1. NAME OF THE MEDICINAL PRODUCT

ZIRABEV Concentrate for Solution for Infusion 100 mg/4 ml
ZIRABEV Concentrate for Solution for Infusion 400 mg/16 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate contains 25 mg of bevacizumab. Each 4 ml single-use vial contains 100 mg of bevacizumab.

Each 16 ml single-use vial contains 400 mg of bevacizumab.

For dilution and other handling recommendations, see section 6.6 Special precautions for disposal and other handling.

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

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to slightly opalescent, colourless to pale brown liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metastatic Carcinoma of the Colon or Rectum (mCRC)

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

Metastatic Breast Cancer (mBC)

ZIRABEV, in combination with paclitaxel, is indicated for the treatment of patients who have not received chemotherapy for metastatic human epidermal growth factor receptor 2 (HER2)-negative breast cancer.

ZIRABEV, in combination with capecitabine, is indicated for first-line treatment of patients with HER2-negative metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with ZIRABEV in combination with capecitabine.

The effectiveness of bevacizumab in metastatic breast cancer is based on an improvement in progression-free survival. Currently, no data are available that demonstrate an improvement in disease-related symptoms or increased survival with bevacizumab in breast cancer.

Non-Small Cell Lung Cancer (NSCLC)

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

ZIRABEV, in combination with erlotinib, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations.

Malignant Glioma (WHO Grade IV) - Glioblastoma

ZIRABEV, as a single agent, is indicated for the treatment of patients with glioblastoma after relapse or disease progression following prior therapy.

The effectiveness of bevacizumab in glioblastoma is based on an improvement in objective response rate. There are no data demonstrating an improvement in disease-related symptoms or increased survival with bevacizumab.

Advanced and/or Metastatic Renal Cell Cancer (mRCC)

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

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

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

ZIRABEV, 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 who have not received prior bevacizumab or other vascular endothelial growth factor (VEGF)-targeted angiogenesis inhibitors.

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

Cervical Cancer

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

4.2 Posology and method of administration

Posology

Standard Dosage

Metastatic Carcinoma of the Colon or Rectum (mCRC)

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

First-line treatment:	5 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg of body weight given once every 3 weeks.
Second-line treatment:	10 mg/kg of body weight given every 2 weeks with 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX-4). 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks when used in combination with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy regimen in patients who have progressed on a first-line bevacizumab-containing regimen (see section 5.1 Pharmacodynamic properties – Study ML18147).

It is recommended that ZIRABEV treatment be continued until progression of the underlying disease. Patients previously treated with ZIRABEV can continue with ZIRABEV treatment following first progression (see section 5.1 Pharmacodynamic properties – Study ML18147).

Metastatic Breast Cancer (mBC)

The recommended dose of ZIRABEV, administered as an intravenous infusion, is as follows:
In combination with paclitaxel: 10 mg/kg of body weight given once every 2 weeks.
In combination with capecitabine: 15 mg/kg of body weight given once every 3 weeks.

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

Non-Small Cell Lung Cancer (NSCLC)

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

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

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

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

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

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

Please refer to the full prescribing information for erlotinib for patient selection and posology.

Malignant Glioma (WHO Grade IV) - Glioblastoma

The recommended dose of ZIRABEV is 10 mg/kg of body weight given once every 2 weeks.

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

Advanced and/or Metastatic Renal Cell Cancer (mRCC)

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

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

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

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

Front-line treatment:	15 mg/kg of body weight given once every 3 weeks when administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of ZIRABEV as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier.
Treatment of recurrent disease:	Platinum sensitive: 15 mg/kg of body weight given once every 3 weeks when administered in combination with carboplatin and paclitaxel for 6 cycles and up to 8 cycles followed by continued use of ZIRABEV as a single agent until disease progression. Alternatively, 15 mg/kg every 3 weeks when administrated in combination with carboplatin and gemcitabine for 6 cycles and up to 10 cycles followed by continued use of ZIRABEV as single agent until disease progression. Platinum resistant:

10 mg/kg body weight given once every 2 weeks when administered in combination with one of the following agents – paclitaxel, topotecan (given weekly) or pegylated liposomal doxorubicin (see section 5.1 Pharmacodynamic properties – Study MO22224 for chemotherapy regimens).

Alternatively, 15 mg/kg every 3 weeks when administered in combination with topotecan given on Days 1-5, every 3 weeks (see section 5.1 Pharmacodynamic properties – Study MO22224 for chemotherapy regimen).

It is recommended that treatment be continued until disease progression.

Cervical Cancer

The recommended dose of ZIRABEV is 15 mg/kg every 3 weeks as an intravenous infusion administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin, or paclitaxel and topotecan (see section 5.1 Pharmacodynamic properties – Study GOG-0240 for further details on the chemotherapy regimens).

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

Special Dosage Instructions

Paediatric Use

The safety and efficacy of bevacizumab in children and adolescents (<18 years) have not been established (see section 4.4 Special warnings and precautions for use). ZIRABEV is not recommended for use in children and adolescents due to a lack of data on safety and efficacy (see also section 5.3 Preclinical safety data).

Geriatric Use

No dose adjustment is required in patients ≥65 years of age. However, there was an increased risk of adverse events in patients above 65 years of age (see section 4.8 Undesirable effects – Clinical Trials – Elderly Patients).

Renal Impairment

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

Hepatic Impairment

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

Method of Administration

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

The safety and efficacy of alternating or switching between ZIRABEV and products that are biosimilar but not deemed interchangeable to ZIRABEV has not been established. Therefore, the benefit/risk of alternating or switching need to be carefully considered.

ZIRABEV should be prepared by a healthcare professional using aseptic technique. Withdraw the volume of ZIRABEV equivalent to the required dose per body weight and dilute in a total volume of 100 ml of sterile, pyrogen-free 0.9% sodium chloride. For further instructions, see sections 6.4 Special precautions for storage and 6.6 Special precautions for disposal and other handling.

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

ZIRABEV infusions should not be administered or mixed with dextrose or glucose solutions (see section 6.2 Incompatibilities).

Do not administer as an intravenous push or bolus.

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

The initial dose of ZIRABEV should be administered following chemotherapy, all subsequent doses can be given before or after chemotherapy.

ZIRABEV is not formulated for intravitreal use (see section 4.4 Special warnings and precautions for use).

4.3 Contraindications

ZIRABEV is contraindicated in:

- Patients with known hypersensitivity to any components of the product.
- Patients with known hypersensitivity to Chinese Hamster Ovary cell products or other recombinant human or humanised antibodies.
- Pregnancy.

4.4 Special warnings and precautions for use

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

Gastrointestinal (GI) Perforations and Fistulae

Patients may be at increased risk for the development of gastrointestinal perforation (see also section 4.8 Undesirable effects – Clinical Trials) and gallbladder perforation (see section 4.8 Undesirable effects – Post-marketing Experience) when treated with bevacizumab. ZIRABEV should be permanently discontinued in patients who develop gastrointestinal perforation. Patients treated for persistent, recurrent or metastatic cervical cancer with bevacizumab may be at increased risk of fistulae between the vagina and any part of the GI tract (GI-vaginal fistulae) (see section 4.8 Undesirable effects – Clinical Trials – Gastrointestinal Perforation and Fistulae). Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients.

Non-GI Fistulae (see section 4.8 Undesirable effects – Clinical Trials)

Patients may be at increased risk for the development of fistulae when treated with bevacizumab (see section 4.8 Undesirable effects – Clinical Trials). Permanently discontinue ZIRABEV in patients with tracheoesophageal (TE) fistula or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae.

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

Hypertension

An increased incidence of hypertension was observed in patients treated with bevacizumab. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre-existing hypertension should be adequately controlled before starting ZIRABEV treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy.

Monitoring of blood pressure is recommended during ZIRABEV therapy (see section 4.8 Undesirable effects – Clinical Trials).

In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. The use of diuretics to manage hypertension is not advised in patients who receive a cisplatin-based chemotherapy regimen. ZIRABEV should be permanently discontinued, if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy (see section 4.8 Undesirable effects – Clinical Trials, and Post-marketing Experience).

Wound Healing

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

ZIRABEV therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experience wound healing

complications during ZIRABEV treatment, ZIRABEV should be withheld until the wound is fully healed. ZIRABEV therapy should be withheld for elective surgery (see section 4.8 Undesirable effects).

Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab; usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. ZIRABEV therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated (see also section 4.8 Undesirable effects – Post-marketing Experience).

Arterial Thromboembolism

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

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

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

Venous Thromboembolism

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

Patients treated for persistent, recurrent or metastatic cervical cancer with bevacizumab may be at increased risk of venous thromboembolic events (see section 4.8 Undesirable effects – Clinical Trials – Venous Thromboembolism).

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

Haemorrhage (see section 4.8 Undesirable effects)

The risk of central nervous system (CNS) haemorrhage in patients with CNS metastases receiving bevacizumab could not be fully evaluated, as these patients were excluded from clinical trials. Thus, ZIRABEV should not be used in these patients.

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

Patients with untreated CNS metastases were routinely excluded from clinical trials with bevacizumab based on imaging procedures or signs and symptoms. Therefore, the risk of

CNS haemorrhage in such patients has not been prospectively evaluated in randomized clinical studies (see section 4.8 Undesirable effects – Clinical Trials – Haemorrhage). Patients should be monitored for signs and symptoms of CNS bleeding, and ZIRABEV treatment discontinued in case of intracranial bleeding.

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

Severe Eye Infections Following Compounding for Unapproved Intravitreal Use (see section 4.8 Undesirable effects – Post-marketing Experience)

Individual cases and clusters of serious ocular adverse events have been reported (including infectious endophthalmitis and other ocular inflammatory conditions) following unapproved intravitreal use of bevacizumab compounded from vials approved for intravenous administration in cancer patients. Some of these events have resulted in various degrees of visual loss, including permanent blindness.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with PRES, a rare neurologic disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of ZIRABEV. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known (see section 4.8 Undesirable effects – Clinical Trials, and Post-marketing Experience).

Proteinuria

Patients with a history of hypertension may be at increased risk for development of proteinuria when treated with bevacizumab. There is evidence suggesting that Grade 1 (US National Cancer Institute – Common Toxicity Criteria [NCI-CTC] version 2.0) proteinuria may be related to the dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Therapy should be permanently discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome) (see section 4.8 Undesirable effects).

Pulmonary Haemorrhage/Haemoptysis

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

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 ZIRABEV, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Ovarian Failure/Fertility (see sections 4.6 Fertility, pregnancy and lactation – Females and Males of Reproductive Potential and 4.8 Undesirable effects – Clinical Trials)

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

Congestive Heart Failure (CHF)/Cardiomyopathy

Events consistent with CHF were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation. Caution should be exercised when treating patients with clinically significant cardiovascular disease or pre-existing congestive heart failure with ZIRABEV.

Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF, such as pre-existing coronary heart disease or concomitant cardiotoxic therapy.

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

Hypersensitivity Reactions, Infusion Reactions (see section 4.8 Undesirable effects – Clinical Trials, and Post-marketing Experience)

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

Neutropenia

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

Osteonecrosis of the Jaw (ONJ)

Cases of ONJ have been reported in cancer patients treated with bevacizumab, the majority of whom had received prior or concomitant treatment with intravenous bisphosphonates, for which ONJ is an identified risk. Caution should be exercised when ZIRABEV and intravenous bisphosphonates are administered simultaneously or sequentially.

