ARKETIN 00802

Approved date:

ARKETIN (bevacizumab) is biosimilar to AVASTIN ® (bevacizumab)

ARKETIN(Bevacizumab)

Read all of this leaflet carefully and talk to your doctor before you start using this medicine.

[NAME OF THE MEDICINAL PRODUCT]

Trade Name: Arketin

Generic Name: Bevacizumab Injection

[COMPOSITION]

Each ml of concentrate contains 25 mg of bevacizumab*.

Each 4 ml vial contains 100 mg of bevacizumab.

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

Bevacizumab injection contains the following inactive ingredients: trehalose, sodium dihydrogen phosphate, disodium hydrogen phosphate, polysorbate 20 and water preservative-free.

[DESCRIPTION]

Bevacizumab injection is a sterile, clear to slightly opalescent, colorless to pale brown solution. The pH is 6.0~6.4.

[INDICATIONS]

Metastatic Colorectal Cancer

Bevacizumab in combination with fluorouracil-based chemotherapy, is indicated for treatment of metastatic colorectal cancer.

Advanced, Recurrent or Metastatic Non–Small Cell Lung Cancer

Bevacizumab in combination with carboplatin-based chemotherapy, is indicated for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic non–squamous non–small cell lung cancer (NSCLC).

Recurrent Glioblastoma

Bevacizumab is indicated for the treatment of recurrent glioblastoma (GBM) in adults.

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

Bevacizumab, in combination with carboplatin and paclitaxel, followed by Bevacizumab as a single agent, is indicated for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection.

Cervical Cancer

Bevacizumab, in combination with paclitaxel and cisplatin or paclitaxel and topotecan, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.

[STRENGTHS]

100 mg/4 ml (25 mg/ml) in a single-dose vial.

[DOSAGE AND ADMINISTRATION]

Bevacizumab should be prepared by a healthcare professional using aseptic technique and formulated using sterile needles and syringes. Withdraw necessary amount of bevacizumab and dilute to the required dosing volume with 0.9% Sodium Chloride Injection The initial dose should be delivered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

Continue bevacizumab treatment is recommended until disease progression or unacceptable toxicity.

Metastatic Colorectal (mCRC)

The recommended dosage when Bevacizumab is administered in combination chemotherapy is: 5 mg/kg intravenously every 2 weeks or 7.5 mg/kg intravenously every 3 weeks.

Advanced, Recurrent or Metastatic Non–Small Cell Lung Cancer (NSCLC)

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

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

Recurrent Glioblastoma (rGBM)

The recommended dosage is 10 mg/kg intravenously every 2 weeks.

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer (OC)

The recommended dosage is 15 mg/kg intravenously every 3 weeks in combination with carboplatin and paclitaxel for up to 6 cycles, followed by bevacizumab 15 mg/kg every 3 weeks as a single agent for a total of up to 22 cycles or until disease progression, whichever occurs earlier.

Cervical Cancer (CC)

Bevacizumab is administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin or paclitaxel and topotecan. The recommended dose of bevacizumab is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

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

Special Populations

Pediatric and young adult: The safety and effectiveness in children aged less than 18 years old have not been establishe

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

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

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

Special Precautions for Administering, Disposal and Other Handling

Bevacizumab infusions should not be administered or mixed with dextrose nor glucose solutions.

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

Bevacizumab 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 0.9% sodium chloride 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.

Bevacizumab is for single-use only, as the product contains no preservatives. Any unused medicinal product or waste material should be disposed. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration.

Compatibility

No incompatibilities between Bevacizumab and polyvinyl chloride or polyolefine bags or infusion sets have been observed. Concentration-dependent degradation of bevacizumab was observed when diluted with 5% dextrose solution.

Disposal of unused/expired medicines

Avoid the release of drugs in the environment. Do not throw away any medicines via wastewater or household waste. An established collection system should be used for disposal in accordance with local requirements.

Dosage Modifications

Dose reduction is not recommended.

