undesirable effects").

Avastin should be permanently discontinued in the case of nephrotic syndrome.

Hypersensitivity reactions, anaphylactic reactions (including anaphylactic shock), infusion-related reactions

Patients may be at risk of developing hypersensitivity reactions, anaphylactic reactions (including anaphylactic shock), and infusion-related reactions.Hypersensitivity reactions/infusion reactions occurred frequently (in up to 5% of patients treated with bevacizumab) in some clinical trials. Infusion reactions reported in clinical trials and postmarketing experience included hypertension, hypertensive crises associated with neurological signs and symptoms, wheezing, oxygen desaturation, NCI-CTC Grade 3 hypersensitivity, chest pain, headaches, flu symptoms and diaphoresis. Symptoms can occur during or immediately after the infusion, or up to 2 days later. It is recommended that patients be closely monitored during and after Avastin administration.

If an anaphylactic reaction occurs, the infusion should be permanently discontinued and appropriate medical therapies should be administered.

If an infusion-related reaction occurs, treatment should be temporarily interrupted until resolution of symptoms. Permanently discontinue Avastin in case of severe (grade ≥3) infusion-related reactions. No

data are available on the use of premedication. There are likewise no data regarding the most appropriate method for identifying patients who may safely be re-treated with Avastin after a serious infusion reaction.

Immunogenicity

Patients from two phase III studies on the adjuvant treatment of colon cancer were screened by immunoassay for anti-Avastin antibodies. Of the 2233 patients, 14 were found to be positive (0.6%), three of whom showed neutralising antibodies.

The clinical significance of such immune reaction to Avastin is unknown. However, no adverse event in any patient developing anti-Avastin antibodies showed any relationship with a type I hypersensitivity reaction or type III immune complex-mediated reaction.

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

Osteonecrosis of the jaw (ONJ)

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

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

Invasive dental procedures are also an additional risk factor.

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

Intravitreal use

Avastin is not suitable for intravitreal use.

Eye disorders

Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intravitreal use of Avastin. These 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, and there is a theoretical risk that these may relate to VEGF inhibition.

Ovarian failure/fertility (see "Pregnancy, lactation" and "Undesirable effects")
Avastin may impair female fertility. Therefore fertility preservation strategies should be discussed with women of childbearing potential prior to starting treatment 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.

Sodium
This medicinal product contains less than 1 mmol of sodium (23 mg) per vial, i.e. it is virtually "sodium-free".

Interactions

Pharmacokinetic interactions
In-vivo *data*
Effect of antineoplastic agents on bevacizumab pharmacokinetics
No clinically relevant pharmacokinetic interaction of coadministered chemotherapy on Avastin pharmacokinetics has been observed, based on the results of a population pharmacokinetic analysis. There were neither statistically significant nor clinically relevant differences in Avastin clearance 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
The results of a relevant interaction study (AVF3135g) showed that bevacizumab has no significant effect on the pharmacokinetics of irinotecan and its active metabolite SN38.

Results from a study in metastatic colorectal cancer patients (NP18587) demonstrated no significant effect of bevacizumab on the pharmacokinetics of capecitabine and its metabolites, nor on the pharmacokinetics of oxaliplatin (as determined by measurement of free and total platinum).

The results of study BO17704 showed no significant effect of bevacizumab on the pharmacokinetics of cisplatin.

Because of high interpatient variability and the limited number of patients studied, the results of study BO17704 do not allow firm conclusions to be drawn on the impact of bevacizumab on gemcitabine pharmacokinetics.

The results of study BO17705 showed no significant effect of bevacizumab on the pharmacokinetics of interferon alfa-2a.

Pharmacodynamic interactions
In-vivo data
Non-steroidal anti-inflammatory drugs and anticoagulants
Use of non-steroidal anti-inflammatory drugs (NSAIDs) or anticoagulants with Avastin therapy: see "Warnings and precautions".

Combination of bevacizumab and sunitinib

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

MAHA is a haemolytic disorder that 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 these findings were reversible on discontinuing bevacizumab and sunitinib.

Radiotherapy

There is evidence that infection rates are increased when Avastin is used in conjunction with radiotherapy (not approved for any disease; see "Undesirable effects").

Pregnancy, lactation

Pregnancy

Since angiogenesis is critical to fetal development, the inhibition of angiogenesis after the administration of Avastin could have a negative effect on pregnancy outcome. Avastin has been shown to be embryotoxic and teratogenic after administration in rabbits (see "Preclinical data").

No adequate and well-controlled studies have been conducted in pregnant women. Since IgG crosses the placental barrier, it is conceivable that Avastin inhibits angiogenesis in the fetus. In the postmarketing setting, cases of abnormalities of the unborn child (including limb deformities, cardiac abnormalities) have been observed in women treated with bevacizumab as monotherapy or in combination with known embryotoxic chemotherapeutics (see "Undesirable effects"). Avastin is contraindicated during pregnancy. Women of childbearing age must be strongly advised to use a reliable method of contraception during Avastin therapy. On pharmacokinetic grounds, the contraceptive measures should be continued for at least 6 months after the last dose of Avastin.

Lactation

It is not known whether bevacizumab is secreted in human milk. Because maternal IgG is secreted into human milk and Avastin could inhibit the growth and development of the infant, women should discontinue breast-feeding during Avastin therapy and should not breast-feed for at least 6 months after the last dose of Avastin.

Fertility

A substudy in the ongoing clinical development programme with 295 premenopausal women has shown a higher incidence of new cases of ovarian failure in the bevacizumab group compared to the control group. After discontinuation of bevacizumab treatment, ovarian function recovered in the majority of patients. The long-term effects of treatment with bevacizumab on fertility are unknown (see "Warnings and precautions" and "Undesirable effects"). Repeated-dose safety studies in animals have shown that bevacizumab may have an adverse effect on female fertility (see "Properties/Effects" and "Preclinical data").

Effects on ability to drive and use machines

No relevant studies of the effect on the ability to drive or operate machinery have been conducted. However, there is no evidence that Avastin treatment results in an increase in adverse effects which could impair the ability to drive or operate machinery, or negatively affect mental performance.

Undesirable effects

Over 5700 patients with various malignancies were treated in clinical studies with Avastin (mostly in combination with chemotherapy). The safety profile of this study population is shown below.

The adverse events most frequently observed across all clinical trials were hypertension, fatigue or asthenia, diarrhoea, nausea and abdominal pain.

The most serious adverse events were the following:

- Gastrointestinal perforations.
- Haemorrhage, including pulmonary haemorrhage/haemoptysis, which was more common in NSCLC patients.
- Arterial thromboembolism.

Hypertension, proteinuria and mucocutaneous and pulmonary haemorrhage are dose-dependent.

Adverse events are listed by MedDRA system organ class (SOC) and grouped into the following categories: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000). Most adverse events are reactions that commonly occur on chemotherapy. However, Avastin may exacerbate these reactions when combined with chemotherapeutic agents. Examples include palmar-plantar erythrodysaesthesia (hand-foot syndrome) with pegylated liposomal doxorubicin or capecitabine, peripheral sensory neuropathy with paclitaxel or oxaliplatin, and nail disorders or alopecia with paclitaxel.

Infections and infestations
Common: sepsis, abscess, cellulitis, infection.

Rare: necrotising fasciitis.

Blood and lymphatic system diseases
Very common: febrile neutropenia, leukopenia, neutropenia, thrombocytopenia.

Common: anaemia, lymphopenia.

Immune system diseases
Common: Hypersensitivity, anaphylactic reactions, infusion-related reactions.

Endocrine diseases
Very common: ovarian failure.

Metabolism and nutrition disorders
Very common: anorexia, hypomagnesaemia, hyponatraemia.

Common: dehydration.

Nervous system disorders
Very common: peripheral sensory neuropathy, dysgeusia, headache, dysarthria.