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

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Antineoplastic Agents on Bevacizumab Pharmacokinetics

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

Effect of Bevacizumab on the Pharmacokinetics of other Antineoplastic Agents

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

Combination of Bevacizumab and Sunitinib Malate

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

MAHA is a haemolytic disorder which can present with red cell fragmentation, anaemia, and thrombocytopenia. In addition, hypertension (including hypertensive crisis), elevated creatinine, and neurological symptoms were observed in some of these patients. All of these findings were reversible upon discontinuation of bevacizumab and sunitinib malate (see section 4.4 Special warnings and precautions for use – Hypertension, Proteinuria, PRES).

Combination with Platinum- or Taxane-based Therapies

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

Radiotherapy

The safety and efficacy of concomitant administration of radiotherapy and bevacizumab has not been established in other indications.

EGFR Monoclonal Antibodies in Combination with Bevacizumab Chemotherapy Regimens

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

4.6 Fertility, pregnancy and lactation

Females and Males of Reproductive Potential

Fertility

Bevacizumab may impair female fertility. Women of child-bearing potential should be advised of fertility preservation strategies prior to starting treatment with ZIRABEV (see sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects – Clinical Trials).

Repeat dose safety studies in animals have shown that bevacizumab may have an adverse effect on female fertility (see section 5.3 Preclinical safety data – Reproductive Toxicity). A substudy with 295 premenopausal women has shown a higher incidence of new cases of ovarian failure in the bevacizumab group compared to the control group (39.0 vs. 2.6%). After discontinuation of bevacizumab treatment, ovarian function recovered in the majority (86%) of patients. Long term effects of the treatment with bevacizumab on fertility are unknown (see section 4.8 Undesirable effects).

Contraception

In women with childbearing potential, appropriate contraceptive measures should be used during ZIRABEV therapy. Based on pharmacokinetic considerations, contraceptive measures should be used for at least 6 months following the last dose of ZIRABEV.

Pregnancy

Bevacizumab has been shown to be embryotoxic and teratogenic when administered to rabbits. Observed effects included decreases in maternal and foetal body weights, an increased number of foetal resorptions and an increased incidence of specific gross and skeletal foetal alterations. Adverse foetal outcomes were observed at all tested doses of 10-100 mg/kg. Information on foetal malformations observed in the post-marketing setting are provided in section 4.8 Undesirable effects – Post-marketing Experience.

Angiogenesis has been shown to be critically important to foetal development. The inhibition of angiogenesis following administration of bevacizumab could result in an adverse outcome of pregnancy. There are no adequate and well-controlled studies in pregnant women. Immunoglobulin G (IgGs) are known to cross the placental barrier, and bevacizumab may inhibit angiogenesis in the foetus. In the post-marketing setting, cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see section 4.8 Undesirable effects – Post-marketing Experience).

Therefore, ZIRABEV should not be used during pregnancy.

Lactation

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical Trials

Summary of Safety Profile

Clinical trials have been conducted in patients with various malignancies treated with bevacizumab, predominantly in combination with chemotherapy. The safety profile from a clinical trial population of approximately 5,500 patients is presented in this section. For post-marketing experience, see Post-marketing Experience below. See section 5.1 Pharmacodynamic properties – Clinical Efficacy for details of major studies, including study designs and major efficacy results.

The most serious adverse events were:

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

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

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

Tabulated Summary of Adverse Drug Reactions from Clinical Trials

Table 1 lists adverse drug reactions associated with the use of bevacizumab in combination with different chemotherapy regimens in multiple indications, by Medical Dictionary for Regulatory Activities (MedDRA) system organ class.

The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). These reactions had occurred either with at least a 2% difference compared to the control arm (NCI-CTC Grade 3-5 reactions) or with at least a 10% difference compared to the control arm (NCI-CTC Grade 1-5 reactions), in at least one of the major clinical trials.

Adverse drug reactions are added to the appropriate category in the table below according to the highest incidence seen in any of the major clinical trials.

Within each frequency grouping adverse drug reactions are presented in the order of decreasing seriousness. Some of the adverse drug reactions are reactions commonly seen with chemotherapy; however, bevacizumab may exacerbate these reactions when combined with chemotherapeutic agents. Examples include palmar-plantar erythrodysaesthesia syndrome with pegylated liposomal doxorubicin or capecitabine, peripheral sensory neuropathy with paclitaxel or oxaliplatin, nail disorders or alopecia with paclitaxel, and paronychia with erlotinib.

Table 1 Very Common and Common Adverse Drug Reactions

System Organ Class (SOC)	**NCI-CTC Grade 3-5 Reactions (≥2% difference between the study arms in at least one clinical trial)**		**All Grade Reactions (≥10% difference between the study arms in at least one clinical trial)**
	Very Common	**Common**	**Very Common**
Infections and infestations		Sepsis Abscess Cellulitis Infection	Paronychia
Blood and the lymphatic systems disorders	Febrile neutropenia Leucopenia Neutropenia Thrombocytopenia	Anaemia Lymphopenia	
Metabolism and nutrition disorders		Dehydration Hyponatraemia	Anorexia Hypomagnesaemia Hyponatraemia
Nervous system disorders	Peripheral sensory neuropathy	Cerebrovascular accident	Dysgeusia Headache

		Syncope Somnolence Headache	Dysarthria
Eye disorders			Eye disorder Lacrimation increased
Cardiac disorders		Cardiac failure congestive Supraventricular tachycardia	
Vascular disorders	Hypertension	Thromboembolism (arterial) Deep vein thrombosis Haemorrhage	Hypertension
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism Dyspnoea Hypoxia Epistaxis	Dyspnoea Epistaxis Rhinitis Cough
Gastrointestinal disorders	Diarrhoea Nausea Vomiting Abdominal pain	Intestinal perforation Ileus Intestinal obstruction Recto-vaginal fistulae** Gastrointestinal disorder Stomatitis Proctalgia	Constipation Stomatitis Rectal haemorrhage Diarrhoea
Endocrine disorders			Ovarian failure*
Skin and subcutaneous tissue disorders		Palmar-plantar erythrodysaesthesia syndrome	Exfoliative dermatitis Dry skin Skin discolouration
Musculoskeletal, connective tissue and bone disorders		Muscular weakness Myalgia Arthralgia Back pain	Arthralgia
Renal and urinary disorders		Proteinuria Urinary tract infection	Proteinuria
General disorders and administration site conditions	Asthenia Fatigue	Pain Lethargy Mucosal inflammation	Pyrexia Asthenia Pain Mucosal inflammation
Reproductive system and breast		Pelvic pain	
Investigations			Weight decreased

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

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

Description of Selected Adverse Drug Reactions from Clinical Trials

Gastrointestinal Perforation and Fistulae *(see section 4.4 Special warnings and precautions for use)*

Bevacizumab has been associated with serious cases of gastrointestinal perforation.

Gastrointestinal perforation have been reported in clinical trials with an incidence of less than 1% in patients with metastatic breast cancer or non-squamous non-small cell lung cancer, up to 2.0% in patients with metastatic renal cell cancer, newly diagnosed glioblastoma, or ovarian cancer, and up to 2.7% (including gastrointestinal fistula and abscess) in patients with metastatic colorectal cancer. Cases of GI perforations have also been observed in patients with relapsed glioblastoma.

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

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

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

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

In a trial of patients with persistent, recurrent or metastatic cervical cancer, the incidence of GI-vaginal fistulae was 8.3% in bevacizumab-treated patients and 0.9% in control patients, all of whom had a history of prior pelvic radiation. Patients who develop GI-vaginal fistulae may also have bowel obstructions and require surgical intervention as well as diverting ostomies. The presentation of these events varied in type and severity, ranging from free air seen on the plain abdominal X-ray, which resolved without treatment, to intestinal perforation with abdominal abscess and fatal outcome. In some cases underlying intra-abdominal inflammation was present, either from gastric ulcer disease, tumour necrosis, diverticulitis, or chemotherapy-associated colitis.

Non-GI Fistulae *(see section 4.4 Special warnings and precautions for use)*

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

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), 1.8% of bevacizumab-treated patients and 1.4% of control patients were reported to have had non-gastrointestinal vaginal, vesical, or female genital tract fistulae.

Uncommon (≥0.1% to <1%) reports of fistulae that involve areas of the body other than the gastrointestinal tract (e.g., bronchopleural, biliary fistulae) were observed across various indications. Fistulae have also been reported in post-marketing experience.

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

Wound Healing *(see section 4.4 Special warnings and precautions for use)*

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

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

Cases of serious wound healing complications have been reported during bevacizumab use, some of which had a fatal outcome (see section 4.4 Special warnings and precautions for use).

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

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

Hypertension *(see section 4.4 Special warnings and precautions for use)*

In clinical trials, with the exception of study JO25567, the overall incidence of hypertension (all grades) ranged up to 42.1% in the bevacizumab-containing arms compared with up to 14% in the control arms. The overall incidence of NCI-CTC Grade 3 and 4 hypertension (requiring oral anti-hypertensive medication) in patients receiving bevacizumab ranged from 0.4% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of patients treated with bevacizumab and chemotherapy compared with up to 0.2% of patients treated with the same chemotherapy alone.

In study JO25567, all grade hypertension was observed in 77.3% of the patients who received bevacizumab in combination with erlotinib as first-line treatment for non-squamous NSCLC with EGFR activating mutations, compared to 14.3% of patients treated with erlotinib alone. Grade 3 hypertension was 60.0% in patients treated with bevacizumab in combination with

erlotinib compared to 11.7% in patients treated with erlotinib alone. There were no Grade 4 or 5 hypertension events.

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

Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal.

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

Posterior Reversible Encephalopathy Syndrome *(see section 4.4 Special warnings and precautions for use)*

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

Proteinuria *(see section 4.4 Special warnings and precautions for use)*

In clinical trials, proteinuria has been reported within the range of 0.7% to 54.7% of patients receiving bevacizumab.

Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome, with the great majority as Grade 1 proteinuria. Grade 3 proteinuria was reported in up to 8.1% of treated patients, Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with bevacizumab. Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence suggesting that Grade 1 proteinuria may be related to bevacizumab dose. Testing for proteinuria is recommended prior to start of ZIRABEV therapy. In most clinical studies urine protein levels of ≥2 g/24 h led to the holding of bevacizumab until recovery to <2 g/24 h.

Hypersensitivity Reactions, Infusion Reactions *(see section 4.4 Special warnings and precautions for use)*

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

Haemorrhage *(see section 4.4 Special warnings and precautions for use)*

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 bevacizumab-treated patients, compared with up to 4.5% of patients in chemotherapy control group.

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

Tumour-associated Haemorrhage *(see section 4.4 Special warnings and precautions for use)*

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

In patients with NSCLC excluding predominant squamous histology, all grade events were seen with a frequency of up to 9.3% when treated with bevacizumab plus chemotherapy compared with up to 5% in the patients treated with chemotherapy alone. Grade 3-5 events have been observed in up to 2.3% of patients treated with bevacizumab plus chemotherapy as compared with <1% with chemotherapy alone. Major or massive pulmonary haemorrhage/haemoptysis can occur suddenly and up to two thirds of the serious pulmonary haemorrhages resulted in a fatal outcome.

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

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

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

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

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

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

Thromboembolism *(see section 4.4 Special warnings and precautions for use)*

Arterial Thromboembolism

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

In clinical trials, the overall incidence ranged up to 5.9% in the bevacizumab-containing arms compared with up to 1.7% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving bevacizumab in combination with chemotherapy compared to 0.5% in patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischemic attacks) were reported in up to 2.7% of bevacizumab-treated patients versus up to 0.5% of patients in the control group; myocardial infarction was reported in up to 1.4% of bevacizumab-treated versus up to 0.7% of patients in control groups.