The administration of bevacizumab should be permanently discontinued if:

- Gastrointestinal perforations (gastrointestinal perforations, fistulae, abdominal abscess), visceral fistula (see **[WARNINGS]** and **[PRECAUTIONS]**)
- Wound dehiscence requiring intervention and Wound Healing Complications (see **[PRECAUTIONS]**)
- Serious haemorrhage (For example, intervention treatment is needed) (see **[WARNINGS]** and **[PRECAUTIONS]**)
- Severe arterial thrombosis (see **[PRECAUTIONS]**)
- Life-threatening (grade 4) venous thromboembolic events, including pulmonary embolism (see **[PRECAUTIONS]**)
- Hypertensive crisis or hypertensive encephalopathy (see **[PRECAUTIONS]**)
- Posterior reversible encephalopathy syndrome (PRES) (see **[PRECAUTIONS]**)
- Nephrotic syndrome (see **[PRECAUTIONS]**)

The administration of bevacizumab should be temporarily suspended:

- At least 4 weeks before elective surgery (see **[PRECAUTIONS]**)
- Severe hypertension with poor drug control (see **[PRECAUTIONS]**)
- Moderate to severe proteinuria needs further evaluation (see **[PRECAUTIONS]**)
- Severe infusion reaction (see **[PRECAUTIONS]**)

[ADVERSE REACTIONS]

Clinical Trials Experience

The overall safety profile of bevacizumab is based on data from over 5,500 patients with various malignancies, predominantly treated with bevacizumab in combination with chemotherapy in clinical trials.

The most serious adverse reactions were:

- Gastrointestinal perforation (see **[PRECAUTIONS]**),
- Haemorrhage, including pulmonary haemorrhage/haemoptysis, which is more common in NSCLC (non- small cell lung cancer) patients (see **[PRECAUTIONS]**),
- Arterial thromboembolism (see **[PRECAUTIONS]**)

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

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

According to System Organ Class of MedDRA, Tables 1 list adverse reactions associated with the use of bevacizumab in combination with different chemotherapy regimens in multiple indications. The incidences of adverse reactions (in at least one major clinical trial) comparative noted between clinical trial treatment arms, at least a 2% difference compared to the control arm for NCI-CTCAE Grade 3-5 reactions or at least a 10% difference compared to the control arm for NCI-CTCAE Grade 1-5 reactions. The adverse reactions listed in this section fall into the following frequency categories: 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). Adverse reactions are added to the appropriate frequency category in the tables below according to the highest incidence seen in any indication. Within each frequency category, adverse reactions are presented in the order of decreasing seriousness. Some of the adverse reactions are reactions commonly seen with chemotherapy (for example, palmar-plantar erythrodysaesthesia syndrome with capecitabine, and peripheral sensory neuropathy with paclitaxel or oxaliplatin); 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 and alopecia with paclitaxel.

Table 1: Adverse Reactions (Very Common and Common)

System organ class (SOC)	NCI-CTC Grades 3-5 (The difference was greater than 2% compared to the control arm in at least one clinical trial)		All Grades (The difference was greater than 10% compared to the control arm in at least one clinical trial)
	Very Common	Common	Very Common
Infectious and Infectious		Sepsis, Abscess, Cellulitis Infection	
Blood and lymphatic system disorders	Febrile neutropenia, Leukopenia, Neutropenia, Thrombo-cytopenia	Anaemia, Lymphopenia	
Metabolism and nutrition disorders		Dehydration, Hyponatremia	Anorexia, Hypomagnesemia, Hyponatremia
Nervous system disorders	Peripheral sensory neuropathy	Cerebrovascular accident Syncope, Somnolence, Headache	Taste disorder, Headache, Dysarthria
Eye disorders			Eye disorder, Increased tears
Cardiac disorders		Congestive heart failure, Supraventricular tachycardia	
Vascular disorders	Hypertension	Thromboembolism (arterial)b Deep vein Thrombosis, Haemorrhage	Hypertension
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism, Dyspnea, Hypoxia, Epistaxis	Dyspnea, Epistaxis, Rhinitis, Cough
Gastrointestinal disorders	Diarrhea, Nausea, Vomiting, Abdominal pain	Intestinal perforation, Ileus, Intestinal obstruction, Recto-vaginal fistula* Gastrointestinal Disorder, Stomatitis, Anal Pain	Constipation, Stomatitis, Rectal bleeding, Diarrhea
Endocrine system			Ovarian Failure **
Skin and subcutaneous tissue disorders		Palmar-plantar erythro-dysaesthesia syndrome	Exfoliative dermatitis, Dry skin disease, Skin discoloration
Musculoskeletal and connective tissue disorders		Muscular weakness, Myalgia, Arthralgia, Back pain	Arthritis
Renal and urinary disorders		Proteinuria, Urinary tract infection	Proteinuria
General disorders and administration site conditions	Asthenia, Fatigue	Pain, Sleepy, Mucosal inflammation	Fever, Weakness, Pain, Mucosal inflammation
Reproductive system and breast disorders		Pelvic Pain	
Investigations			Weight decreased

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

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

Description of Serious Adverse Reactions

The following adverse reactions reported using the NCI-CTC toxicity evaluation criteria (common toxicity evaluation criteria) were observed in patients treated with bevacizumab.