Common: cerebrovascular accident, syncope, somnolence.

Rare: posterior reversible leukoencephalopathy syndrome (PRLS).

Very rare: hypertensive encephalopathy.

Eye diseases
Very common: eye disorder, lacrimation increased.

Cardiac disorders
Common: congestive heart failure, supraventricular tachycardia.

Vascular diseases
Very common: hypertension.

Common: arterial thromboembolism, deep vein thrombosis, haemorrhage.

Frequency not known: renal thrombotic microangiopathy, manifested clinically as proteinuria, aneurysms and artery dissections.

Respiratory, thoracic and mediastinal disorders
Very common: dyspnoea, epistaxis, rhinitis, cough.

Common: pulmonary embolism, hypoxia, dyspnoea, epistaxis, dysphonia.

Frequency not known: nasal septum perforation, pulmonary hypertension.

Gastrointestinal diseases
Very common: diarrhoea, nausea, vomiting, abdominal pain, constipation, stomatitis, rectal haemorrhage.

Common: intestinal perforation, ileus, intestinal obstruction, rectovaginal fistulae (occurring most commonly in the enterovaginal fistula category), gastrointestinal disorder, stomatitis, proctalgia.

Frequency not known: gastrointestinal ulceration.

Hepatobiliary disorders
Frequency not known: gall bladder perforation.

Skin and subcutaneous tissue disorders
Very common: exfoliative dermatitis, dry skin, skin discolouration.

Common: palmar-plantar hand-foot syndrome.

Musculoskeletal and connective tissue disorders
Very common: arthralgia.

Common: muscle weakness, myalgia, back pain.

Frequency not known: osteonecrosis of the jaw. Osteonecrosis at sites other than the jaw has been observed in paediatric patients receiving treatment with Avastin (see “Dosage/Administration, Special dosage instructions”).

Renal and urinary disorders
Very common: proteinuria.
Common: urinary tract infection.

Reproductive system and breast disorders
Common: pelvic pain.

Congenital, familial and genetic disorders
Cases of abnormalities of the unborn child (limb deformities; encephalocele; ventricular septal defects, persistent ductus arteriosus or absent coronary artery) have been observed in women treated with bevacizumab as monotherapy or in combination with known embryotoxic chemotherapeutics (see also "Pregnancy" and "Preclinical data").

General disorders and administration site conditions
Very common: asthenia, tiredness, pyrexia, pain, mucosal inflammation.
Common: lethargy, pain, mucosal inflammation.

Investigations
Very common: weight loss.

Description of selected adverse reactions
Gastrointestinal perforation and fistula (see "Warnings and precautions")
Avastin has been associated with serious cases of gastrointestinal perforation. The presentation of these events varied in type and severity, ranging from free air seen on 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.

Gastrointestinal perforation has 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% in patients with metastatic renal cell cancer or ovarian cancer and up to 2.7% (including gastrointestinal fistula and abscess) in patients with metastatic colorectal cancer. Cases of gastrointestinal perforation have also been observed in patients with relapsed glioblastoma. In a clinical trial in patients with persistent, recurrent or metastatic cervical cancer (study GOG-0240), gastrointestinal perforations (all grades) occurred in 3.2% of patients, all of whom had a history of prior pelvic radiation.

Fatal outcome was reported in approximately a third of serious cases of gastrointestinal perforation, which represents 0.2%-1% of all Avastin-treated patients.

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

In a trial in patients with persistent, recurrent or metastatic cervical cancer, the incidence of enterovaginal fistulae was 8.3% on treatment with Avastin and 0.9% in the control group. All these patients had a history of prior pelvic radiation. Patients with enterovaginal fistulae may also develop bowel obstruction and require surgical intervention as well as diverting ostomies.

Non-gastrointestinal fistulae (see "Warnings and precautions")

Avastin has been associated with serious cases of fistula, including events resulting in death.

In a trial in patients with persistent, recurrent or metastatic cervical cancer (GOG-0240), 1.8% of Avastin-treated patients and 1.4% of control patients developed vaginal, vesical or genital fistulae unconnected to the gastrointestinal tract.

Uncommon (≥0.1% to <1%) reports of other types of fistula (e.g. tracheo-oesophageal, bronchopleural, urogenital and biliary fistula) were observed across various indications. Cases of fistula have also been reported in postmarketing 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 cases occurring within the first 6 months of therapy.

Haemorrhage

In clinical trials across all indications the overall incidence of NCI-CTC Grade 3-5 bleeding events ranged from 0.4% to 6.9% in Avastin-treated patients, compared with 0% to 4.5% of patients in the chemotherapy control group.

Tumour-associated haemorrhage (see below) and mild mucocutaneous bleeding (e.g. epistaxis) accounted for the majority of bleeding events observed.

Tumour-associated haemorrhage

Major or massive and sometimes fatal pulmonary haemorrhage/haemoptysis has been observed primarily in studies in patients with non-small cell lung cancer (NSCLC). There have also been cases of central nervous system (CNS) bleeding in patients with CNS metastases and in patients with glioblastoma.

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

Possible risk factors include squamous cell histology, treatment with antirheumatic/anti-inflammatory drugs (NSAIDs), 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 correlation with bleeding were Avastin therapy and squamous cell histology.

The incidence of major or fatal haemoptysis in NSCLC patients was 31% in those with squamous histology and 9% in those without (all-grade events) vs 5% on chemotherapy alone.

Grade 3-5 events have been observed in up to 2.3% of patients treated with Avastin + chemotherapy compared to <1% of patients treated with chemotherapy alone.

Major or massive pulmonary haemorrhage/haemoptysis can occur suddenly, and up to two-thirds of serious pulmonary haemorrhages resulted in a fatal outcome (see "Warnings and precautions").

Gastrointestinal haemorrhages, including rectal bleeding and melaena, have been reported in colorectal cancer patients, and have been assessed as tumour-associated haemorrhages. Their incidence on Avastin in combination with chemotherapy is increased compared to chemotherapy alone.

Tumour-associated haemorrhage was also seen rarely in other tumour types and locations, including CNS bleeding and continuous oozing of blood from a necrotic thigh sarcoma in a patient with hepatoma with occult CNS metastases.

In an exploratory retrospective analysis of data from 13 randomised trials in patients with various tumour types, three patients out of 91 (3.3%) with brain metastases experienced CNS bleeding (all Grade 4) when treated with Avastin, compared to one case (Grade 5) out of 96 patients (1%) in the group not exposed to Avastin. One case of Grade 2 CNS bleeding on Avastin was reported in patients with treated brain metastases.

Across all Avastin clinical trials, mucocutaneous bleeding was observed in up to 50% of patients treated with Avastin. In most cases it consisted of Grade 1 epistaxis lasting under 5 minutes, resolving without medical intervention and necessitating no change in the Avastin treatment regimen, and less frequently of low-grade bleeding from the oral mucosa or vagina. Occurrence appears to be dose-dependent.

Hypertension (see "Warnings and precautions")

The incidence of hypertension (all grades) was up to 42.1% with Avastin compared with up to 14% in the comparator arm. Grade 3 and 4 hypertension ranged from 0.4% to 17.9%, while Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% vs 0.2% with chemotherapy alone.

Hypertension was generally adequately controlled with oral antihypertensives such as ACE inhibitors, diuretics and calcium channel blockers. It only rarely resulted in discontinuation of Avastin treatment or hospitalisation.

Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal (see "Warnings and precautions"). The risk of Avastin-related hypertension did not correlate with patient baseline characteristics, underlying disease or concomitant therapy.

Posterior reversible leukoencephalopathy syndrome

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

Thromboembolism

Arterial thromboembolism

An increased incidence of arterial thromboembolism, including cerebrovascular accidents, myocardial infarction, transient ischaemic attacks and other arterial thromboembolic events, has been observed.