In one clinical trial, AVF2192g, patients with metastatic colorectal cancer who were not candidates for treatment with irinotecan were included. In this trial arterial thromboembolic events were observed in 11% (11/100) of patients compared to 5.8% (6/104) in the chemotherapy control group.

In an uncontrolled clinical trial, AVF3708g, in patients with relapsed glioblastoma, arterial thromboembolic events were observed in up to 6.3% (5/79) of patients who received bevacizumab in combination with irinotecan compared to up to 4.8% (4/84) of patients who received bevacizumab alone.

Venous Thromboembolism

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

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

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

Congestive Heart Failure (CHF)

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

Most patients who developed CHF during mBC trials showed improved symptoms and/or left ventricular function following appropriate medical therapy.

In most clinical trials of bevacizumab, patients with pre-existing CHF of New York Heart Association (NYHA) II-IV were excluded, therefore, no information is available on the risk of CHF in this population.

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

An increased incidence of CHF has been observed in a clinical trial of patients with diffuse large B cell lymphoma when receiving bevacizumab with a cumulative doxorubicin dose greater than 300 mg/m^2. This phase III clinical trial compared rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) plus bevacizumab to R-CHOP without bevacizumab. While the incidence of CHF was, in both arms, above that previously observed for doxorubicin therapy, the rate was higher in the R-CHOP plus bevacizumab arm. These results suggest that close clinical observation with appropriate cardiac assessments should be considered for patients exposed to cumulative doxorubicin doses greater than 300 mg/m^2 when combined with bevacizumab.

Ovarian Failure/Fertility *(see sections 4.4 Special warnings and special precautions for use and 4.6 Fertility, pregnancy and lactation – Pregnancy)*

The incidence of new cases of ovarian failure, defined as amenorrhea lasting 3 or more months, follicle stimulating hormone (FSH) level ≥30 mIU/ml and a negative serum β-HCG (human chorionic gonadotropin) pregnancy test, has been evaluated. New cases of ovarian failure were reported more frequently in patients receiving bevacizumab (39.0% vs. 2.6%). After discontinuation of bevacizumab treatment, ovarian function recovered in a majority of women (86%). Long term effects of the treatment with bevacizumab on fertility are unknown.

Elderly Patients

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

and all grade neutropenia, diarrhoea, nausea, headache and fatigue as compared to those aged ≤65 years when treated with bevacizumab (see section 4.4 Special warnings and precautions for use and Thromboembolism).

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

Paediatric Use

Bevacizumab is not approved for use in patients under the age of 18 years. The safety and efficacy of bevacizumab in this population have not been established. Addition of bevacizumab to standard of care did not demonstrate clinical benefit in paediatric patients in two phase II clinical trials: one in paediatric high grade glioma and one in paediatric metastatic rhabdomyosarcoma or non-rhabdomyosarcoma soft tissue sarcoma.

In published reports, cases of osteonecrosis at sites other than the jaw have been observed in patients under the age of 18 years exposed to bevacizumab (see Post-marketing Experience and section 5.3 Preclinical safety data – Physeal Development).

Laboratory Abnormalities

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

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

Clinical trials have shown that transient increases in serum creatinine (ranging between 1.5-1.9 times baseline level), both with and without proteinuria, are associated with the use of bevacizumab. The observed increase in serum creatinine was not associated with a higher incidence of clinical manifestations of renal impairment in patients treated with bevacizumab.

Post-marketing Experience

The following adverse drug reactions have been identified from post-marketing experience with bevacizumab (Table 2) based on spontaneous case reports and literature cases. Adverse drug reactions are listed according to system organ classes in MedDRA and the corresponding frequency category estimation for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 2 Adverse Drug Reactions from Post-marketing Experience

Adverse Reactions	**Frequency Category**

Infections and infestations	
Necrotising fasciitis[1,2]	Rare
Immune system disorders	
Hypersensitivity[3]	Unknown
Infusion reactions[3]	Unknown
Nervous system disorders	
Hypertensive encephalopathy[2,4]	Very rare
Posterior reversible encephalopathy syndrome (PRES)[2]	Rare
Vascular disorders	
Renal thrombotic microangiopathy, clinically manifested as proteinuria[2,4], aneurysms and artery dissections	Unknown
Respiratory, thoracic and mediastinal disorders	
Nasal septum perforation	Unknown
Pulmonary hypertension	Unknown
Dysphonia	Common
Gastrointestinal disorders	
Gastrointestinal ulcer	Unknown
Hepatobiliary disorders	
Gallbladder perforation	Unknown
Musculoskeletal and connective tissue disorders	
Osteonecrosis of the jaw (ONJ)[5]	Unknown
Osteonecrosis at sites other than the jaw[6,7]	Unknown
Congenital, familial and genetic disorders	
Foetal abnormalities[8]	Unknown

[1] Usually secondary to wound healing complications, gastrointestinal perforation or fistula formation.
[2] See section 4.4. Special warnings and precautions for use.
[3] The following are possible co-manifestations: dyspnoea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting.
[4] See Clinical Trials.
[5] Cases of ONJ observed in bevacizumab-treated patients mainly in association with prior or concomitant use of bisphosphonates.
[6] Cases observed in bevacizumab-treated paediatric patients. See section 4.8 Undesirable effects – Paediatric Use.
[7] Osteonecrosis observed in paediatric population in non-company clinical trials was identified through post-marketing surveillance and has therefore been added to the post-marketing section as neither CTC grade nor reporting rate were available from published data.
[8] Cases have been observed in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics. See section 4.6 Fertility, pregnancy and lactation – Pregnancy.

Description of Selected Adverse Drug Reactions from Post-marketing Experience

Eye Disorders (Reported from Unapproved Intravitreal Use)

Infectious endophthalmitis (frequency not known; some cases leading to permanent blindness; one case reported extraocular extension of infection resulting in meningoencephalitis); Intraocular inflammation (some cases leading to permanent blindness; including a cluster of serious eye inflammation leading to blindness after compounding an anticancer chemotherapy product for intravenous administration) such as sterile endophthalmitis, uveitis, and vitritis; Retinal detachment (frequency not known); Retinal pigment epithelial tear (frequency not known); Intraocular pressure increased (frequency not known); Intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage (frequency not known); Conjunctival haemorrhage (frequency not known).

An observational claims database study comparing unapproved intravitreal bevacizumab to an approved treatment in patients treated for wet age-related macular degeneration has reported an increased risk of intraocular inflammation for bevacizumab (adjusted hazard ratio [HR]: 1.82; 99% confidence interval [CI]: 1.20, 2.76) (Incidence 0.46 events per 100 patients per year; comparator 0.26 events per 100 patients per year) as well as an increased risk for cataract surgery (adjusted HR: 1.11; 99% CI: 1.01, 1.23) (Incidence 6.33 events per 100 patients per year; comparator 5.64 events per 100 patients per year).

Following variable and non-validated methods in compounding, storage, and handling of bevacizumab, serious ocular adverse events (including infectious endophthalmitis and other ocular inflammatory conditions) affecting multiple patients have been reported.

Systemic Events (Reported from Unapproved Intravitreal Use)

An observational claims database study comparing unapproved intravitreal bevacizumab to an approved treatment in patients treated for wet age-related macular degeneration has reported an increased risk of haemorrhagic stroke for bevacizumab (adjusted HR: 1.57; 99% CI: 1.04, 2.37) (Incidence 0.41 events per 100 patients per year; comparator 0.26 events per 100 patients per year) as well as an increased risk for overall mortality (adjusted HR: 1.11; 99% CI: 1.01, 1.23) (Incidence 6.03 events per 100 patients per year; comparator 5.51 events per 100 patients per year).

A second observational study found similar results for all-cause mortality. A randomized controlled clinical trial comparing unapproved bevacizumab to an approved treatment for patients with wet age-related macular degeneration has reported an increased risk of serious systemic adverse events for bevacizumab, most of which resulted in hospitalisation (adjusted risk ratio 1.29; 95% CI: 1.01, 1.66) (Incidence 24.1%; comparator 19.0%).

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

Bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab contains human framework regions with the complementarity-determining regions of a humanised murine antibody that binds to VEGF. Bevacizumab is produced by recombinant DNA technology in a Chinese Hamster Ovary mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps. Bevacizumab consists of 214 amino acids and has a molecular weight of approximately 149,000 daltons.

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

Clinical Efficacy

Metastatic carcinoma of the colon or rectum (mCRC)

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

- AVF2107g: A weekly schedule of irinotecan/bolus 5-fluorouracil/leucovorin (IFL regimen) for a total of 4 weeks of each 6-week cycle.

- AVF0780g: In combination with bolus 5-fluorouracil/leucovorin (5-FU/LV) for a total of 6 weeks of each 8-week cycle (Roswell Park regimen).

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

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

- NO16966: Bevacizumab 7.5 mg/kg of body weight every 3 weeks in combination with oral capecitabine and intravenous oxaliplatin (XELOX) or bevacizumab 5 mg/kg every

2 weeks in combination with leucovorin plus 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4).

- E3200: Bevacizumab 10 mg/kg of body weight every 2 weeks in combination with leucovorin and 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4) in bevacizumab-naïve patients.

- ML18147: Bevacizumab 5 mg/kg of body weight every 2 weeks or bevacizumab 7.5 mg/kg of body weight every 3 weeks in combination with fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin in patients with disease progression following first-line treatment with bevacizumab. Use of irinotecan- or oxaliplatin-containing regimen was switched depending on first-line usage of either oxaliplatin or irinotecan.

Bevacizumab in Combination with Irinotecan, 5-Fluorouracil and Leucovorin (IFL) for First-line Treatment of Metastatic Carcinoma of the Colon or Rectum (AVF2107g)

This was a phase III randomized, double-blind, active-controlled clinical trial evaluating bevacizumab in combination with IFL as first-line treatment for metastatic carcinoma of the colon or rectum. Eight hundred-thirteen patients were randomized to receive IFL + placebo (Arm 1) or IFL + bevacizumab (5 mg/kg every 2 weeks, Arm 2) (see Table 3). A third group of 110 patients received bolus 5-FU/LV + bevacizumab (Arm 3). Enrolment in Arm 3 was discontinued, as pre-specified, once safety of bevacizumab with the IFL regimen was established and considered acceptable. All treatments were continued until disease progression. The overall mean age was 59.4 years; 56.6% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 43% had a value of 1 and 0.4% had a value of 2. 15.5% had received prior radiotherapy and 28.4% prior chemotherapy.

Table 3 Treatment Regimens in Study AVF2107g

	Treatment	Starting Dose	Schedule
Arm 1	Irinotecan	125 mg/m^2 intravenous	Given once weekly for 4 weeks every 6 weeks
	5-Fluorouracil	500 mg/m^2 intravenous	
	Leucovorin	20 mg/m^2 intravenous	
	Placebo	Intravenous	Every 2 weeks
Arm 2	Irinotecan	125 mg/m^2 intravenous	Given once weekly for 4 weeks every 6 weeks
	5-Fluorouracil	500 mg/m^2 intravenous	
	Leucovorin	20 mg/m^2 intravenous	
	Bevacizumab	5 mg/kg intravenous	Every 2 weeks
Arm 3	5-Fluorouracil	500 mg/m^2 intravenous	Given once weekly for 6 weeks every 8 weeks
	Leucovorin	500 mg/m^2 intravenous	
	Bevacizumab	5 mg/kg intravenous	Every 2 weeks
5-Fluorouracil: Intravenous bolus injection immediately after leucovorin. Leucovorin: Intravenous bolus injection (over 1-2 minutes) immediately after each irinotecan dose.			