Gastrointestinal Perforations and Fistulae

Bevacizumab has been associated with serious cases of gastrointestinal perforation. Gastrointestinal perforations have been reported in clinical trials with an incidence of less than 1% in patients with metastatic breast cancer and non-squamous non-small cell lung cancer; up to 2% in patients with metastatic renal cell cancer, newly diagnosed glioblastoma or ovarian cancer, and up to 2.7% in patients with metastatic colorectal cancer (including gastrointestinal fistula and abscess). Gastrointestinal perforations were also observed in patients with recurrent glioblastoma.

In a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (GOG-0240), the incidence of gastrointestinal perforation (any level) was 3.2% in patients with a history of prior pelvic radiation treated with bevacizumab.

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 relationship between intra-abdominal inflammatory and gastrointestinal perforation to bevacizumab exposure 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 clinical trial in patients with persistent, recurrent or metastatic cervical cancer, the incidence of gastrointestinal vaginal fistula in bevacizumab treatment group compared to control group were 8.3% vs. 0.9%. All patients had a history of pelvic radiation. Patients who develop a gastrointestinal vaginal fistula may also have a bowel obstruction and require surgical intervention, as well as a diverting ostomy.

Non-gastrointestinal fistulae

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

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (GOG-240), 1.8% of 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 and biliary fistulae) were observed across various indications. Fistulae have also been reported in post-marketing experience.

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

Hemorrhage

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

- Tumour-associated haemorrhage

Major or massive pulmonary haemorrhage/haemoptysis has been observed primarily in trials in patients with non-small cell lung cancer (NSCLC). Possible risk factors include squamous cell histology, treatment with antirheumatic/anti-inflammatory substances, treatment with anticoagulants, prior radiotherapy, 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 trials, while patients with unknown tumour histology were included.

In patients with NSCLC excluding predominant squamous histology, all Grade reactions were seen with a frequency of 9% when treated with Bevacizumab plus chemotherapy compared with up to 5% in the patients treated with chemotherapy alone. Grade 3-5 reactions 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 (see **[PRECAUTIONS]**).

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

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

The incidence of CNS bleeding in patients with untreated CNS metastases receiving bevacizumab has not been prospectively evaluated in randomised clinical trials. In an exploratory retrospective analysis of data from 13 completed randomised trials in patients with various tumour types, 3 patients out of 91 (3.3%) with brain metastases experienced CNS bleeding (all Grade 4) when treated with bevacizumab, compared to 1 case (Grade 5) out of 96 patients (1%) that were not exposed to bevacizumab. In two subsequent studies in patients with treated brain metastases (which included around 800 patients), one case of Grade 2 CNS haemorrhage was reported.

Intracranial Haemorrhage can occur in patients with recurrent glioblastoma. In Study AVF3708g, the incidences of CNS bleeding in patients receiving bevacizumab alone compared to patients receiving bevacizumab combination with irinotecan were 2.4% (2/84) (Grade 1 bleeding) vs. 3.8% (3/79) (grades 1, 2 and 4), Separately.

Across all clinical trials, ***mucocutaneous haemorrhage*** has been seen in up to 50% of Bevacizumab-treated patients. These were most commonly NCI-CTCAE 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 reactions of minor mucocutaneous haemorrhage in other locations, such as gingival bleeding or vaginal bleeding.

Hypertension (see [PRECAUTIONS])

In clinical trials, 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. In clinical trials for various indications, the overall incidence of NCI-CTC Grade 3 and 4 hypertensions 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 to up to 0.2% of patients treated with the same chemotherapy alone.

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

Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal (see [PRECAUTIONS]). The risk of bevacizumab-associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy.

Posterior Reversible Encephalopathy Syndrome (PRES)

In a clinical study (multicenter, randomized, double-blind, placebo-controlled phase III study of carboplatin and gemcitabine in combination with bevacizumab in patients with platinum-sensitive recurrent ovarian, primary peritoneal, or fallopian tube cancer), 2 cases of PRES have been reported (0.8%). Symptoms usually resolve or improve within days, although some patients have experienced some neurologic sequelae.