The overall incidence of arterial thromboembolic events with Avastin ranged up to 5.9% compared with up to 2.1% in the control arm, with fatal outcome in 0.8% vs 0.5%. Cerebrovascular accidents (including transient ischaemic attacks) occurred in up to 2.3% vs 0.5%, and myocardial infarction in 1.4% vs 0.7%.

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

Venous thromboembolism (see "Warnings and precautions")

Grade 3-5 venous thromboembolic events were observed in up to 7.8% of patients treated with Avastin plus chemotherapy compared to 4.9% in the chemotherapy control arm. Patients who have experienced a venous thromboembolic event may be at higher risk for a recurrence if they receive Avastin in combination with chemotherapy than patients on chemotherapy alone.

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

Congestive heart failure (CHF)

Congestive heart failure (CHF) has been observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. An Avastin-induced increase in CHF of Grade 3 or more was reported in up to 3.5% of patients with metastatic breast cancer treated with Avastin vs 0.9% in the control arm. In most clinical trials of Avastin, patients with pre-existing CHF (NYHA Grade II-IV) were excluded. Therefore no information is available on the risk of CHF in this study population.

Prior anthracycline treatment and/or radiotherapy to the chest wall may be possible risk factors for the development of CHF (see "Warnings and precautions").

An increased incidence of CHF was observed in a clinical trial of patients with diffuse large B-cell lymphoma receiving bevacizumab at a cumulative doxorubicin dose exceeding 300 mg/m^2. This phase III 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 monotherapy, the rate was higher in the R-CHOP plus bevacizumab arm (16.1% vs 6.1%). Study recruitment and ongoing bevacizumab treatments were stopped at the request of the Data Safety Monitoring Board.

Wound healing (see "Warnings and precautions")

Since Avastin may impair wound healing, patients who had undergone major surgery in the previous 28 days were excluded from the phase III studies.

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

Serious wound healing complications have occurred on treatment with Avastin, some of which have been fatal (see "Warnings and precautions, General").

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

In a study of patients with relapsed glioblastoma (study AVF3708g), the incidence of postoperative wound healing complications (including craniotomy site wound dehiscence and cerebrospinal fluid leak) was 3.6% in patients treated with single-agent Avastin and 1.3% in patients treated with Avastin plus irinotecan.

Proteinuria

In clinical trials, proteinuria has been reported within the range of 0.7% to 38% of patients receiving Avastin.

Severity ranged from clinically asymptomatic, transient, mild proteinuria to nephrotic syndrome. Grade 3 proteinuria was reported in up to 8.1% of treated patients and Grade 4 (nephrotic syndrome) in up to 1.4%. Patients with a history of hypertension may be at increased risk of developing proteinuria if treated with Avastin. There is evidence suggesting that an association could exist between Grade 1 proteinuria and the dose of Avastin. Testing for proteinuria is recommended prior to starting Avastin therapy. In most clinical studies, urine protein levels of ≥2 g/24 h led to the withholding of Avastin until recovery to <2 g/24 h.

Hypersensitivity reactions, anaphylactic reactions (including anaphylactic shock), infusion-related reactions

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

Ovarian failure/fertility (see "Warnings and precautions" and "Pregnancy, lactation")

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 ß-HCG pregnancy test, was evaluated in a substudy in 295 premenopausal women as part of the ongoing clinical development programme. New cases of ovarian failure were reported more frequently in patients receiving bevacizumab compared to the control group (39% vs 2.6%). After discontinuation of bevacizumab treatment, ovarian function recovered in the majority of patients. The long-term effects of treatment with bevacizumab on fertility are unknown.

Infections

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

Osteonecrosis of the jaw (see "Warnings and precautions")

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

Elderly patients

In randomised clinical studies the risk of developing arterial thromboembolic events such as stroke, transient ischaemic attack and myocardial infarction was higher in Avastin-treated patients over 65 years of age than in those under 65 (see "Warnings and precautions" and "Undesirable effects" under "Thromboembolism").

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

Changes in laboratory values

Proteinuria and decreased neutrophil and leukocyte counts may occur on Avastin therapy.

Across clinical trials, the following Grade 3 and 4 laboratory abnormalities were seen with an increased (≥2%) incidence compared to the control group in patients who were treated with Avastin in combination with chemotherapy:

Hyperglycaemia, decreased haemoglobin, hypokalaemia, hypophosphataemia, hyponatraemia, increased serum alkaline phosphatase, decreased platelet count, and increased prothrombin time and international normalised ratio (INR). Clinical trials have shown that Avastin use is associated with a transient increase in serum creatinine (to between 1.5 and 1.9 times baseline level), both with and without proteinuria. The increase in serum creatinine observed on treatment with Avastin was not associated with an increased incidence of clinically manifest renal impairment.

Immunogenicity

Clinical studies with Avastin did not provide a solid antibody assessment

carried out against the active ingredient.

Reporting suspected side effects after approval is of great importance. It enables continuous monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are requested to report any suspicion of a new or serious side effect

Overdose

The highest dosage tested in humans (20 mg/kg body weight, i.v.) caused severe migraine in some patients.

Properties/Effects

ATC code

L01FG01Mechanism of action

Avastin inhibits the binding of VEGF to its Flt 1 (VEGFR-1) and KDR (VEGFR-2) receptors on the surface of endothelial cells. Neutralisation of the biological activity of VEGF reduces tumour vascularisation, thereby inhibiting tumour growth.

Pharmacodynamics

Avastin (bevacizumab) is a recombinant humanised monoclonal antibody (IgG1 kappa) which binds selectively to human vascular endothelial growth factor (VEGF) and inhibits its biological activity. Bevacizumab contains human sequences with antigen-binding regions of a humanised murine antibody that binds to VEGF. Bevacizumab is produced by recombinant DNA technology in a Chinese hamster ovarian cell expression system. The subsequent purification process comprises specific virus inactivation and impurity removal steps. Bevacizumab consists of 214 amino acids and has a molecular weight of approximately 149,000 daltons.

Administration of bevacizumab or its parental murine antibody to xenotransplant tumour models in nude mice resulted in extensive antitumour activity in human cancers, including colon, breast, pancreas and prostate. Metastatic spread was inhibited and microvascular permeability decreased.

Clinical efficacy

Metastatic colorectal cancer

Combination therapies with Avastin, first-line therapy (overview)

Four randomised, active-controlled clinical studies tested the efficacy and safety of the recommended dose of Avastin (5 mg/kg body weight every 2 weeks) in combination with first-line 5-FU-based chemotherapy in metastatic carcinoma of the colon or rectum. Avastin was combined with the following chemotherapy regimens:

- *AVF2107g*: Once weekly bolus irinotecan/5-FU/LV (IFL regimen) for a total of 4 weeks in each 6-week treatment cycle (Saltz regimen) (n=402).
- *AVF0780g*: Combination with bolus 5-FU/LV for a total of 6 weeks in each 8-week treatment cycle (Roswell Park regimen) (n=35).
- *AVF2192g*: Combination with bolus 5-FU/LV for a total of 6 weeks in each 8-week treatment cycle (Roswell Park regimen) in patients who were not optimal candidates for first-line therapy with irinotecan (n=104).
- *NO16966*: Avastin 7.5 mg/kg 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-FU bolus, followed by 5-FU infusion, with intravenous oxaliplatin (FOLFOX-4).