The primary efficacy parameter of the trial was duration of survival. The addition of bevacizumab to IFL resulted in a statistically significant increase in overall survival (see Table 4 and Figure 1 for details). The clinical benefit of bevacizumab, as measured by overall survival, was seen in all pre-specified patient subgroups, including those defined by age, sex,

performance status, location of primary tumour, number of organs involved, and duration of metastatic disease (see Figure 2).

The efficacy results of bevacizumab in combination with IFL-chemotherapy are displayed in Table 4 and Figure 1 (Kaplan Meier plot for duration of survival).

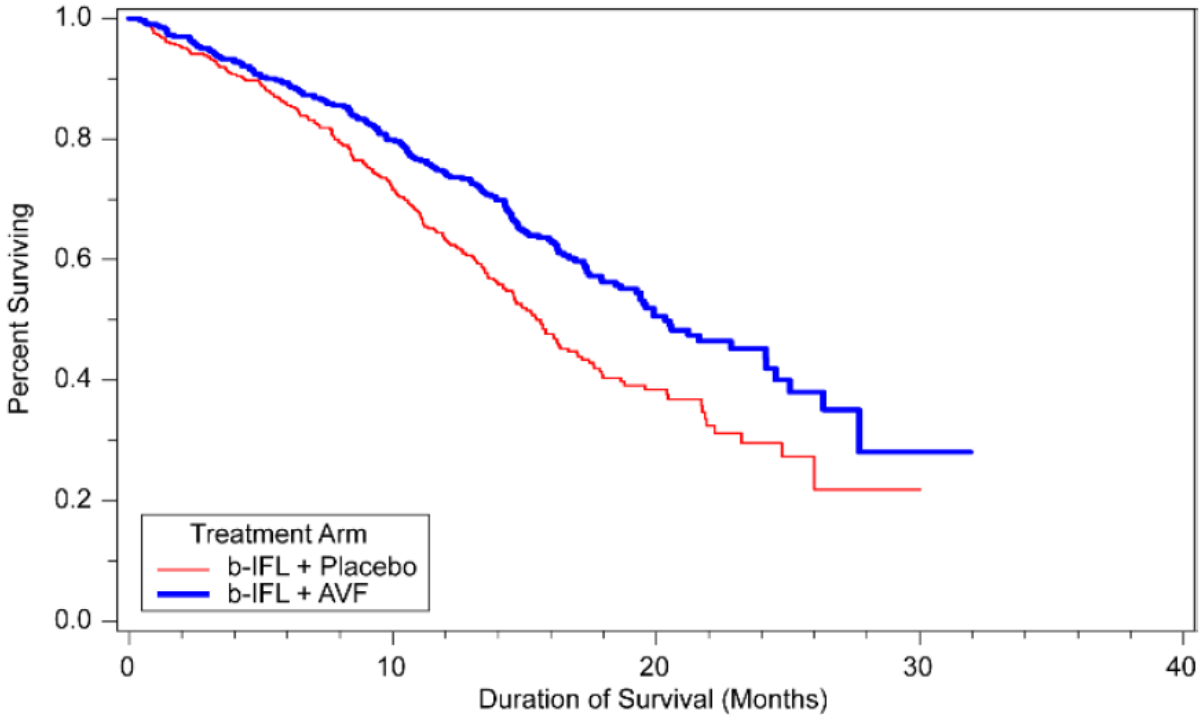
Table 4 Efficacy Results for Study AVF2107g

	AVF2107g	
	Arm 1 (IFL + Placebo)	Arm 2 (IFL + Bevacizumab[a])
Number of Patients	411	402
Overall Survival		
Median (months)	15.6	20.3
95% confidence interval	14.29-16.99	18.46-24.18
Hazard ratio[b]	0.660	
p-value	0.00004	
Progression-Free Survival		
Median (months)	6.2	10.6
Hazard ratio	0.54	
p-value	<0.00001	
Overall Response Rate		
Rate (percent)	34.8	44.8
95% confidence interval	30.2-39.6	39.9-49.8
p-value	0.0036	
Duration of Response		
Median (months)	7.1	10.4
25-75 percentile (months)	4.7-11.8	6.7-15.0

[a] 5 mg/kg every 2 weeks.
[b] Relative to control arm.

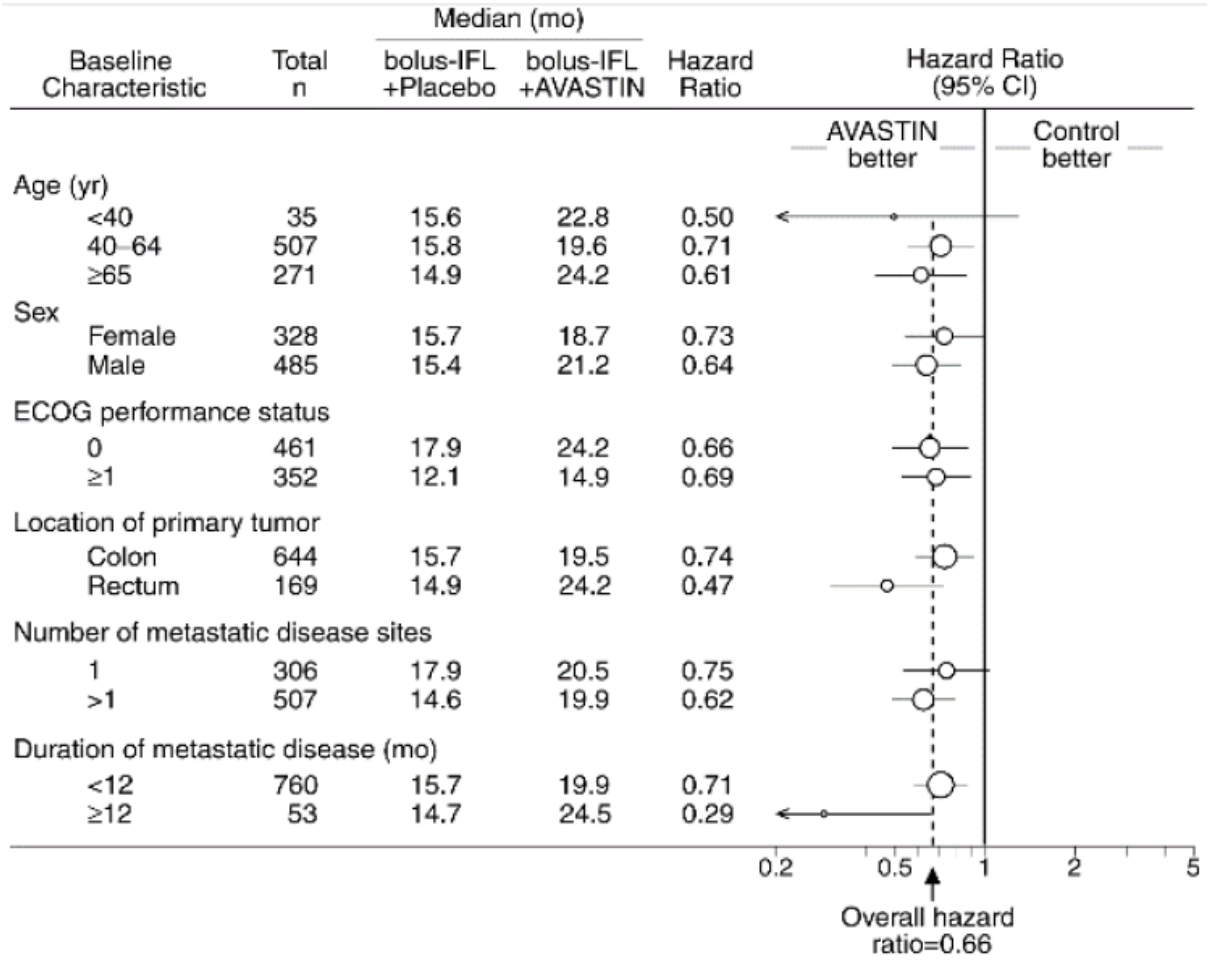
Among the 110 patients randomized to Arm 3 (5-FU/LV + bevacizumab), the median overall survival was 18.3 months, median progression-free survival was 8.8 months, overall response rate was 39% and median duration of response was 8.5 months.

Figure 1 Plot of Kaplan Meier Estimates for Survival in Study AVF2107g



IFL = Irinotecan, 5-FU, Leucovorin.
AVF = Bevacizumab.

Figure 2 Duration of Survival by Baseline Risk Factor in Study AVF2107g



CI = interval; IFL = irinotecan/5-fluorouracil/leucovorin.
Hazard ratio <1 indicates a lower hazard of death in the IFL + bevacizumab arm compared with the IFL + placebo arm. Size of circle is proportional to the number of patients in the subgroup.
Confidence interval is indicated by the horizontal line.

Bevacizumab in Combination with 5-FU/LV Chemotherapy for the First-line Treatment of Metastatic Carcinoma of the Colon or Rectum in Patients who were Not Optimal Candidates for First-line Irinotecan Treatment (AVF2192g)

This was a phase II randomized, double-blind, active-controlled clinical trial investigating bevacizumab 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. Patients had to be either more susceptible to irinotecan toxicity (≥65 years, prior radiotherapy to pelvis or abdomen) or less likely to benefit from irinotecan treatment (performance status [PS] ≥1, baseline albumin <3.5 g/dl) in order to be eligible for enrolment. One hundred and five patients were randomized to 5-FU/LV + placebo arm and 104 patients randomized to 5-FU/LV + bevacizumab (5 mg/kg every 2 weeks) arm. All treatments were continued until disease progression. The overall age was 71 years; 28.2% of patients had an ECOG performance status of 0, 65.1% had a value of 1 and 6.7% had a value of 2. The addition of bevacizumab 5 mg/kg every two weeks to 5-FU/LV resulted in higher objective response rates, significantly longer progression-free survival, and a trend in longer survival, compared with 5-FU/LV chemotherapy alone (see Table 5). These efficacy data were consistent with the results observed in studies AVF2107g and AVF0780g.

Table 5 Treatment Regimens in Study AVF2192g

	Treatment	Starting Dose	Schedule
Arm 1	5-Fluorouracil	500 mg/m^2 intravenous	Given once weekly for 6 weeks of 8-week cycle
	Leucovorin	500 mg/m^2 intravenous	
	Placebo	Intravenous	Every 2 weeks
Arm 2	5-Fluorouracil	500 mg/m^2 intravenous	Given once weekly for 6 weeks of 8-week cycle
	Leucovorin	500 mg/m^2 intravenous	
	Bevacizumab	5 mg/kg intravenous	Every 2 weeks
5-Fluorouracil: Intravenous bolus (slow push) 1 hour after initiation of the 2-hour leucovorin infusion. Leucovorin: Intravenous infusion over 2 hours.			

Bevacizumab in Combination with 5-FU/LV Chemotherapy for the First-line Treatment of Metastatic Carcinoma of the Colon or Rectum (AVF0780g)

This was a phase II randomized, active-controlled, open-labelled clinical trial investigating bevacizumab in combination with 5-FU/LV as first-line treatment of metastatic colorectal cancer. Seventy-one patients were randomized to receive bolus 5-FU/LV or 5-FU/LV + bevacizumab (5 mg/kg every 2 weeks). A third group of 33 patients received bolus 5-FU/LV + bevacizumab (10 mg/kg every 2 weeks). Patients were treated until disease progression. The primary endpoints of the trial were objective response rate and progression-free survival. The addition of 5 mg/kg every two weeks of bevacizumab to 5-FU/LV resulted in higher objective response rates, longer progression-free survival, and a trend in longer survival, compared with 5-FU/LV chemotherapy alone (see Table 6). This efficacy data is consistent with the results from study AVF2107g.

The efficacy data from studies AVF0780g and AVF2192g investigating bevacizumab in combination with 5-FU/LV-chemotherapy are summarized in Table 6.