Thromboembolism

- Arterial thromboembolism

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

In clinical trials, the overall incidence of arterial thromboembolic reactions 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 compared to 0.5% in patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischaemic attacks) were reported in up to 2.3% of patients treated with bevacizumab in combination with chemotherapy compared to up to 0.5% of patients treated with chemotherapy alone. Myocardial infarction was reported in up to 1.4% of patients treated with Bevacizumab in combination with chemotherapy compared to up to 0.7% of patients treated with chemotherapy alone.

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

- Venous thromboembolism (see **[PRECAUTIONS]**)

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

Grade 3-5 venous thromboembolic reactions have been reported in up to 7.8% of patients treated with chemotherapy plus bevacizumab compared with up to 4.9% in patients treated with chemotherapy alone. Patients who have experienced a venous thromboembolic reaction 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 Bevacizumab in combination with chemotherapy compared with up to 5.4% of patients treated with chemotherapy alone.

In clinical study BO21990, the incidences of grade 3-5 venous thromboembolism were 7.6% vs. 8.0% in patients with newly diagnosed glioblastoma who received this product in combination with chemoradiotherapy compared to chemoradiotherapy alone.

Congestive heart failure

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 five phase III trials (AVF2119g, E2100, BO17708, AVF3694g and AVF3693g) in patients with metastatic breast cancer CHF Grade 3 or higher was reported in up to 3.5% of patients treated with 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 metastatic breast cancer 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 NYHA (New York Heart Association) II-IV were excluded, therefore, no information is available on the risk of CHF in this population.

Prior anthracyclines exposure and/or prior radiation to the chest wall may be possible risk factors for the development of CHF (see **[PRECAUTIONS]**).

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.

Wound healing (see [PRECAUTIONS])

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.

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

Serious wound healing complications have been reported, some of which had a fatal outcome (see **[PRECAUTIONS]**). 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 a study of patients with glioma recurrence (AVF3708g), the incidences of wound healing complications (including craniotomy wound dehiscence and cerebrospinal fluid leakage) were 3.6% in the bevacizumab alone group and 1.3% in the bevacizumab combined with irinotecan group.

The incidences of Grade 3-5 wound healing complications (including complications after craniotomy) were 3.3% (bevacizumab combined with radiotherapy and chemotherapy) and 1.6% (radiotherapy and chemotherapy), respectively.

Proteinuria (see [PRECAUTIONS])

In clinical trials, proteinuria has been reported within the range of 0.7% to 38% of patients receiving bevacizumab. Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome. Grade 3 proteinuria was reported in up to 8.1% of treated patients. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of treated patients. Patients with a history of hypertension may be at increased risk of developing proteinuria when treated with bevacizumab. There is evidence that the occurrence of Grade 1 proteinuria may be dose-related with bevacizumab. Testing for proteinuria is recommended prior to start of bevacizumab therapy. In most clinical trials urine protein levels of ≥ 2g/24 hrs led to the holding of bevacizumab until recovery to < 2g/24 hrs.

Hypersensitivity reactions/infusion reactions (see [PRECAUTIONS])

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).

Ovarian failure/fertility (see [PRECAUTIONS], [Pregnancy and breast feeding])

An evaluation of ovarian failure (defined as amenorrhoea lasting 3 or more months, FSH level ≥ 30 mIU/ml and a negative serum β-HCG pregnancy test) found that new reports of adverse events of ovarian failure were more frequent in patients receiving bevacizumab. Ovarian function can be restored in most women after discontinuation of bevacizumab treatment. The long-term effects of receiving bevacizumab on fertility have not been established.

Infections (see [PRECAUTIONS])

In a randomized, double-blind, placebo-controlled, multicenter phase III clinical study in the treatment of newly diagnosed glioblastoma (BO21990), the incidences of all Grades and Grades 3-5 infection were 54.4% and 12.8% in patients with bevacizumab combined with chemoradiotherapy, compared to 39.1% and 7.8% in the chemoradiotherapy alone group, respectively.

Elderly patients

In randomised clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic reactions, including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs), as compared to those aged ≤ 65 years when treated with bevacizumab (see **[PRECAUTIONS]**, **[ADVERSE REACTIONS]**). 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.

In a clinical trial in metastatic colorectal cancer (study AVF2107), the increase had not been observed 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 patients

This product is not approved for use in persons under the age of 18 years. In two phase II clinical trials of bevacizumab with current standard of care, one study in paediatric patients with high-grade glioma and another with metastatic rhabdomyosarcoma or non-rhabdomyosarcoma sarcoma soft tissue, no clinical benefit showed in children. In published literature reports, cases of non-mandibular osteonecrosis have been observed in patients under the age of 18 years treated with bevacizumab.