Combination therapies with Avastin, second-line therapy (overview)

Two studies with Avastin have been conducted in metastatic colorectal cancer: second-line therapy with no previous Avastin treatment (E3200), and second-line therapy with previous Avastin treatment after disease progression during first-line therapy (ML18147). In these studies, Avastin was used in combination with FOLFOX-4 (5-FU/LV/oxaliplatin) or fluoropyrimidine/irinotecan and fluoropyrimidine/oxaliplatin with the following dosing regimens:

- *E3200*: Avastin 10 mg/kg body weight every 2 weeks in combination with leucovorin and 5-FU bolus, followed by 5-FU infusion, with intravenous oxaliplatin (FOLFOX-4).
- *ML18147*: Avastin 5.0 mg/kg body weight every 2 weeks or Avastin 7.5 mg/kg body weight every 3 weeks in combination with fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin in patients with disease progression following first-line treatment with Avastin in combination with oxaliplatin- or irinotecan-based chemotherapy. Treatment with irinotecan or oxaliplatin was assigned on the basis of the first-line therapy used.

Study details

AVF2107g: This randomised, double-blind, active-controlled clinical phase III study evaluated Avastin in combination with IFL as first-line therapy in metastatic carcinoma of the colon or rectum. After randomisation 813 patients received either IFL + placebo (arm 1) or IFL + Avastin (5 mg/kg every 2 weeks, arm 2) (Table 1). A third group of patients received 5-FU/LV (bolus) + Avastin (arm 3).

Inclusion in arm 3, as prespecified in the study protocol, was discontinued after the safety of Avastin in combination with the IFL regimen had been confirmed and deemed acceptable.

The primary efficacy parameter of this trial was overall survival. Addition of Avastin to IFL significantly prolonged overall survival, progression-free survival and overall response rate (details in Table 1). At the time of data cut-off, 399 deaths had occurred in the patients randomised to arm 1 (n=225) and arm 2 (n=174). Estimated median survival increased statistically significantly from 15.6 months in the IFL + placebo arm to 20.3 months in the IFL + Avastin arm (p=0.00004). This represents, according to Cox regression analysis, a 34% decrease in mortality risk. A similar increase was recorded in the duration of progression-free survival (6.2 vs 10.6 months, p<0.00001), response rate (34.8% vs 44.8%, p=0.0036) and duration of response (7.1 vs 10.4 months). The clinical benefit of Avastin, measured by duration of survival, duration of progression-free survival and objective response, was seen in all prespecified patient subgroups, including in the groups defined by age, sex, performance status, location of primary tumour, number of organs involved and duration of metastatic disease.

Table 1 shows the efficacy results for Avastin in combination with IFL chemotherapy.

Table 1: Efficacy results for study AVF2107g

	Arm 1 IFL + placebo	**Arm 2 IFL + Avastin[a]**	**Arm 3 5-FU/LV bolus + Avastin[a]**
Number of patients	411	402	110[b]
Overall survival			
Median (months)	15.6	20.3	18.3
95% confidence interval	14.29-16.99	18.46-24.18	16.23-23.13
Hazard ratio	0.660		-
p value	0.00004		-
Progression-free survival			
Median (months)	6.2	10.6	8.8
Hazard ratio	0.54		-
p value	<0.00001		-
Overall response rate			
Rate (percent)	34.8	44.8	40.0
95% confidence interval	30.2-39.6	39.9-49.8	30.9-49.8
p value	0.0036		-

[a] 5 mg/kg every 2 weeks.

[b] Recruitment discontinued as per protocol.

AVF2192g: In this randomised, active-controlled, double-blind, clinical phase II trial, Avastin was investigated in combination with 5-FU/LV as first-line treatment for metastatic colorectal cancer in patients who were not optimal candidates for first-line irinotecan treatment. After randomisation 105 patients received 5-FU/LV + placebo and 104 patients 5-FU/LV + Avastin (5 mg/kg every 2 weeks). Patients were treated until disease progression. The addition of Avastin (5 mg/kg every 2 weeks) to 5-FU/LV resulted in higher objective response rates and significantly longer progression-free survival than on 5-FU/LV chemotherapy alone. The duration of survival was also somewhat longer.

AVF0780g: In this randomised, active-controlled, open, phase II clinical study, Avastin was investigated in combination with 5-FU/LV as first-line treatment of metastatic colorectal cancer. After randomisation 71 patients received bolus 5-FU/LV or 5-FU/LV + Avastin (5 mg/kg every 2 weeks). A third group of 33 patients received bolus 5-FU/LV + Avastin (10 mg/kg every 2 weeks). Patients were treated until disease progression. Primary study endpoints were objective response rate and progression-free survival. The addition of Avastin (5 mg/kg every 2 weeks) to 5-FU/LV resulted in higher objective response rates and longer progression-free survival than on 5-FU/LV chemotherapy alone. The duration of survival was also somewhat longer. The poorer efficacy in the 10 mg/kg group than in the 5 mg/kg group remains unclear. Avastin 10 mg/kg + 5-FU/LV was not significantly different from 5-FU/LV alone.

NO16966: This was a phase III, randomised, double-blind (for bevacizumab) clinical trial investigating Avastin 7.5 mg/kg, administered in combination with oral capecitabine and i.v. oxaliplatin (XELOX) every 3 weeks. Alternatively, Avastin 5 mg/kg was administered in combination with leucovorin with a 5-fluorouracil bolus, followed by 5-fluorouracil infusion with i.v. oxaliplatin (FOLFOX-4) every 2 weeks. The study contained two parts: an initial unblinded 2-arm part (Part I), in which patients were randomised to two different treatment groups (XELOX and FOLFOX-4), and a subsequent 2 × 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.

In total, approximately 350 patients were randomised to each of the 4 treatment groups in Part II of the study.

Table 2: Treatment regimens in study NO16966 (mCRC)

	Treatment	**Starting dose**	**Schedule**
FOLFOX-4 or **FOLFOX-4 + Avastin**	Oxaliplatin	85 mg/m^2 i.v. 2 h	Oxaliplatin on day 1
	Leucovorin	200 mg/m^2 i.v. 2 h	Leucovorin on days 1 & 2
	5-Fluorouracil	400 mg/m^2 i.v. bolus, 600 mg/m^2 i.v. 22 h	5-Fluorouracil i.v. bolus/infusion, each on days 1 & 2
	Placebo or Avastin	5 mg/kg i.v. 30-90 min	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or **XELOX+ Avastin**	Oxaliplatin	130 mg/m^2 i.v. 2 h	Oxaliplatin on day 1
	Capecitabine	1000 mg/m^2 orally bid	Capecitabine orally bid for 2 weeks (followed by 1 week off treatment)
	Placebo or Avastin	7.5 mg/kg i.v. 30-90 min	Day 1, prior to XELOX, every 3 weeks
5-Fluorouracil: i.v. bolus injection immediately after leucovorin			

The primary efficacy parameter of the study was the duration of progression-free survival (PFS). The study pursued two primary objectives: to show that XELOX was non-inferior to FOLFOX-4 and that Avastin in combination with FOLFOX-4 or XELOX chemotherapy was superior to chemotherapy alone. On overall comparison in the eligible per-protocol population, the XELOX arm was found to be non-inferior to the FOLFOX-4 arm in terms of progression-free survival and overall survival.

Table 3: Key efficacy results for the superiority analysis (ITT population, study NO16966)

	Investigator assessment*			**Independent review assessment**		
	Median PFS (months)	HR	p value	**Median PFS** (months)	HR	p value
Oxaliplatin-based chemotherapy + placebo vs **oxaliplatin-based chemotherapy + Avastin***	8.0 vs 9.4	0.83	0.0023	8.5 vs 11.0	0.70	<0.0001
Subgroup analysis	**Investigator assessment***			**Independent review assessment**		
	Median PFS (months)	HR	p value	**Median PFS** (months)	HR	p value
FOLFOX + placebo vs **FOLFOX + Avastin**	8.6 vs 9.4	0.89	0.1871	9.5 vs 11.5	0.73	0.0071
XELOX + placebo vs **XELOX + Avastin**	7.4 vs 9.3	0.77	0.0026	7.8 vs 10.2	0.66	0.0002

* Primary analysis as defined by protocol.