Table 6 Efficacy Results from Studies AVF0780g and AVF2192g

	AVF0780g			AVF2192g	
	5-FU/LV	5-FU/LV + bevacizumab[a]	5-FU/LV + bevacizumab[b]	5-FU/LV + placebo	5-FU/LV + bevacizumab
Number of Patients	36	35	33	105	104
Overall Survival					
Median (months)	13.6	17.7	15.2	12.9	16.6
95% confidence interval				10.35-16.95	13.63-19.32
Hazard ratio[c]	-	0.52	1.01		0.79
p-value		0.073	0.978		0.16
Progression-Free Survival					
Median (months)	5.2	9.0	7.2	5.5	9.2
Hazard ratio		0.44	0.69		0.5
p-value	-	0.0049	0.217		0.0002
Overall Response Rate					
Rate (percent)	16.7	40.0	24.2	15.2	26
95% confidence interval	7.0-33.5	24.4-57.8	11.7-42.6	9.2-23.9	18.1-35.6
p-value	-	0.029	0.43		0.055

Duration of Response					
Median (months)	NR	9.3	5.0	6.8	9.2
25-75 percentile (months)	5.5-NR	6.1-NR	3.8-7.8	5.59-9.17	5.88-13.01

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

NO16966

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

Approximately 350 patients were randomized into each of the 4 study arms in the Part II of the trial.

Table 7 Treatment Regimens in Study N016966 (mCRC)

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

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

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

ii) Superiority of the bevacizumab-containing arms versus the chemotherapy alone arms in the overall comparison was demonstrated in terms of progression-free survival in the intent to treat (ITT) population (Table 8).

Secondary PFS analyses, based on 'on-treatment'-based response assessments, confirmed the significantly superior clinical benefit for patients treated with bevacizumab (analyses shown in Table 8), consistent with the statistically significant benefit observed in the pooled analysis.

Table 8 Key Efficacy Results for The Superiority Analysis (ITT population, Study NO16966)

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

* Overall survival analysis at clinical cut-off 31 January 2007.
** Primary analysis at clinical cut-off 31 January 2006.
[a] Relative to control arm.

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

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

ECOG E3200

This was a phase III randomized, active-controlled, open-label study investigating bevacizumab 10 mg/kg in combination with leucovorin with 5-fluorouracil bolus and then 5-fluorouracil infusional, with intravenous oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule in previously-treated patients (second line) with advanced colorectal

cancer. In the chemotherapy arms, the FOLFOX-4 regimen used the same doses and schedule as shown in Table 7 for Study NO16966.

The primary efficacy parameter of the trial was overall survival, defined as the time from randomization to death from any cause. Eight hundred and twenty-nine patients were randomized (292 FOLFOX-4, 293 bevacizumab + FOLFOX-4 and 244 bevacizumab monotherapy). The addition of bevacizumab to FOLFOX-4 resulted in a statistically significant prolongation of survival. Statistically significant improvements in progression-free survival and objective response rate were also observed (see Table 9).

Table 9 Efficacy Results for Study E3200

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

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

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

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

ML18147

This was a phase III randomized, controlled, open-label trial investigating bevacizumab 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks in combination with fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone in patients with mCRC who have progressed on a first-line bevacizumab-containing regimen.

Patients with histologically confirmed mCRC and disease progression were randomized 1:1 within 3 months after discontinuation of bevacizumab first-line therapy to receive fluoropyrimidine/oxaliplatin- or fluoropyrimidine/irinotecan-based chemotherapy (chemotherapy switched depending on first-line chemotherapy) with or without bevacizumab. Treatment was given until progressive disease or unacceptable toxicity. The primary outcome

measure was overall survival defined as the time from randomization until death from any cause.

A total of 820 patients were randomized. The addition of bevacizumab to fluoropyrimidine-based chemotherapy resulted in a statistically significant prolongation of survival in patients with mCRC who have progressed on a first-line bevacizumab-containing regimen (ITT = 819) (see Table 10).

Table 10 Efficacy Results for Study ML18147

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

[a] 2.5 mg/kg/week.

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

Metastatic Breast Cancer (mBC)

E2100

Study E2100 was an open-label, randomized, active-controlled, multicentre clinical trial evaluating bevacizumab in combination with paclitaxel for locally recurrent or metastatic breast cancer in patients who had not previously received chemotherapy for locally recurrent and metastatic disease. Patients were randomized to paclitaxel alone (90 mg/m^2 intravenous over 1 hour once weekly for three out of four weeks) or in combination with bevacizumab (10 mg/kg intravenous infusion every two weeks). Prior hormonal therapy for the treatment of metastatic disease was allowed. Adjuvant taxane therapy was allowed only if it was completed at least 12 months prior to study entry. Of the 722 patients in the study, the majority of patients had HER2-negative disease (90%), with a small number of patients with unknown (8%) or confirmed HER2-positive status (2%), who had previously been treated with or were considered unsuitable for trastuzumab therapy. Furthermore, 65% of patients

had received adjuvant chemotherapy including 19% prior taxanes and 49% prior anthracyclines. Patients with central nervous system metastasis, including previously treated or resected brain lesions, were excluded.

In Study E2100, patients were treated until disease progression. In situations where early discontinuation of chemotherapy was required, treatment with bevacizumab as a single agent continued until disease progression. The patient characteristics were similar across the study arms. The primary endpoint was progression-free survival (PFS), as assessed by investigators. In addition, an independent review of the primary endpoint was also conducted. The results of this study are presented in Table 11.

Table 11 Study E2100 Efficacy Results: Eligible Patients

Progression-Free Survival				
	Investigator Assessment*		IRF Assessment	
	Paclitaxel (n = 354)	Paclitaxel/ Bevacizumab (n = 368)	Paclitaxel (n = 354)	Paclitaxel/ Bevacizumab (n = 368)
Median PFS (months)	5.8	11.4	5.8	11.3
HR (95% CI)	0.421 (0.343, 0.516)		0.483 (0.385, 0.607)	
p-value	<0.0001		<0.0001	
Response Rates (for patients with measurable disease)				
	Investigator Assessment		IRF Assessment	
	Paclitaxel (n = 273)	Paclitaxel/ Bevacizumab (n = 252)	Paclitaxel (n = 243)	Paclitaxel/ Bevacizumab (n = 229)
% patients with objective response	23.4	48.0	22.2	49.8
p-value	<0.0001		<0.0001	

* Primary analysis.
IRF = Independent review facility.

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

AVF3694g

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

Chemotherapy was chosen at the investigator's discretion prior to randomization in a 2:1 ratio to receive either chemotherapy plus bevacizumab or chemotherapy plus placebo. The choices of chemotherapy included capecitabine, taxane (protein-bound paclitaxel, docetaxel), and anthracycline-based agents (doxorubicin/cyclophosphamide,

epirubicin/cyclophosphamide, 5-fluorouracil/doxorubicin/cyclophosphamide, 5-fluorouracil/epirubicin/cyclophosphamide) given every three weeks (q3w). Bevacizumab or placebo was administered at a dose of 15 mg/kg q3w.

This study included a blinded treatment phase, an optional open-label post-progression phase, and a survival follow-up phase. During the blinded treatment phase, patients received chemotherapy and study drug (bevacizumab or placebo) every 3 weeks until disease progression, treatment-limiting toxicity, or death. On documented disease progression, patients who entered the optional open-label phase could receive open-label bevacizumab together with a wide-range of second line therapies.

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

The results of this study from the final protocol defined analyses for progression-free survival and response rates for the independently powered capecitabine cohort of Study AVF3694g are presented in Table 12. Results from an exploratory overall survival analysis which include an additional 7 months of follow-up (approximately 46% of patients had died) are also presented. The percentage of patients who received bevacizumab in the open-label phase was 62.1% in the capecitabine + placebo arm and 49.9% in the capecitabine + bevacizumab arm.

Table 12 Efficacy results for study AVF3694g – Capecitabine[a] and Bevacizumab/Placebo (Cap + Bevacizumab/Pl)

Progression-Free Survival[b]				
	Investigator Assessment		IRC Assessment	
	Cap + Pl (n = 206)	Cap + Bevacizumab (n = 409)	Cap + Pl (n = 206)	Cap + Bevacizumab (n = 409)
Median PFS (months)	5.7	8.6	6.2	9.8
Hazard ratio versus placebo arm (95% CI)	0.69 (0.56, 0.84)		0.68 (0.54, 0.86)	
p-value	0.0002		0.0011	
Response Rate (for patients with measurable disease)[b]				
	Cap + Pl (n = 161)		Cap + Bevacizumab (n = 325)	
% patients with objective response	23.6		35.4	
p-value	0.0097			
Overall Survival[b]				
HR (95% CI)	0.88 (0.69, 1.13)			
p-value (exploratory)	0.33			

[a] 1000 mg/m^2 oral twice daily for 14 days administered every 3 weeks.

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

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

Non-Small Cell Lung Cancer (NSCLC)

First-line Treatment of Non-squamous NSCLC in Combination with Platinum-based Chemotherapy

The safety and efficacy of bevacizumab, in addition to platinum-based chemotherapy, in the first-line treatment of patients with non-squamous non-small cell lung cancer (NSCLC), was investigated in studies E4599 and BO17704. An overall survival benefit has been demonstrated in study E4599 with a 15 mg/kg q3w dose of bevacizumab. Study BO17704 has demonstrated that both 7.5 mg/kg q3w and 15 mg/kg q3w bevacizumab doses increase progression-free survival and response rate. Due to the short duration of follow-up in study BO17704 no conclusions can be drawn regarding a benefit in overall survival.

E4599

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

Patients were randomized to platinum-based chemotherapy (paclitaxel 200 mg/m^2 and carboplatin AUC = 6.0, both by intravenous infusion) (PC) on Day 1 of every 3-week cycle for up to 6 cycles or PC in combination with bevacizumab at a dose of 15 mg/kg intravenous infusion Day 1 of every 3-week cycle. After completion of six cycles of carboplatin-paclitaxel chemotherapy or upon premature discontinuation of chemotherapy, patients on the bevacizumab + carboplatin–paclitaxel arm continued to receive bevacizumab as a single agent every 3 weeks until disease progression. 878 patients were randomized to the two arms.

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

The primary endpoint was duration of survival. Results are presented in Table 13.

Table 13 Efficacy results for study E4599

	Arm 1 Carboplatin/Paclitaxel	**Arm 2 Carboplatin/Paclitaxel + Bevacizumab 15 mg/kg q3w**
Number of patients	444	434
Overall Survival		
Median (months)	10.3	12.3
Hazard ratio	0.80 (p = 0.003) 95% CI (0.69, 0.93)	

Progression-Free Survival		
Median (months)	4.8	6.4
Hazard ratio	0.65 (p <0.0001) 95% CI (0.56, 0.76)	
Overall Response Rate		
Rate (percent)	12.9	29.0 (p <0.0001)

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

YO25404 (BEYOND)

Study YO25404 was a randomized, double-blind, placebo-controlled, multicenter phase III study of bevacizumab used in addition to carboplatin and paclitaxel (CP) chemotherapy in Chinese patients with unresectable, advanced, metastatic or recurrent non-squamous NSCLC who had not received prior chemotherapy for advanced disease. The primary endpoint was progression-free survival, secondary endpoints for the study included overall survival and objective response.

Patients were randomized to CP (carboplatin AUC = 6.0 and paclitaxel 175 mg/m^2, both by intravenous infusion) on Day 1 of every 3-week cycle for up to 6 cycles or CP in combination with bevacizumab at a dose of 15 mg/kg intravenous infusion on Day 1 of every 3-week cycle. After completion of six cycles of CP chemotherapy or upon premature discontinuation of chemotherapy, patients were to continue to receive bevacizumab or placebo as a single agent every 3 weeks until disease progression or unacceptable toxicity.