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 occurred in patients treated with bevacizumab with at least a 2% difference compared to the corresponding control groups: hyperglycaemia, decreased haemoglobin, hypokalaemia, hyponatraemia, decreased white blood cell count, prolonged PT (coagulation time), increased international 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.

Immunogenicity

This product has potential immunogenicity as all other therapeutic proteins.

In a clinical trial of adjuvant therapy for colon cancer, anti-bevacizumab antibodies positive in 14 patients (0.63%) of 2233 evaluable patients by chemiluminescence detection (ECL). Three of the 14 patients were positive for neutralizing antibody against bevacizumab by enzyme-linked immunosorbent assay (ELISA). The clinical significance of these anti bevacizumab antibodies has not been established.

The results are highly related to the sensitivity and specificity of the detection method in immunogenicity test. The influencing factors of test include: handling of blood samples, timing of sampling, concomitant medications, and comorbidities, etc. It may be misleading to compare the incidence of anti-bevacizumab antibodies with the incidence of antibodies to other drugs.

Post-Marketing Experience

Based on spontaneous case reports and literature cases, the following adverse reactions were identified from post-marketing experiences of bevacizumab (Table 2). Drug adverse reactions are classified according to the MedDRA system organ classification, and the corresponding incidence of each drug adverse reaction is based on the following conventions: 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 reactions reported during post-marketing use

Adverse Reaction	Reactions (frequency*)
Infectious and infestations	
Necrotizing fasciitis[1,2]	rare
Immune system disorders	
Hypersensitivity reactions[2,4]	not known
Infusion reactions[3]	not known
Nervous system disorders	
Hypertensive encephalopathy[3,4]	very rare
Posterior reversible encephalopathy syndrome (PRES) [2]	rare
Vascular and lymphatics disorders	
Renal thrombotic microangiopathy, which may be clinically manifested as proteinuria	not known
Respiratory, thoracic and mediastinal disorders	
Nasal septum perforation	not known
Nasal septum perforation	not known
Dysphonia	common
Gastrointestinal disorders	
Gastrointestinal ulcer	not known
Hepatobiliary disorders	
Gall bladder perforation	not known
Musculoskeletal and connective tissue disorders	
Osteonecrosis of the Jaw (ONJ) [5]	not known
Non-mandibular osteonecrosis[6,7]	not known
Congenital, familial and genetic disorders	
foetal abnormalities[8]	not known

1 Usually secondary to wound healing complications, perforation of the digestive tract, or fistula formation

3 with the following possible co-manifestations: dyspnoea, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors, and nausea/vomiting.

4 See Adverse reactions in clinical trials

5 Cases of osteonecrosis of the Jaw (ONJ) have been reported in patients treated with bevacizumab, the majority of whom had received prior or concomitant treatment with bisphosphates.

6 Cases of non-mandibular osteonecrosis have been observed in bevacizumab treated paediatric patients (see Special Populations, Paediatric and young adult).

7 Osteonecrosis events in children in non-corporate clinical trials have been identified by post-marketing monitoring, and had been added to the post-marketing adverse reactions section, but the published data did not provide enough information such as CTC rating or reporting rates.

8. Cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see [Pregnancy and breast feeding])

A description of specific adverse reactions from post-marketing experience

Eye disorders (following unapproved intravitreal use)

Infectious endophthalmitis4 (frequency unknown, some cases can lead to permanent blindness, 1 case reported extraocular extension of infection and leading to meningoencephalitis), intraocular inflammation (some cases can lead to permanent blindness, including 1 severe group event of eye infection leading to blindness after mixed intravenous anti-cancer chemotherapy drugs), such as aseptic endophthalmitis, uveitis, and vilititis; retinal detachment (frequency unknown); retinitis tearing (frequency unknown); increased intraocular pressure (frequency unknown) Intraocular bleeding, such as vitreous or retinal hemorrhage (frequency unknown); conjunctival bleeding (frequency unknown).

An observational medical reimbursement database study in patients with unapproved intravitreal use of bevacizumab and approved wet age-related macular degeneration showed: the risk of intraocular inflammation was increased in bevacizumab group (adjusted HR: 1.82; 99% CI: 1.20, 2.76) (incidence were 0.46 events/100 patients/year vs. 0.26 events/100 patients/year), and increased risk of cataract surgery (adjusted HR: 1.11; 99% CI: 1.01, 1.23) (incidence were 6.33 events/100 patients/year vs. 5.64 events/100 patients/year).