ECOG E3200: This was a phase III, randomised, controlled, open-label study investigating Avastin 10 mg/kg as monotherapy or in combination with leucovorin and a 5-fluorouracil bolus, followed by infusion of 5-fluorouracil with i.v. oxaliplatin (FOLFOX-4), administered in a two-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 2 for study NO16966.

The primary efficacy parameter in this study was overall survival, defined as the time from randomisation to death from any cause. A total of 829 patients were randomised (292 to the FOLFOX-4 arm, 293 to the Avastin + FOLFOX-4 arm and 244 to the Avastin monotherapy arm). The addition of Avastin to FOLFOX-4 resulted in a statistically significant prolongation of overall survival. Statistically significant improvements in progression-free survival and objective response rate were also observed (see Table 4).

Table 4: Efficacy results for study E3200

	E3200	
	FOLFOX-4	**FOLFOX-4 + Avastin[a]**
Number of patients	292	293
Overall survival		
Median (months)	10.8	13.0
95% confidence interval	10.12-11.86	12.09-14.03
Hazard ratio[b]	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.

Patients receiving Avastin monotherapy (group terminated early) in study E3200 showed no significant difference in overall survival compared to those treated with FOLFOX-4. Progression-free survival and objective response rate in the Avastin monotherapy arm were inferior to the FOLFOX arm (median PFS 2.5 months vs 4.5 months, RR 3.3% vs 8.6%).

ML18147: 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 metastatic colorectal cancer after failure of first-line therapy with Avastin plus chemotherapy. Patients with histologically confirmed metastatic colorectal cancer and disease progression were randomised 1:1 within 3 months after discontinuation of Avastin first-line therapy to receive fluoropyrimidine/oxaliplatin- or fluoropyrimidine/irinotecan-based chemotherapy (chemotherapy assigned depending on first-line chemotherapy) with or without Avastin. The oxaliplatin/fluoropyrimidine- or irinotecan/fluoropyrimidine-based chemotherapy regimens varied according to local preferences and included: simplified FOLFIRI, XELIRI, LV5FU2 CPT11 (Douillard regimen), FOLFOX-6, XELOX, FOLFOX-4, FUFOX, simplified FOLFOX-4, AIO-IRI, CAPIRI, FOLFIRI3, Nordic FLIRI, CAPOX, mFOLFOX-4, mFOLFOX-7, Nordic FLOX. Treatment was continued until disease progression or unacceptable toxicity. The primary endpoint was overall survival (OS), defined as the time from randomisation until death from any cause. A total of 820 patients were randomised. The addition of Avastin to fluoropyrimidine-based chemotherapy resulted in a statistically significant prolongation of survival in patients with metastatic colorectal cancer after failure of an Avastin-containing first-line therapy (ITT = 819) (see Table 5).

Table 5: Efficacy results from study ML18147 Total population, n=819

	Chemotherapy Total	Chemotherapy + Avastin	HR (95% CI)/p-value
Median OS (months)	9.8	11.2	0.81 (0.69, 0.94)/0.0062
Median PFS (months)	4.1	5.7	0.68 (0.59, 0.78)/<0.0001
Objective response rate (ORR%)	16 (3.9%)	22 (5.4%)	1.5* (-1.5, 4.5)/0.3113

* Corresponds to a difference in response rates.

Irinotecan-pretreated population, n=476

	Oxaliplatin	Oxaliplatin + AVA	HR (95% CI)/p-value
Median OS (months)	9.3	10.9	0.82 (0.67, 1.00)/0.0454
Median PFS (months)	3.8	5.4	0.67 (0.56, 0.81)/<0.0001
Objective response rate (ORR%)	11 (4.7%)	13 (5.4%)	0.74* (-3.4, 4.9)/0.7145

* Corresponds to a difference in response rates.

Oxaliplatin-pretreated population, n=343

	Irinotecan	Irinotecan + AVA	HR (95% CI)/p-value
Median OS (months)	10.0	12.0	0.79 (0.62, 1.00)/0.0524
Median PFS (months)	4.2	6.2	0.68 (0.55, 0.85)/0.0005
Objective response rate (ORR%)	5 (2.9%)	9 (5.5%)	2.55* (-2.0, 7.1)/0.2414

* Corresponds to a difference in response rates.

The efficacy results per chemotherapy were consistent with the results for the overall population.

Metastatic breast cancer

ECOG 2100: Study E2100 was an open-label, randomised, active-controlled, multicentre trial evaluating Avastin in combination with paclitaxel for treatment of locally recurrent or metastatic HER2-negative breast cancer in patients who had not previously received chemotherapy for locally recurrent and metastatic disease. Prior hormonal therapy for the treatment of metastatic disease was allowed. Adjuvant taxane therapy was allowed only if it was completed at least 12 months prior to study entry.

Patients were randomised to paclitaxel alone (90 mg/m^2 i.v. over 1 hour once weekly for three out of four weeks) or in combination with Avastin (10 mg/kg body weight every two weeks). The study medication was continued until disease progression. Patients discontinuing chemotherapy early continued treatment with Avastin as a single agent until disease progression. The primary study endpoint was investigator-assessed progression-free survival (PFS). An independent review of the primary endpoint was also conducted.

Sixty-five percent of patients had received adjuvant chemotherapy (including 19% with taxanes and 49% with anthracyclines). The patient characteristics were similar across the two study arms.

The results of the study are presented in Table 6.

Table 6: Study E2100 – Efficacy results: Patients meeting the inclusion criteria

	Independent review facility assessment	
	Paclitaxel	**Paclitaxel + Avastin**
Number of patients	354	368
Progression-free survival		
Median (months)[a]	5.8	11.3
Hazard ratio	0.483	
95% confidence interval	(0.385; 0.607)	
p value (log-rank test)	<0.0001	
Objective response rate in patients with measurable tumour		
Number of patients	243	229
Response rate (partial response) [%]	22.2	49.8
p value	<0.0001	
Overall survival (months)	**Paclitaxel**	**Paclitaxel + Avastin**
Number of patients	354	368
Median (months)	24.8	26.5
Hazard ratio	0.869	
95% confidence interval	(0.722; 1.046)	
p value	0.1374	

Advanced, metastatic or recurrent non-small cell lung cancer (NSCLC)

Study BO17704 investigated the safety and efficacy of Avastin in combination with platinum-based chemotherapy in the first-line treatment of patients with NSCLC excluding predominant squamous histology.

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

Patients were randomised either to a platinum-based chemotherapy (cisplatin 80 mg/m^2 i.v. infusion on day 1 and gemcitabine 1250 mg/m^2 i.v. infusion on days 1 and 8 of every 3-week treatment cycle) for up to 6 cycles (CG) with placebo or CG chemotherapy with Avastin 7.5 or 15 mg/kg i.v. infusion on day 1 of every 3-week cycle. In the Avastin arms, patients could receive Avastin as a single agent every 3 weeks until disease progression or unacceptable side effects. Study results show that 94% (277/296) of eligible patients went on to receive single-agent bevacizumab at cycle 7. A high proportion of patients (approximately 62%) went on to receive a variety of non-protocol cancer treatments, which may have impacted survival.

Table 7 shows the efficacy results.

Table 7: Efficacy results in study 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	6.5
		(p=0.0024)	(p=0.0301)
Hazard ratio		0.75	0.82
		[0.62; 0.90]	[0.68; 0.98]
Best overall response rate[a]	20.1%	34.1%	30.4%
		(p <0.0001)	(p=0.0023)
Overall survival			
Median (months)	13.1	13.6	13.4
		(p=0.4203)	(p=0.7613)
Hazard ratio		0.93	1.03
		[0.78; 1.11]	[0.86; 1.23]

[a] Patients with measurable disease at baseline.