Study results show that 78% (107/138) of patients in the bevacizumab-containing treatment arm went on to receive single agent bevacizumab at cycle 7, and 57% (78/138) of patients in the placebo-containing arm went on to receive single agent placebo at cycle 7. The efficacy results are presented in Table 14.

Table 14 Efficacy Results for Study YO25404

	Arm 1 **Carboplatin/Paclitaxel + placebo**	**Arm 2** **Carboplatin/Paclitaxel + Bevacizumab** **15 mg/kg q 3 weeks**
Number of Patients	138	138
Progression-Free Survival		
Median (months)	6.5	9.2
Hazard ratio	0.4 (p <0.0001) 95% CI (0.29, 0.54)	
Overall Response Rate*		
Rate (percent)	26.3	54.4
p-value	<0.0001	
Overall Survival		
Median (months)	17.7	24.3
Hazard ratio	0.68 (p = 0.0154) 95% CI (0.50, 0.93)	
* Only patients with measurable disease at baseline were analysed.		

BO17704

Study BO17704 was a randomized, double-blind phase III study of bevacizumab in addition to cisplatin and gemcitabine versus placebo, cisplatin and gemcitabine in patients with locally advanced (stage IIIB with supraclavicular lymph node metastases or with malignant pleural or pericardial effusion), metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy. The primary endpoint was progression-free survival (PFS); secondary endpoints for the study included the duration of overall survival.

Patients were randomized to platinum-based chemotherapy, cisplatin 80 mg/m^2 intravenous infusion on Day 1 and gemcitabine 1250 mg/m^2 intravenous infusion on Days 1 and 8 of every 3-week cycle for up to 6 cycles (CG) with placebo or CG with bevacizumab at a dose of 7.5 or 15 mg/kg intravenous infusion day 1 of every 3-week cycle. In the bevacizumab-containing arms, patients could receive bevacizumab as a single-agent every 3 weeks until disease progression or unacceptable toxicity. Study results show that 94% (277/296) of eligible patients went on to receive single agent bevacizumab at cycle 7. A high proportion of patients (approximately 62%) went on to receive a variety of non-protocol specified anti-cancer therapies, which may have impacted the analysis of overall survival.

The efficacy results are presented in Table 15.

Table 15 Efficacy Results for Study BO17704

	Cisplatin/ Gemcitabine + Placebo	**Cisplatin/ Gemcitabine + Bevacizumab 7.5 mg/kg q3w**	**Cisplatin/ Gemcitabine + Bevacizumab 15 mg/kg q 3 weeks**
Number of Patients	347	345	351
Progression-Free Survival			
Median (months)	6.1	6.7 (p = 0.0026)	6.5 (p = 0.0301)
Hazard ratio (95% CI)		0.75 (0.62, 0.91)	0.82 (0.68, 0.98)
Best overall response rate[a]	20.1%	34.1% (p <0.0001)	30.4% (p = 0.0023)
Overall Survival			
Median (months)	13.1	13.6 (p = 0.4203)	13.4 (p = 0.7613)
Hazard ratio (95% CI)		0.93 (0.78, 1.11)	1.03 (0.86, 1.23)

[a] Patients with measurable disease at baseline.

First-line Treatment of Non-squamous NSCLC with EGFR Activating Mutations in Combination with Erlotinib

JO25567

Study JO25567 was a randomized, open-label, multicenter phase II study conducted in Japan to evaluate the efficacy and safety of bevacizumab used in addition to erlotinib in patients with non-squamous NSCLC with EGFR activating mutations who had not received prior systemic therapy for stage IIIB/IV or recurrent disease.

The primary endpoint was progression-free survival (PFS) based on independent review assessment. Secondary endpoints included overall survival, response rate, disease control rate, duration of response, safety and Health Related Quality of Life based on the FACT-L (Functional Assessment of Cancer Therapy for Patients with Lung Cancer) questionnaire.

EGFR mutation status was determined for each patient prior to patient screening and 154 patients were randomized to receive either erlotinib + bevacizumab (erlotinib 150 mg oral daily + bevacizumab [15 mg/kg intravenous every 3 weeks]) or erlotinib monotherapy (150 mg oral daily) until disease progression (PD) or unacceptable toxicity. In the absence of PD, discontinuation of one component of study treatment in the erlotinib + bevacizumab arm did not lead to discontinuation of the other component of study treatment as specified in the study protocol.

The efficacy results of the study are presented in table 16.

Table 16 Efficacy Results for Study JO25567

	Erlotinib N = 77[#]	**Erlotinib + Bevacizumab N = 75[#]**
Progression-Free Survival^		
Median (months)	9.7	16.0
HR (95% CI)	0.54 (0.36, 0.79)	
p-value	0.0015	
Overall Response Rate		
Rate	63.6%	69.3%
p-value	0.4951	
Duration of Response		
Median (months)	9.3	13.3
HR (95% CI)	0.68 (0.43, 1.10)	
p-value	0.118	
Disease Control Rate		
Rate	88.3%	98.7%
p-value	0.0177	
Overall Survival*		
Median (months)	NR	NR
HR (95% CI)	1.04 (0.61, 1.77)	
p-value	0.8926	

A total of 154 patients were randomized. However two of the randomized patients discontinued the study before receiving any study treatment.
^ Blinded independent review (protocol-defined primary analysis).
* Exploratory analysis: OS updated analysis at clinical cut-off on Nov 2014, approx. 35% of patients had died and OS is therefore considered immature.
CI = confidence interval; HR = hazard ratio from unstratified Cox regression analysis; NR = not reached.

In the open-label study JO25567, Health Related Quality of life (HRQoL) was assessed by the FACT-L total and trial outcome index (TOI) scores and lung cancer symptoms, as assessed by the FACT-L lung cancer symptom subscale (LCS). During the progression-free time, mean baseline FACT-L scores were maintained in both treatment arms. There were no clinically meaningful differences in the FACT-L HRQoL observed between the two treatment arms. Of note, patients in the erlotinib + bevacizumab arm were treated for a longer

duration and received intravenous administration of bevacizumab as opposed to oral erlotinib monotherapy in the control arm.

Advanced and/or Metastatic Renal Cell Cancer (mRCC)

Bevacizumab in Combination with Interferon Alfa-2a for the First-line Treatment of Advanced and/or Metastatic Renal Cell Cancer (BO17705)

BO17705 was a multicenter randomized, double-blind phase III trial conducted to evaluate the efficacy and safety of bevacizumab in combination with interferon (IFN) alfa-2a versus IFN alfa-2a alone as first-line treatment in mRCC. The 649 randomized patients (641 treated) had clear cell mRCC, Karnofsky Performance Status (KPS) of ≥70%, no CNS metastases and adequate organ function. IFN alfa-2a (three times a week at a recommended dose of 9 MIU) plus bevacizumab (10 mg/kg every two weeks [q2w]) or placebo was given until disease progression. Patients were stratified according to country and Motzer score and the treatment arms were shown to be well balanced for the prognostic factors.

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

The efficacy results are presented in Table 17.

Table 17 Efficacy Results for Study BO17705

	BO17705	
	IFN + Placebo	IFN + Bevacizumab
Number of Patients	322	327
Progression-Free Survival		
Median (months)	5.4	10.2
Hazard ratio (95% CI)	0.63 (0.52, 0.75) (p-value <0.0001)	
Objective Response Rate (%) (in patients with measurable disease)		
n	289	306
Response rate	12.8%	31.4%
	p-value <0.0001	
Overall Survival		
Median (months)	21.3	23.3
Hazard ratio (95% CI)	0.91 (0.76, 1.10) (p-value = 0.3360)	

An exploratory multivariate Cox regression model using backward selection indicated that the following baseline prognostic factors were strongly associated with survival independent of treatment: gender, white blood cell count, platelets, body weight loss in the 6 months prior to study entry, number of metastatic sites, sum of longest diameter of target lesions, Motzer

score. Adjustment for these baseline factors resulted in a treatment hazard ratio of 0.78 (95% CI [0.63, 0.96], p = 0.0219), indicating a 22% reduction in the risk of death for patients in the bevacizumab + IFN alfa-2a arm compared to IFN alfa-2a arm.

Ninety-seven (97) patients in the IFN alfa-2a arm and 131 patients in the bevacizumab arm reduced the dose of IFN alfa-2a from 9 MIU to either 6 or 3 MIU, three times a week as pre-specified in the protocol. Dose reduction of IFN alfa-2a did not appear to affect the efficacy of the combination of bevacizumab and IFN alfa-2a, based on PFS event free rates over time, as shown by a subgroup analysis. The 131 patients in the bevacizumab + IFN alfa-2a arm who reduced and maintained the IFN alfa-2a dose at 6 or 3 MIU during the study, exhibited at 6, 12 and 18 months, PFS event free rates of 73, 52 and 21% respectively, as compared to 61, 43 and 17% in the total population of patients receiving bevacizumab + IFN alfa-2a.

AVF2938

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

Malignant Glioma (WHO Grade IV) - Glioblastoma

AVF3708g

The efficacy and safety of bevacizumab as treatment for patients with glioblastoma was studied in an open-label, multicentre, randomized, non-comparative study (study AVF3708g). Patients in first or second relapse after prior radiotherapy (completed at least 8 weeks prior to receiving bevacizumab) and temozolomide, were randomized (1:1) to receive bevacizumab (10 mg/kg intravenous infusion every 2 weeks) or bevacizumab plus irinotecan (125 mg/m^2 intravenous or 340 mg/m^2 intravenous for patients on enzyme-inducing anti-epileptic drugs every 2 weeks) until disease progression or until unacceptable toxicity. The primary endpoints of the study were 6-month progression-free survival (PFS) and objective response rate (ORR) as assessed by an independent review facility (IRF). Other outcome measures were duration of PFS, duration of response and overall survival. Results of the study are summarized in Table 18.

Table 18 Efficacy Results from Study AVF3708g

	Bevacizumab	**Bevacizumab + Irinotecan**
Number of Patients	85	82
Primary Endpoints		
6-month Progression-Free Survival (97.5% CI)	42.6% (29.6%, 55.5%)	50.3% (36.8%, 63.9%)
Objective Response Rate (97.5% CI)	28.2% (18.5%, 40.3%)	37.8% (26.5%, 50.8%)

Secondary Endpoints		
Progression-Free Survival (months)		
Median (95% CI)	4.2 (2.9, 5.8)	5.6 (4.4, 6.2)
Duration of Objective Response (months)		
Median (95% CI)	5.6 (3.0, 5.8)	4.3 (4.2, *)
Overall Survival (months)		
Median (95% CI)	9.3 (8.2, *)	8.8 (7.8, *)
ORR was determined using modified MacDonald criteria. * Upper limit of the confidence interval could not be obtained.		

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

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

Front-line Ovarian Cancer

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

GOG-0218

The GOG-0218 study was a phase III multicenter, randomized, double-blind, placebo-controlled, three arm study evaluating the effect of adding bevacizumab to an approved chemotherapy regimen (carboplatin and paclitaxel) in patients with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer.

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

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

- CPP arm: Five cycles of placebo (started cycle 2) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles followed by placebo alone, for a total of up to 15 months of therapy.

- CPB15 arm: Five cycles of bevacizumab (15 mg/kg q3w started cycle 2) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles followed by placebo alone, for a total of up to 15 months of therapy.

- CPB15+ arm: Five cycles of bevacizumab (15 mg/kg q3w started cycle 2) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles followed by continued use of bevacizumab (15 mg/kg q3w) as single agent for a total of up to 15 months of therapy.