Serious ocular adverse events (including infective endophthalmitis and other ocular inflammations) had been reported due to the use of different unvalidated methods for dispensing, storage, and use of bevacizumab.

Systemic events (following unapproved intravitreal use)

An observational medical reimbursement database study in patients with unapproved intravitreal use of bevacizumab and approved wet age-related macular degeneration showed: the risk of hemorrhagic stroke was increased in bevacizumab group (adjusted HR: 1.57; 99% CI: 1.04, 2.37) (incidence were 0.41 events/100 patients/year vs. 0.26 events/100 patients/year), and the risk of overall mortality was also increased (adjusted HR: 1.11; 99% CI: 1.01, 1.23) (incidence were 6.03 events/100 patients/year vs. 5.51 events/100 patients/year). Another observational study found similar outcomes for mortality from any cause. A randomized, controlled clinical study in patients with unapproved bevacizumab and approved therapy in patients with wet-AMD reported an increased risk of serious systemic adverse events in the bevacizumab group, most of which resulted in hospitalization (adjusted hazard ratio was 1.29; 95% CI: 1.01, 1.66) (incidence were 24.1% vs. 19.0%).

[CONTRAINDICATIONS]

Bevacizumab is contraindicated in patients with known hypersensitivity to:

- Hypersensitivity to the active substance or to any of the excipients;
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies.

[PRECAUTIONS]

Gastrointestinal (GI) perforations and Fistulae

Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation when treated with bevacizumab (see **[ADVERSE REACTIONS]**). Therapy should be permanently discontinued in patients who develop gastrointestinal perforation. Patients with persistent, recurrent, or metastatic cervical cancer receiving bevacizumab may be at increased risk of fistula formation between the vagina and any part of the gastrointestinal tract (gastrointestinal-vaginal fistula) (see **[ADVERSE REACTIONS]**).***Non-GI Fistulae***

Patients may be at increased risk for the development of fistulae when treated with bevacizumab (see **[ADVERSE REACTIONS]**). Permanently discontinue bevacizumab 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 gastrointestinal tract, discontinuation of bevacizumab should be considered.

Haemorrhage

Patients treated with bevacizumab have an increased risk of haemorrhage, especially tumour-associated haemorrhage. Bevacizumab should be discontinued permanently in patients who experience Grade 3 or 4 bleeding during bevacizumab therapy (see **[ADVERSE REACTIONS]**).

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 randomised clinical trials. Patients should be monitored for signs and symptoms of CNS bleeding, and bevacizumab treatment discontinued in cases 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 therapy in these patients. However, patients who developed venous thrombosis while receiving therapy did not appear to have an increased rate of Grade 3 or above bleeding when treated with a full dose of warfarin and bevacizumab concomitantly

Severe eye infection due to unapproved intravitreal use (see [ADVERSE REACTIONS])

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

Pulmonary haemorrhage/haemoptysis (see [ADVERSE REACTIONS])

Patients with non-small cell lung cancer treated with bevacizumab may be at risk of serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis (see **[ADVERSE REACTIONS]** haemorrhage). Patients with recent pulmonary haemorrhage/haemoptysis (> 1/2 teaspoon of red blood) should not be treated with bevacizumab.

Hypertension

An increased incidence of hypertension was observed in bevacizumab-treated patients. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating therapy. Monitoring of blood pressure is generally recommended during therapy (see **[ADVERSE REACTIONS]**).

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. Bevacizumab 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 **[ADVERSE REACTIONS]** and **post-marketing experience).**

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 bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known (see **[ADVERSE REACTIONS]** and **post-marketing experience).**

Arterial thromboembolism (see [ADVERSE REACTIONS])

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

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

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 reactions during therapy. Caution should be taken when treating these patients with bevacizumab.

Venous thromboembolism (see [ADVERSE REACTIONS])

Patients may be at risk of developing venous thromboembolic reactions, 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 **[ADVERSE REACTIONS]**)

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

Congestive heart failure (CHF) (see [ADVERSE REACTIONS])

Reactions consistent with CHF were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation.

Caution should be exercised when treating patients with clinically significant cardiovascular disease with bevacizumab.

Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present.

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

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.

Wound healing complications

Bevacizumab may adversely affect the wound healing process. Serious wound healing complications with a fatal outcome have been reported. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for elective surgery (see **[ADVERSE REACTIONS]**).

Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated (see **[ADVERSE REACTIONS]**).

Proteinuria (see [ADVERSE REACTIONS])

The incidence of proteinuria was higher in patients receiving bevacizumab combined with chemotherapy than in who receiving chemotherapy only. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with bevacizumab. Bevacizumab should be permanently discontinued in patients who develop nephrotic syndrome

Hypersensitivity reactions/infusion reactions (see [ADVERSE REACTIONS])

Patients may be at risk of developing infusion/hypersensitivity reactions. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic 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.

Ovarian failure/fertility (see [ADVERSE REACTIONS] and Medication for pregnant and lactating women)

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

Driving and using machines

The effects of bevacizumab on the ability to drive and use machinery had not been established. However, there is no evidence that bevacizumab may reduce the ability to drive or operate machines, or increase the incidence of adverse events due to decreased mental capacity.

[PREGNANT AND LACTATION]

Fertility (see [ADVERSE REACTIONS] and [PRECAUTIONS])

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

Repeat-dose toxicity studies in animals have shown that bevacizumab may have adverse effect on female fertility (see **[PHARMACOLOGY]** and **[TOXICOLOGY]**). A sub-study with 295 premenopausal women has shown a higher incidence of new cases of ovarian failure in the bevacizumab group compared to the control group. After discontinuation of bevacizumab therapy, ovarian function recovered in the majority patients. Long-term effects of the treatment with bevacizumab on fertility are unknown.

Contraception

Women of childbearing potential have to use effective contraceptive during treatment with bevacizumab. For pharmacokinetic reasons, contraception should be taken at least 6 months after the last dose.

Pregnancy

Researches had shown that angiogenesis is critical to fetal development. Inhibition of angiogenesis following administration of bevacizumab may lead to adverse pregnancy outcomes.

There are no clinical trial data on the use of bevacizumab in pregnant women (see **[TOXICOLOGY]** Teratogenicity). IgGs are known to cross the placental barrier, and bevacizumab is anticipated to inhibit angiogenesis in the fetus. In the post-marketing setting, cases of fetus abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see **[ADVERSE REACTIONS]**).

Therefore, bevacizumab is contraindicated in 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 must discontinue breast-feeding during therapy and not breast-feed for at least 6 months following the last dose of bevacizumab.

[PEDIATRIC 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 showed no clinical benefit in pediatric patients enrolled in two randomized clinical studies, one in high grade glioma and one in metastatic rhabdomyosarcoma or non-rhabdomyosarcoma soft tissue sarcoma.

In published literature reports, cases of non-mandibular osteonecrosis have been observed in patients under the age of 18 years who have received Bevacizumab.(see **[ADVERSE REACTIONS]**)

[GERIATRIC USE]

In an exploratory pooled analysis of 1745 patients from five randomized, controlled studies, 35% of patients were ≥ 65 years old. The overall incidence of ATE was increased in all patients receiving bevacizumab with chemotherapy as compared to those receiving chemotherapy alone, regardless of age; however, the increase in the incidence of ATE was greater in patients≥ 65 years (8% vs 3%) as compared to patients < 65 years (2% vs 1%) (see **[PRECAUTIONS]).**

[DRUG INTERACTIONS]

Interactions with other medicinal products and other forms of interaction

Effect of antineoplastic agents on bevacizumab pharmacokinetics

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

Effect of bevacizumab on the pharmacokinetics of other antineoplastic agents

The results of the drug interaction study (AVF3135g) showed that bevacizumab had no significant effect on the pharmacokinetics of irinotecan and its active metabolite SN38.

The results of study NP18587 showed that bevacizumab had no significant effect on the pharmacokinetics of capecitabine and its metabolites, nor on the pharmacokinetics of oxaliplatin as determined free and total platinum.

The results of study BO17705 confirmed that bevacizumab had no significant effect on the pharmacokinetics of alpha-2a interferon.

The results of study BO17704 showed that bevacizumab had no significant effect on the pharmacokinetics of cisplatin. Due to the high inter-patient variability and limited sample size, definite conclusions regarding the effect of bevacizumab on gemcitabine pharmacokinetics cannot be drawn from the results of BO17704.

Bevacizumab in combination with sunitinib malate

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

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

Radiotherapy

Study BO21990 was a phase III randomized, double-blind, placebo-controlled clinical trial in 921 patients with newly diagnosed glioblastoma. The study evaluated the safety and effectiveness of chemotherapy (temozolomide), radiotherapy combination with bevacizumab, No new adverse events related to bevacizumab had been reported.