Advanced and/or metastatic renal cell cancer

BO17705: This was a multicentre, randomised, double-blind phase III trial conducted to evaluate the efficacy and safety of Avastin in combination with interferon (IFN) alfa-2a versus IFN alfa-2a alone as first-line treatment in metastatic renal cell cancer (mRCC). The 649 randomised patients (641 treated) with metastatic renal cell carcinoma (mRCC) had a Karnofsky Performance Status (KPS) of ≥70%, no CNS metastases and adequate organ function. Both IFN alfa-2a (three times weekly at the recommended dose of 9 MIU) plus Avastin (10 mg/kg every 2 weeks) and placebo or IFN alfa-2a were given until disease progression. Patients were stratified according to country and Motzer score. The treatment arms were shown to be well balanced for the prognostic factors.

The primary endpoint was overall survival. One of the secondary endpoints was progression-free survival (PFS). The addition of Avastin to IFN alfa-2a improved both PFS and the objective tumour response rate. These results were confirmed by independent radiological review. However, the improvement in the primary endpoint of overall survival by 2 months was not significant (HR=0.91). Non-achievement of a statistically significant overall survival result can be explained by novel second-line therapies that first became available only in the course of the study and by biasing of the result by control group patients who switched to Avastin after unblinding of the study in connection with the PFS analysis (13 patients). A high proportion of patients (approximately 63% IFN/placebo, 55% Avastin/IFN) received a variety of non-specific post-protocol antineoplastic therapies, including administration of antineoplastic agents. Table 8 shows the efficacy results.

Table 8: Efficacy results from study BO17705

	BO17705	
	IFN + placebo/(IRC)	**IFN + Avastin/(IRC)**
Number of patients	322/(281)	327/(288)
Progression-free survival		
Median (months)	5.4/(5.5)	10.2/(10.4)
Hazard ratio [95% CI]	0.63 [0.52; 0.75]/0.57 [0.450; 0.723] (p value <0.0001)/(p value <0.0001)	
Objective response rate (%) in patients with measurable disease		
n	289/(220)	306/(226)
Response rate	12.8%/(12.3%)	31.4%/(31.4%)
	(p value <0.0001)/(p value <0.0001)	
Overall survival		
Median (months)	21.3	23.3
Hazard ratio [95% CI]	0.91 [0.76;1.10] (p value=0.3360)	

An exploratory multivariate Cox regression model indicated that the following prognostic factors were strongly associated with survival, independently of treatment: gender, white blood cell count, platelets, weight loss in the 6 months prior to study entry, number of organs with metastases, sum of longest diameter of target lesions, Motzer score. Statistical adjustment of the data for these baseline factors resulted in a treatment hazard ratio of 0.78 (95% CI [0.63; 0.96], p=0.0219), indicating a marked effect of treatment with Avastin.

Ninety-seven patients in the IFN alfa-2a + placebo arm and 131 patients in the IFN alfa-2a + Avastin arm reduced the dose of IFN alfa-2a from 9 MIU to either 6 or 3 MIU three times weekly, as prespecified 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, as shown by a subgroup analysis. Of the 131 patients in the Avastin + IFN alfa-2a arm who reduced the IFN alfa-2a dose to 6 or 3 MIU, 73%, 52% and 21% were progression-free at 6, 12 and 18 months, respectively, compared to 61%, 43% and 17% in the total population of patients treated with Avastin + IFN alfa-2a.

AVF2938: This was a randomised, double-blind, phase II clinical study investigating Avastin 10 mg/kg every 2 weeks and the same dose of Avastin in combination with erlotinib 150 mg daily in patients with metastatic RCC. A total of 104 patients were randomised to treatment in this study, 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 vs 9.9 months). Seven patients in each arm had an objective response.

Glioblastoma (WHO Grade IV)

AVF3708g: An open-label, multicentre, randomised, non-comparative study evaluated the efficacy and safety profile of Avastin in the treatment of patients with glioblastoma.

Patients suffering a first or second relapse following radiotherapy (which had to have ended at least 8 weeks before Avastin administration) and temozolomide were randomised 1:1 to receive either Avastin alone (10 mg/kg i.v. infusion every 2 weeks) or Avastin in combination with irinotecan (125 mg/m^2 or – for patients concomitantly receiving enzyme-inducing antiepileptics – 340 mg/m^2 i.v. every 2 weeks) until disease progression or unacceptable toxicity. The primary study endpoints were 6-month progression-free survival (PFS) and objective response rate (ORR) as assessed by an independent review facility (IRF). The other endpoints included the duration of PFS, duration of response and overall survival. The results of this study are summarised in Table 9.

Table 9: Efficacy results from study AVF3708g

	Avastin	**Avastin + irinotecan**
Number of patients	85	82
Primary endpoints		
6-month progression-free survival (97.5% confidence interval) (IRF)	42.6% (29.6%; 55.5%)	50.3% (36.8%; 63.9%)
Objective response rate (ORR)[1] (97.5% confidence interval)	28.2% (18.5%; 40.3%)	37.8% (26.5%; 50.8%)
Secondary endpoints		
Progression-free survival (months) Median (95% confidence interval)	 4.2 (2.9; 5.8)	 5.6 (4.4; 6.2)
Duration of objective response (months) Median (95% confidence interval)	 5.6 (3.0; 5.8)	 4.3 (4.2; *)
Overall survival (months) Median (95% confidence interval)	 9.3 (8.2; *)	 8.8 (7.8; *)

[1] ORR was determined using the modified MacDonald criteria.

* The upper confidence limit could not be determined.

Objective response rate and 6-month progression-free survival (PFS) in both treatment arms were significantly better than historical controls. Median overall survival in the Avastin arm was longer than in the Avastin + irinotecan combination arm (9.3 vs 8.8 months).

Ovarian cancer

BO17707 (ICON7): Study BO17707 was conducted in 1528 patients with epithelial ovarian cancer (FIGO stage I or IIa [Grade 3 or clear cell histology only] or FIGO stage IIb-IV [all grades and all histological types]), fallopian tube cancer or primary peritoneal cancer, following surgery (optimally debulked 2/3 and suboptimally debulked 1/3) and if no further surgery was planned until disease progression.

Arm 1: Carboplatin (AUC6) and paclitaxel (175 mg/m^2) for 6 cycles.

Arm 2: Avastin (7.5 mg/kg, 3-weekly) combined with carboplatin (AUC6) and paclitaxel (175 mg/m^2) for 6 cycles, then Avastin for up to 18 cycles.

The primary endpoint was progression-free survival (PFS) as assessed by the investigator.

The study results are summarised in Table 10.

Table 10: Efficacy results from study BO17707 (ICON7)

Progression-free survival		
	Arm 1 (n=764)	**Arm 2** (n=764)
Median PFS (months)	16.0	18.3
Hazard ratio [95% confidence interval]	0.79 [0.68; 0.91] (p value=0.0010)	
Objective response rate[1]		
	Arm 1 (n=277)	**Arm 2** (n=272)
Response rate	41.9%	61.8%
	(p value <0.0001)	
Overall survival[2]		
	Arm 1 (n=764)	**Arm 2** (n=764)
Median overall survival (months)	58.0	57.4
Hazard ratio [95% confidence interval]	0.99 [0.85; 1.15]	

[1] In patients with measurable disease at baseline.

[2] Final OS (overall survival) analysis after approximately 46.7% of the patients had died.

The trial met its primary objective of PFS improvement. In the overall analysis the PFS difference was 2.3 months. In the suboptimally debulked group (n=294) there was a clear difference in PFS with 16.9 vs 10.1 months (hazard ratio 0.67 [0.52, 0.87]). The positive overall effect was thus borne above all by the suboptimally debulked group.