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

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

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (carboplatin and paclitaxel) alone in the front-line setting, patients who received bevacizumab at a dose of 15 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab alone (CPB15+), had a clinically meaningful and statistically significant improvement in PFS.

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

The results of this study are summarized in Table 19.

Table 19 Efficacy Results from Study GOG-0218

Progression-Free Survival[1]			
	CPP (n = 625)	CPB15 (n = 625)	CPB15+ (n = 623)
Median PFS (months)	10.6	11.6	14.7
Hazard ratio (95% CI)[2]		0.89 (0.78, 1.02)	0.70 (0.61, 0.81)
p-value[3,4]		0.0437	<0.0001
Objective Response Rate[5]			
	CPP (n = 396)	CPB15 (n = 393)	CPB15+ (n = 403)
% patients with objective response	63.4	66.2	66.0
p-value		0.2341	0.2041
Overall Survival[6]			
	CPP (n = 625)	CPB15 (n = 625)	CPB15+ (n = 623)

Median OS (months)	40.6	38.8	43.8
Hazard ratio (95% CI)[2]		1.07 (0.91, 1.25)	0.88 (0.75, 1.04)
p-value[3]		0.2197	0.0641

[1] Investigator-assessed GOG protocol-specified PFS analysis (neither censored for CA-125 progressions nor censored for NPT prior to disease progression) with data cut-off date of 25 February, 2010.
[2] Relative to the control arm; stratified hazard ratio.
[3] One-sided log-rank p-value
[4] Subject to a p-value boundary of 0.0116.
[5] Patients with measurable disease at baseline.
[6] Overall survival analysis performed when 46.9% of the patients had died.

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

- The protocol specified analysis of investigator-assessed PFS (without censoring for CA-125 progression or non-protocol therapy [NPT]) shows a stratified hazard ratio of 0.71 (95% CI: 0.61-0.83, 1-sided log rank p-value <0.0001) when CPB15+ is compared with CPP, with a median PFS of 10.4 months in the CPP arm and 14.1 months in the CPB15+ arm.

- The primary analysis of investigator-assessed PFS (censoring for CA-125 progressions and NPT) shows a stratified hazard ratio of 0.62 (95% CI: 0.52-0.75, 1-sided log-rank p-value <0.0001) when CPB15+ is compared with CPP, with a median PFS of 12.0 months in the CPP arm and 18.2 months in the CPB15+ arm.

- The analysis of PFS as determined by the independent review committee (censoring for NPT) shows a stratified hazard ratio of 0.62 (95% CI: 0.50-0.77, 1-sided log rank p-value <0.0001) when CPB15+ is compared with CPP, with a median PFS of 13.1 in the CPP arm and 19.1 months in the CPB15+ arm.

PFS subgroup analyses by disease stage and debulking status are summarized in Table 20. These results demonstrate robustness of the analysis of PFS as shown in Table 19.

Table 20 PFS[1] Results by Disease Stage and Debulking Status from Study GOG-0218

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

[1] Investigator-assessed GOG protocol-specified PFS analysis (neither censored for CA-125 progressions nor censored for NPT prior to disease progression) with data cut-off date of 25 February 2010.
[2] With gross residual disease.
[3] 3.7% of the overall randomized patient population had stage IIIB disease.
[4] Relative to the control arm.

BO17707 (ICON7)

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

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

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

- CP arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles of 3 weeks duration.

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

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

The primary endpoint was PFS as assessed by the investigator using response evaluation criteria in solid tumours (RECIST) criteria.

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

The results of this study are summarized in Table 21.

Table 21 Efficacy Results from Study BO17707 (ICON7)

Progression-Free Survival		
	CP (n = 764)	CPB7.5+ (n = 764)
Median PFS (months)[2]	16.9	19.3
Hazard ratio (95% CI)[2]	0.86 (0.75, 0.98) (p-value = 0.0185)	
Objective Response Rate[1]		
	CP (n = 277)	CPB7.5+ (n = 272)
Response rate	54.9%	64.7%
	(p-value = 0.0188)	
Overall Survival[3]		
	CP (n = 764)	CPB7.5+ (n = 764)
Median (months)	Not reached	Not reached
Hazard ratio (95% CI)	0.85 (0.70, 1.04) (p-value = 0.1167)	

[1] In patients with measurable disease at baseline.
[2] Investigator-assessed PFS analysis with data cut-off date of 30 November 2010.
[3] Exploratory approximately 25% of patients died.

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

PFS subgroup analyses by disease stage and debulking status are summarized in Table 22. These results demonstrate robustness of the primary analysis of PFS as shown in Table 21.

Table 22 PFS[1] Results by Disease Stage and Debulking Status from Study BO17707 (ICON7)

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

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

[2] With or without gross residual disease.
[3] 5.8% of the overall randomized patient population had stage IIIB disease.
[4] Relative to the control arm.

Recurrent Ovarian Cancer

GOG-0213

GOG-0213, a phase III randomized controlled open-label trial, studied the safety and efficacy of bevacizumab in the treatment of patients with platinum-sensitive, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who have not received prior chemotherapy in the recurrent setting. There was no exclusion criterion for prior anti-angiogenic therapy. The study evaluated the effect of adding bevacizumab to carboplatin + paclitaxel and continuing bevacizumab as a single agent until disease progression or unacceptable toxicity compared to carboplatin + paclitaxel alone.

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

- CP arm: Carboplatin (AUC 5) and paclitaxel (175 mg/m^2 intravenous) every 3 weeks for 6 and up to 8 cycles.

- CPB arm: Carboplatin (AUC 5) and paclitaxel (175 mg/m^2 intravenous) and concurrent bevacizumab (15 mg/kg) every 3 weeks for 6 and up to 8 cycles, followed by bevacizumab (15 mg/kg every 3 weeks) alone until disease progression or unacceptable toxicity.

Most patients in both the CP arm (80.4%) and the CPB arm (78.9%) were White. The median age was 60.0 years in the CP arm and 59.0 years in the CPB arm. The majority of patients (CP: 64.6%; CPB: 68.8%) were in the age category <65 years. At baseline, most patients in both treatment arms had a GOG PS of 0 (CP: 82.4%; CPB: 80.7%) or 1 (CP: 16.7%; CPB: 18.1%). A GOG PS of 2 at baseline was reported in 0.9% of patients in the CP arm and in 1.2% of patients in the CPB arm.

The primary efficacy endpoint was overall survival (OS). The main secondary efficacy endpoint was progression-free survival (PFS). Results are presented in Table 23.

Table 23 Efficacy Results[1,2] from Study GOG-0213

Primary Endpoint		
Overall Survival	CP (n = 336)	CPB (n = 337)
Median OS (months)	37.3	42.6
Hazard ratio (95% CI) (eCRF)[a]	0.823 (0.680, 0.996)	
p-value	0.0447	
Hazard ratio (95% CI) (registration form)[b]	0.838 (0.693, 1.014)	
p-value	0.0683	
Secondary Endpoint		
Progression-Free Survival	CP	CPB

	(n = 336)	(n = 337)
Median PFS (months)	10.2	13.8
Hazard ratio (95% CI)	0.613 (0.521, 0.721)	
p-value	<0.0001	

[1] Final analysis.

[2] Tumour assessments and response evaluations were determined by the investigators using the GOG RECIST criteria (Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228Y247).

[a] Hazard ratio was estimated from Cox proportional hazards models stratified by the duration of platinum-free interval prior to enrolling onto this study per eCRF (electronic case report form) and secondary surgical debulking status Yes/No (Yes = randomized to undergo cytoreduction or randomized to not undergo cytoreduction; No = not a candidate or did not consent to cytoreduction).

[b] Stratified by the duration of treatment-free interval prior to enrolling onto this study per the registration form, and secondary surgical debulking status Yes/No.

The trial met its primary objective of OS improvement. Treatment with bevacizumab at 15 mg/kg every 3 weeks in combination with chemotherapy (carboplatin and paclitaxel) for 6 and up to 8 cycles, followed by bevacizumab until disease progression or unacceptable toxicity resulted, when data were derived from eCRF, in a clinically meaningful and statistically significant improvement in OS compared to treatment with carboplatin and paclitaxel alone.

AVF4095g

The safety and efficacy of bevacizumab in the treatment of patients with platinum-sensitive, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who have not yet received prior chemotherapy in the recurrent setting or prior bevacizumab treatment, was studied in a phase III randomized, double-blind, placebo-controlled trial (AVF4095g). The study compared the effect of adding bevacizumab to carboplatin and gemcitabine chemotherapy and continuing bevacizumab as a single agent to progression, to carboplatin and gemcitabine alone.

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

- Carboplatin (AUC 4, 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 cycles followed by placebo alone until disease progression or unacceptable toxicity.

- Carboplatin (AUC 4, Day 1) and gemcitabine (1000 mg/m^2 on Days 1 and 8) and concurrent bevacizumab (15 mg/kg Day 1) every 3 weeks for 6 and up to 10 cycles followed by bevacizumab (15 mg/kg every 3 weeks) alone until disease progression or unacceptable toxicity.

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

The results of this study are summarized in Table 24.

Table 24 Efficacy Results from Study AVF4095g

Progression-Free Survival				
	Investigator Assessment*		IRC Assessment	
	Placebo + C/G (n=242)	Bevacizumab + C/G (n=242)	Placebo + C/G (n=242)	Bevacizumab + C/G (n=242)
Median PFS (months)	8.4	12.4	8.6	12.3
Hazard ratio (95% CI)	0.484 (0.388, 0.605)		0.451 (0.351, 0.580)	
p-value	<0.0001		<0.0001	
Objective Response Rate				
	Investigator Assessment		IRC Assessment	
	Placebo + C/G (n = 242)	Bevacizumab + C/G (n = 242)	Placebo + C/G (n = 242)	Bevacizumab + 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)		Bevacizumab + C/G (n = 242)	
Median OS (months)	32.9		33.6	
Hazard Ratio (95% CI)	0.952 (0.771, 1.176)			
p-value	0.6479			

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

PFS subgroup analyses depending on recurrence since last platinum therapy are summarized in Table 25.

Table 25 Progression-free Survival by Time from Last Platinum Therapy to Recurrence

	Investigator Assessment	
Time from last platinum therapy to recurrence	Placebo + C/G (n = 242)	Bevacizumab + C/G (n = 242)
6-12 months (n = 202)		
Median	8.0	11.9
Hazard ratio (95% CI)	0.41 (0.29, 0.58)	
>12 months (n = 282)		
Median	9.7	12.4
Hazard ratio (95% CI)	0.55 (0.41, 0.73)	

MO22224 (AURELIA)

Study MO22224 evaluated the efficacy and safety of bevacizumab in combination with chemotherapy for platinum-resistant recurrent ovarian cancer. This study was designed as an

open-label, randomized, two-arm phase III evaluation of bevacizumab plus chemotherapy (CT + BV) versus chemotherapy alone (CT).

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

- CT Arm (chemotherapy alone):
  - Paclitaxel 80 mg/m^2 as 1-hour intravenous infusion on Days 1, 8, 15 and 22 every 4 weeks.
  - Topotecan 4 mg/m^2 as a 30-minute intravenous 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 1 mg/min intravenous infusion on Day 1 only every 4 weeks. After cycle 1, the drug could be delivered as a 1-hour infusion.
- CT + BV Arm (chemotherapy plus bevacizumab):
  - The chosen chemotherapy was combined with bevacizumab 10 mg/kg intravenous 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 on a every 3 weeks schedule.

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

The primary endpoint was progression-free survival, with secondary endpoints including objective response rate and overall survival. Results are presented in Table 26.