Recurrent ovarian cancer

AVF4095g: In this study, 484 patients with platinum-sensitive epithelial ovarian cancer (84%), fallopian tube cancer (6%) or primary peritoneal cancer (10%) experiencing their first recurrence (in most cases >12 months after previous platinum therapy) were randomised 1:1 to one of the following two treatments:

- Carboplatin (AUC4, day 1) and gemcitabine (1000 mg/m^2 on days 1 and 8) and concurrent placebo every 3 weeks for 6 and up to 10 treatment cycles followed by placebo alone until disease progression or the occurrence of unacceptable toxicity.
- Carboplatin (AUC4, day 1) and gemcitabine (1000 mg/m^2 on days 1 and 8) and concurrent Avastin (15 mg/kg on day 1) every 3 weeks for 6 and up to 10 treatment cycles followed by Avastin alone until disease progression or the occurrence of unacceptable toxicity.

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

The results of this study are summarised in Table 11.

Table 11: Efficacy results from study AVF4095g

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

** Final OS analysis after approximately 73% of patients had died.

GOG-0213: GOG-0213 was an open-label, randomised, controlled, phase III study to evaluate the safety and efficacy of Avastin in the treatment of patients with platinum-sensitive, recurrent, epithelial ovarian, fallopian tube or primary peritoneal cancer who had not received prior chemotherapy for recurrence. The study mainly enrolled patients who were not eligible for surgery and whose disease had not progressed at least during a six-month prior chemotherapy. Previous front-line antiangiogenic therapy was not an exclusion criterion. The study evaluated the effect of adding Avastin to combination therapy with carboplatin and paclitaxel followed by Avastin monotherapy compared to combination therapy with carboplatin and paclitaxel only.

A total of 673 patients were randomised in equal proportions to the following two treatment arms:

- CP arm: carboplatin (AUC5) and paclitaxel (175 mg/m^2 i.v. over 3 hours) every 3 weeks for 6 to 8 cycles.
- CPB arm: carboplatin (AUC5) and paclitaxel (175 mg/m^2 i.v. over 3 hours) plus Avastin (15 mg/kg) every 3 weeks for 6 to 8 cycles, followed by Avastin monotherapy (15 mg/kg every 3 weeks) until disease progression or the onset of unacceptable toxicity.

The primary efficacy endpoint was overall survival (OS). The key secondary efficacy endpoint was progression-free survival (PFS). Objective response rates (ORR) were also assessed. The results are shown in Table 12.

Table 12: Efficacy results from study GOG-0213

Primary endpoint		
Overall survival (OS)	CP (n=336)	CPB (n=337)
Median OS (months)	37.3	42.6
Hazard ratio [95% confidence interval]	0.823 (CI: 0.680, 0.996)	
p-value	0.0447	
Secondary endpoint		
Progression-free survival (PFS)	CP (n=336)	CPB (n=337)
Median PFS (months)	10.2	13.8
Hazard ratio [95% confidence interval]	0.613 (CI: 0.521, 0.721)	
Objective response rate (ORR)	CP* (n=286)	CPB* (n=274)
Number (%) of patients with objective response (CR, PR)	159 (55.6%)	213 (77.7%)

* Intent-to-treat population with measurable disease at baseline

Treatment with 15 mg/kg Avastin every 3 weeks in combination with chemotherapy (carboplatin and paclitaxel) for 6 to 8 treatment cycles followed by Avastin monotherapy resulted in clinically meaningful and statistically significant improvement in OS compared to treatment with carboplatin and paclitaxel only.

MO22224 (AURELIA)

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

A total of 361 patients were enrolled in this study and treated with either chemotherapy (paclitaxel, topotecan or pegylated liposomal doxorubicin [PLD]) alone or chemotherapy in combination with bevacizumab until disease progression or the occurrence of unacceptable toxicity:

- CT arm (chemotherapy alone):
  - Paclitaxel 80 mg/m^2 as a 1-hour i.v. infusion on days 1, 8, 15 and 22 every 4 weeks.
  - Topotecan 4 mg/m^2 as a 30-minute i.v. infusion on days 1, 8 and 15 every 4 weeks. Alternatively, a 1.25 mg/m^2 dose could be administered over 30 minutes on days 1-5 every 3 weeks.
  - PLD 40 mg/m^2 as an i.v. infusion at an infusion rate of 1 mg/min on day 1 only every 4 weeks. After cycle 1, the drug could be delivered as a 1-hour infusion.
- CT + BV arm (chemotherapy plus bevacizumab):
  - The chosen chemotherapy was combined with bevacizumab 10 mg/kg i.v. every 2 weeks (or bevacizumab 15 mg/kg every 3 weeks if used in combination with topotecan 1.25 mg/m^2 on days 1-5 every 3 weeks).

The study enrolled ovarian cancer patients who had experienced disease progression within 6 months of previous platinum therapy and had received up to two prior chemotherapies. 92.5% of patients had not been previously treated with an antiangiogenic agent.

The primary endpoint was progression-free survival; secondary endpoints included objective response rate and overall survival. The results of the study are presented in Table 13. A total of 115 patients were treated with paclitaxel (55 CT for a median 4 [3-6] cycles; 60 CT + BV for a median 6 [4-8] cycles), a total of 120 patients with topotecan (63 CT for a median 3 [2-5] cycles; 57 CT + BV for a median 6 [4-8] cycles), and a total of 126 patients with PLD (64 CT for a median 3 [2-6] cycles; 62 CT + BV for a median 4 (3-6) cycles).

Table 13: Efficacy results from study MO22224 (AURELIA)

Primary endpoint		
Progression-free survival		
	CT (n= 182)	CT + BV (n= 179)
Median (months)	3.4	6.7
Hazard ratio (95% confidence interval)	0.379 [0.296; 0.485]	
p-value	<0.0001	
Secondary endpoints		
Objective response rate*		
	CT (n= 144)	CT + BV (n= 142)
% Patients with objective response	18 (12.5%)	40 (28.2%)
p-value	0.0007	
Overall survival (final analysis)**		
	CT (n= 182)	CT + BV (n= 179)
Median overall survival (months)	13.3	16.6
Hazard ratio (95% confidence interval)	0.870 (0.678; 1.116)	
p-value	0.2711	

All analyses presented in this table are stratified analyses.

* Randomised patients with measurable disease at baseline.

** At the time of the final OS analysis (25 January 2013), a total of 266 patients (73.7%) had died in the two treatment arms.

Cervical cancer

GOG-0240: The randomised, four-arm, multicentre, phase III GOG-0240 trial evaluated the efficacy and safety of bevacizumab combined with chemotherapy (paclitaxel and cisplatin or paclitaxel and topotecan) in the treatment of patients with persistent, recurrent or metastatic cervical cancer.

A total of 452 patients were randomised.

Bevacizumab or placebo were administered every 3 weeks (q3w) until disease progression or the onset of unacceptable toxicity in combination with 3-weekly

- paclitaxel 135 mg/m^2 i.v. over 24 hours on day 1 and cisplatin 50 mg/m^2 i.v. on day 2 together with bevacizumab 15 mg/kg i.v. or placebo on day 2, or
- paclitaxel 175 mg/m^2 i.v. over 3 hours on day 1 and cisplatin 50 mg/m^2 i.v. on day 2 together with bevacizumab 15 mg/kg i.v. or placebo on day 2, or
- paclitaxel 175 mg/m^2 i.v. over 3 hours on day 1 and cisplatin 50 mg/m^2 i.v. on day 1 together with bevacizumab 15 mg/kg i.v. or placebo on day 1, or
- paclitaxel 175 mg/m^2 i.v. over 3 hours on day 1 and topotecan 0.75 mg/m^2 i.v. over 30 minutes on days 1-3 together with bevacizumab 15 mg/kg i.v. or placebo on day 1.

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

The primary efficacy endpoint was overall survival (OS).

Overall survival was 12.9 months in the chemotherapy group (n=225) vs 16.8 months in the chemotherapy + bevacizumab group (n=227) (Kaplan-Meier estimates), hazard ratio: 0.74 (0.58, 0.94); p=0.0132 (log-rank test (stratified)).

Safety and efficacy in paediatric patients

Addition of Avastin to standard therapy showed no clinical benefit in paediatric patients in two phase II clinical trials, neither in paediatric patients with high-grade glioma nor in paediatric patients with metastatic rhabdomyosarcoma or non-rhabdomyosarcoma soft-tissue sarcoma.

Pharmacokinetics

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

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

The population pharmacokinetic analysis found no significant differences in bevacizumab pharmacokinetics with regard to age (no correlation between bevacizumab clearance and patient age; the median age was 59 years with 5th and 95th percentiles of 37 and 76 years, respectively).

Low albumin and high tumour burden are generally indicative of disease severity. Compared to typical patients with median values of albumin and tumour burden, bevacizumab clearance was approximately 30% faster in patients with low serum albumin levels and 7% faster in those with higher tumour burden.

Absorption

Not applicable.

Distribution
The typical value for the central volume of distribution (Vc) was 2.73 litres in women and 3.28 litres in men, which is in the range described for IgGs and other monoclonal antibodies. The typical values for peripheral volume of distribution (Vp) were 1.68 litres in women and 2.35 litres in men, when bevacizumab was coadministered with antineoplastic agents. After correction of the data for body weight, men had a higher Vc (+20%) than women.

Metabolism
Assessment of bevacizumab metabolism in rabbits following a single i.v. dose of ^{125}I-bevacizumab indicated that its metabolic profile was similar to that expected for a native IgG molecule that does not bind to VEGF. Based on human data it may be assumed that bevacizumab undergoes metabolism and elimination similar to endogenous IgG. Antibodies are degraded mainly by proteolysis throughout the body, including in endothelial cells, and their breakdown does not depend primarily on elimination via kidneys or liver. Binding of IgG to the neonatal Fc receptor (FcRn) protects against degradation, thereby resulting in a long half-life.

Elimination
The pharmacokinetics of bevacizumab are linear at doses ranging from 1.5 to 10 mg/kg/week. Clearance averages 0.188 litres/day in female patients and 0.220 litres/day in male patients. After correcting for body weight, male patients had a higher bevacizumab clearance (+17%) than females. According to the two-compartment model, the elimination half-life is 18 days for a typical female patient and 20 days for a typical male patient.

Kinetics in specific patient groups
The population pharmacokinetics of bevacizumab were analysed to evaluate the effects of demographic characteristics. The results showed no significant difference in the pharmacokinetics of bevacizumab in relation to age.

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

Renal impairment
No studies have been conducted to investigate the pharmacokinetics of bevacizumab in renally impaired patients since bevacizumab is not metabolised or excreted primarily by the kidneys.

Children and adolescents
The pharmacokinetics of bevacizumab were evaluated in 152 patients (7 months to 21 years old, weighing 5.9 to 125 kg) in 4 clinical studies using a population pharmacokinetic model. The pharmacokinetic results show that the clearance and volume of distribution of bevacizumab were comparable in paediatric and adult patients when normalised by body weight. Age did not play a role in the pharmacokinetics of bevacizumab when body weight was taken into account.

Preclinical data

Repeated-dose toxicity

Epiphyseal development

In studies of up to 26 weeks in macaques, epiphyseal dysplasia occurred during Avastin therapy in animals in the active growth phase with open growth plates. This effect occurred at exposures which – based on average serum concentrations – were slightly below the expected human clinical exposure.

Wound healing

In rabbits, dose-dependent reversible delay of wound healing was observed after three to five doses of bevacizumab ranging from 0.5 to 10 mg/kg.

As effects on wound healing were observed in rabbits at dosages below the recommended clinical dose, it must be assumed that bevacizumab could also have a negative effect on wound healing in humans.

In macaques the effects of bevacizumab on the healing of a linear incision were highly variable and no dose-response relationship was discernible.

Albumin

In male macaques, bevacizumab administered at doses of 10 mg/kg twice weekly or 50 mg/kg once weekly for 26 weeks produced a statistically significant decrease in albumin and the albumin/globulin ratio, and an increase in globulin. These effects were reversible after the substance was withdrawn. Since values for these parameters remained in the normal range, these changes were not considered clinically significant.

Mutagenicity

No studies have been performed to evaluate the mutagenic potential of Avastin.

Carcinogenicity

No studies have been performed to evaluate the carcinogenic potential of Avastin.

Reproductive toxicity

No specific animal studies have been performed to investigate the effects of Avastin on fertility. No adverse effects on the male reproductive organs of macaques were observed in repeated-dose toxicity studies lasting up to 26 weeks. But since no animal fertility studies are available, an influence by Avastin on human male fertility cannot be completely excluded.

Macaques treated with Avastin for 13 or 26 weeks showed inhibition of ovarian function, characterised by decreases in ovarian and/or uterine weight and the number of corpora lutea, reduced endometrial proliferation and inhibition of follicular maturation. The doses at which this effect occurred were ≥twice the exposure anticipated in humans, based on the mean serum concentration in female monkeys. In rabbits, administration of bevacizumab 50 mg/kg resulted in a significant decrease in ovarian weight and the number of corpora lutea. These changes in monkeys and rabbits were reversible on treatment withdrawal. The inhibition of angiogenesis following administration of bevacizumab probably has negative effects on female fertility.

Avastin has been shown to be embryotoxic and teratogenic in rabbits at doses below those causing maternal toxicity. Effects (decreases in maternal and fetal body weights, an increase in fetal resorptions and an increased incidence of skeletal fetal deformities) were observed at all tested doses in the range

10-100 mg/kg (corresponding to 1-12 times the recommended human dose). Fetal malformations (e.g. in the form of limb deformities) observed in the postmarketing setting following preconception or first-trimester exposure are listed under “Undesirable effects”.

Other information

Incompatibilities

No incompatibilities have been observed between Avastin and polyvinyl chloride or polyolefin infusion bags or systems. A concentration-dependent degradation profile is observed when bevacizumab is diluted with glucose solutions (5%). Avastin must therefore not be diluted with glucose solutions, but only with NaCl solutions (0.9%).

Shelf life

This medicinal product must not be used after the expiry date (EXP) shown on the pack.

Shelf life after opening

After dilution with NaCl solution (0.9%) the solution remains chemically and physically stable for 48 hours at 2-30°C. For microbiological reasons the reconstituted solution should be used immediately, unless reconstitution was performed under controlled and validated aseptic conditions.

Special precautions for storage

Store in the refrigerator (2-8°C).

Do not shake. Do not freeze.

Keep the container in the outer carton in order to protect the contents from light.

Keep out of the reach of children.

Instructions for handling

Avastin solution should only be prepared by a healthcare professional under aseptic conditions. Use a sterile needle and syringe to prepare Avastin. Withdraw the necessary amount of Avastin and dilute to the required administration volume with 0.9% sodium chloride solution. The concentration of the final bevacizumab solution should be kept within the range 1.4-16.5 mg/ml.

Dispose of unused substance remaining in the vial as the product contains no preservatives. Drugs for parenteral use should be checked for particulate matter and discolouration prior to administration.

Avastin contains no antimicrobial preservative. Care must therefore be taken to ensure the sterility of the prepared solution.

After completion of treatment or expiry, unused medicinal product should be disposed of in accordance with local regulations.

Packs

Pack containing one 4 ml vial (25 mg/ml) [A]

Pack containing one 16 ml vial (25 mg/ml) [A]

This is a medicament

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

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

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

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

Do not repeat the same prescription without consulting your doctor.

Medicine: keep out of reach of children

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