Table 26 Efficacy Results from Study MO22224 (AURELIA)

Primary Endpoint		
Progression-Free Survival		
	CT (n=182)	CT + BV (n=179)
Median (months)	3.4	6.7
Hazard ratio (95% CI)	0.379 (0.296, 0.485)	
p-value	<0.0001	
Secondary Endpoints		
Objective Response Rate*		
	CT (n=144)	CT + BV (n=142)
% 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 OS (months)	13.3	16.6
Hazard ratio (95% CI)	0.870 (0.678, 1.116)	
p-value	0.2711	

All analyses presented in this table are stratified analyses.
* Randomized patients with measurable disease at baseline.
** At the time of the final OS analysis (25 January 2013), 266 patients (73.7%) had died across the two treatment arms.

The exploratory PFS and OS analyses by chemotherapy cohort (paclitaxel, topotecan and PLD) are summarized in Table 27.

Table 27 Exploratory PFS and OS Analyses by Chemotherapy Cohort

	CT	**CT + BV**
Paclitaxel	n = 115	
Median PFS (months)	3.9	9.2
Hazard ratio (95% CI)	0.47 (0.31, 0.72)	
Median OS (months)	13.2	22.4
Hazard ratio (95% CI)	0.64 (0.41, 0.99)	
Topotecan	n = 120	
Median PFS (months)	2.1	6.2
Hazard ratio (95% CI)	0.28 (0.18, 0.44)	
Median OS (months)	13.3	13.8
Hazard ratio (95% CI)	1.07 (0.70, 1.63)	
PLD	n = 126	
Median PFS (months)	3.5	5.1
Hazard ratio (95% CI)	0.53 (0.36, 0.77)	
Median OS (months)	14.1	13.7
Hazard ratio (95% CI)	0.91 (0.61, 1.35)	

Cervical Cancer

GOG-0240

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

A total of 452 patients were randomized to receive either:

- Paclitaxel 135 mg/m^2 intravenous over 24 hours on Day 1 and cisplatin 50 mg/m^2 intravenous on Day 2, every 3 weeks (q3w); or paclitaxel 175 mg/m^2 intravenous over 3 hours on Day 1 and cisplatin 50 mg/m^2 intravenous on Day 2 (q3w); or paclitaxel 175 mg/m^2 intravenous over 3 hours on Day 1 and cisplatin 50 mg/m^2 intravenous on Day 1 (q3w).

- Paclitaxel 135 mg/m^2 intravenous over 24 hours on Day 1 and cisplatin 50 mg/m^2 intravenous on Day 2 plus bevacizumab 15 mg/kg intravenous on Day 2 (q3w); or paclitaxel 175 mg/m^2 intravenous over 3 hours on Day 1 and cisplatin 50 mg/m^2 intravenous on Day 2 plus bevacizumab 15 mg/kg intravenous on Day 2 (q3w); or paclitaxel 175 mg/m^2 intravenous over 3 hours on Day 1 and cisplatin 50 mg/m^2 intravenous on Day 1 and bevacizumab 15 mg/kg intravenous on Day 1 (q3w).

- Paclitaxel 175 mg/m^2 over 3 hours on Day 1 and topotecan 0.75 mg/m^2 over 30 minutes on Days 1-3 (q3w).

- Paclitaxel 175 mg/m^2 over 3 hours on Day 1 and topotecan 0.75 mg/m^2 over 30 minutes on Days 1-3 plus bevacizumab 15 mg/kg intravenous on Day 1 (q3w).

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

The primary efficacy endpoint was overall survival (OS). Secondary efficacy endpoints included progression-free survival (PFS) and objective response rate (ORR). Results are presented in Table 28.

Table 28 Overall Efficacy by Bevacizumab Treatment (ITT Population) from Study GOG-0240

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

[1] Kaplan-Meier estimates.
[2] Patients with best overall response of confirmed CR or PR.
[3] 95% CI for one sample binomial using Pearson-Clopper method.
[4] Approximate 95% CI for difference of two rates using Hauck-Anderson method.
[5] Log-rank test (stratified).

Immunogenicity

No robust assessment of anti-drug antibodies has been done in bevacizumab clinical trials.

ZIRABEV Clinical Study

The biosimilar clinical development program for ZIRABEV included a randomized, double-blind trial in patients with advanced (unresectable, locally advanced, recurrent or metastatic) non-squamous NSCLC.

B7391003

Study B7391003 was a multinational, double-blind, randomized, parallel-group phase III clinical trial comparing the efficacy and safety of ZIRABEV plus paclitaxel and carboplatin (n=358) versus Avastin-EU plus paclitaxel and carboplatin (n = 361) in patients with newly diagnosed stage IIIB or IV NSCLC or recurrent NSCLC in the first-line treatment setting.

Patients were randomized in a ratio of 1:1 to receive at least 4 but no more than 6 cycles (21-day cycle) of ZIRABEV plus paclitaxel and carboplatin or Avastin-EU plus paclitaxel and carboplatin, followed by the assigned blinded bevacizumab monotherapy until disease progression or unacceptable toxicity.

The primary objective of this trial was to compare the objective response rate (ORR) by Week 19 confirmed by Week 25 in accordance with RECIST 1.1, following treatment with ZIRABEV in combination with paclitaxel and carboplatin to Avastin-EU plus paclitaxel and carboplatin. Secondary endpoints included additional efficacy, safety, pharmacokinetics, and immunogenicity.

Similarity between ZIRABEV and Avastin-EU was statistically demonstrated for the primary efficacy endpoint, ORR, based on pre-specified equivalence criteria. The results of other secondary endpoints were comparable between the 2 treatment groups.

There is no clinically meaningful difference in efficacy, safety, or immunogenicity between ZIRABEV and Avastin-EU in newly diagnosed stage IIIB or IV NSCLC or recurrent non-squamous NSCLC patients.

5.2 Pharmacokinetic properties

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

Absorption

Not applicable.

Distribution

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

Metabolism

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

Elimination

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

In a population pharmacokinetic meta-analysis there was no significant difference in the pharmacokinetics of bevacizumab in relation to race when body weight is taken into account, or in relation to age (no correlation between bevacizumab clearance and patient age [the median age was 59 year with 5th and 95th percentiles of 37 and 76 year]).

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

Pharmacokinetics in Special Populations

The population pharmacokinetics of bevacizumab were analysed to evaluate the effects of demographic characteristics. In adults, the results showed no significant difference in the pharmacokinetics of bevacizumab in relation to age.

Paediatric Population

The pharmacokinetics of bevacizumab were evaluated in 152 patients (7 months to 21 years; 5.9 to 125 kg) across 4 clinical studies using a population pharmacokinetic model. The pharmacokinetic results show that the clearance and the volume of distribution of bevacizumab were comparable between paediatric and adult patients when normalised by

body weight. Age was not associated with the pharmacokinetics of bevacizumab when body weight was taken into account.

Renal Impairment

No studies have been conducted to investigate the pharmacokinetic of bevacizumab in renally impaired patients since the kidneys are not a major organ for bevacizumab metabolism or excretion.

Hepatic Impairment

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

ZIRABEV Comparative Pharmacokinetic Study

Pharmacokinetic comparability of ZIRABEV and Avastin was evaluated in Study B7391001 in 102 healthy adult subjects in a three-arm, double-blind, randomized, (1:1:1) parallel group, single-dose study comparing ZIRABEV, Avastin-EU and Avastin-US following intravenous administration of 5 mg/kg to healthy male subjects.

The 3 study drugs exhibited a similar serum concentrations-versus-time profile, which was characterised by a multi-phasic decline in serum drug concentrations after attaining C_{max} at the end of infusion. The 90% CIs for test-to-reference ratios of C_{max}, AUC_t, and $AUC_{0-\infty}$ were contained within the pre-specified acceptance boundaries of 80% to 125% for the comparisons of ZIRABEV to Avastin-EU and ZIRABEV to Avastin-US. The test-to-reference ratios (90% CIs of the ratios) of adjusted geometric means of C_{max}, AUC_t, and $AUC_{0-\infty}$ were 104.42% (98.36%, 110.84%), 99.62% (93.69%, 105.93%), and 98.58% (92.16%, 105.44%), respectively, for the ZIRABEV to Avastin-EU comparison; and 109.79% (103.38%, 116.60%), 104.32% (98.06%, 110.97%), and 103.33% (96.55%, 110.58%), respectively, for the ZIRABEV to Avastin-US comparison. For the comparison of Avastin-EU to Avastin-US, the 90% CIs for test-to-reference ratios of C_{max}, AUC_t, and $AUC_{0-\infty}$ were also within 80.00% to 125.00%. The test-to-reference ratios (90% CIs of the ratios) of adjusted geometric means of C_{max}, AUC_t, and $AUC_{0-\infty}$ were 105.15% (99.05%, 111.62%), 104.71% (98.48%, 111.34%), and 104.82% (98.00%, 112.12%), respectively, for the Avastin-EU to Avastin-US comparison. Overall, the study demonstrates the PK similarity of ZIRABEV to both Avastin-US and Avastin-EU, and of Avastin-EU to Avastin-US.

In the comparative efficacy and safety Study B7391003 in patients with newly diagnosed stage IIIB or IV NSCLC or recurrent NSCLC, mean and median C_{trough} and apparent C_{max} values at selected cycles were comparable between the ZIRABEV and Avastin-EU arms, supporting PK similarity in the PK study B7391001.

5.3 Preclinical safety data

Physeal Development

In studies of up to 26 weeks duration in cynomolgus monkeys, bevacizumab was associated with physeal dysplasia. Physeal dysplasia was characterised primarily by thickened growth

plate cartilage, subchondral bony plate formation and inhibition of vascular invasion of the growth plate. This effect occurred at doses ≥0.8 times the human therapeutic dose and exposure levels slightly below the expected human clinical exposure, based on average serum concentrations. It should be noted, however, that physeal dysplasia occurred only in actively growing animals with open growth plates.

Wound Healing

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

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

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

Renal Function

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

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

Albumin

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

Hypertension

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

Hemostasis

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

Genotoxicity/Carcinogenicity

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

Reproductive Toxicity

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Succinic acid
Sucrose
Edetate disodium dihydrate (EDTA)
Polysorbate 80
Sodium hydroxide
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6 Special precautions for disposal and other handling.

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

Do not administer or mix with glucose or dextrose solutions.

6.3 Shelf life

Refer to outer carton for expiration date.

6.4 Special precautions for storage

Store intact vial in a refrigerator (2°C to 8°C).

Do not freeze or shake.

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

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C to 30°C in sodium chloride 9 mg/ml (0.9%) solution for injection. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

ZIRABEV is packaged in Type 1 clear glass vials with chlorobutyl stoppers and crimp seals with flip-off caps.

ZIRABEV is available in the following presentations (pack of 1 vial):
- 100 mg/4 ml single-use vial
- 400 mg/16 ml single-use vial

6.6 Special precautions for disposal and other handling

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

The necessary amount of bevacizumab should be withdrawn and diluted to the required administration volume with sodium chloride 9 mg/ml (0.9%) solution for injection. The concentration of the final bevacizumab solution should be kept within the range of 1.4 mg/ml to 16.5 mg/ml. In the majority of the occasions the necessary amount of ZIRABEV can be diluted with 0.9% sodium chloride solution for injection to a total volume of 100 ml.

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

No incompatibilities between ZIRABEV and polyvinyl chloride or polyolefin bags or infusion sets have been observed.

ZIRABEV is for single-use only, as the product contains no preservatives.

Any unused medicinal product or waste material should be disposed in accordance with local requirements.

7. PRODUCT OWNER

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