The safety and efficacy of bevacizumab combined with concurrent radiotherapy have not been established in other indications.

[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.

[CLINICAL STUDIES]

Metastatic Colorectal Cancer (mCRC)

Studies abroad

The efficacy and safety of the recommended dose of bevacizumab (5 mg/kg body weight administered every 2 weeks) in metastatic carcinoma of the colon or rectum were studied in three randomised, active-controlled clinical trials in combination with fluoropyrimidine-based first-line chemotherapy. Bevacizumab was combined with two chemotherapy regimens:

- AVF2107g: A weekly schedule of irinotecan/bolus injection of 5-fluorouracil/leucovorin (IFL) for a total of 4 weeks of each 6 week-cycle.
- AVF0780g: In combination with bolus 5-fluorouracil/leucovorin (5-FU/LV), once a week, for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen).
- AVF2192g: In combination with bolus 5-FU/LV, once a week, 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 metastatic colorectal cancer patients: first-line (NO16966), second-line with no previous bevacizumab (E3200), and second-line with previous bevacizumab treatment following disease progression in first-line (ML18147). In these studies, bevacizumab was administered at following dosing regimens in combination with FOLFOX-4 (5-FU/LV/oxaliplatin), XELOX (capecitabine/oxaliplatin), and fluoropyrimidine/irinotecan and fluoropyrimidine/oxaliplatin :

- NO16966: Bevacizumab 7.5 mg/kg regimens in combination with FOLFOX-4 (5-FU/LV/oxaliplatin), XELOX (capecitabine/oxaliplatin), and fluoropyrimidine/irinotecan and fluoropyrimidine/oxaliplatin
- 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 5.0 mg/k of body weight every 2 weeks or Avastin 7.5 mg/kg of body weight every 3 weeks in combination with fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin in patients with disease progression following first-line treatment with bevacizumab. Use of irinotecan- or oxaliplatin-containing regimen was switched depending on first-line usage of either oxaliplatin or irinotecan.

AVF2107g:

This was a phase III randomised, double-blind, active-controlled clinical trial evaluating bevacizumab in combination with IFL as first-line treatment for metastatic carcinoma of the colon or rectum. Eight hundred and thirteen patients were randomised to receive IFL + placebo (Arm 1) or IFL + bevacizumab (5 mg/kg every 2 weeks, Arm 2). A third group of 110 patients received bolus 5-FU/FA + 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.

The primary efficacy variable of the trial was overall survival. The addition of bevacizumab to IFL resulted in statistically significant increases in overall survival, progression-free survival and overall response rate (Table 3). The clinical benefit, as measured by overall survival, was seen in all pre-specified patient subgroups, including those defined by age, sex, performance status, location of primary tumour, number of organs involved and duration of metastatic disease.

Table 3: Efficacy Results for Study AVF2107g

	AVF2107g	
	Arm 1 IFL+Placebo	Arm 2 IFL+Bevacizumab[a]
Number of patients	411	402
Overall Survival		
Median, in months	15.6	20.3
95%CI	14.29-16.99	18.46-24.18
Hazard ratio[b]	0.660 (p=0.00004)	
Progression-Free Survival		
Median, in months	6.2	10.6
Hazard ratio	0.54 (p<0.0001)	
Overall Response Rate%	34.8%	44.8%
	(p<0.0036)	

a 5 mg/kg, every 2 weeks

b Relative to control arm

Among the 110 patients who were randomly assigned to arm 3 (5-FU/LV + bevacizumab) prior to discontinuation of enrollment, the overall median survival was 18.3 months and the median progression-free survival was 8.8 months.

AVF2192g

This was a phase II randomised, double-blind, active-controlled clinical trial evaluating the efficacy and safety of 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. One hundred and five patients were randomised to 5-FU/FA + placebo arm and 104 patients to 5-FU/LV + bevacizumab (5 mg/kg every 2 weeks) arm. All treatments were continued until disease progression.

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 as compared to 5-FU/LV chemotherapy alone.

NO16966

This was a phase III randomised, double-blind (for bevacizumab), clinical trial investigating bevacizumab 7.5 mg/kg in combination with oral capecitabine and IV 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 IV oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule. The trial contained two parts: an initial unblinded 2-arm part (Part I) in which patients were randomised to two different treatment groups (XELOX and FOLFOX-4) and a subsequent 2 x 2 factorial 4-arm part (Part II) in which patients were randomised to four treatment groups (XELOX + placebo, FOLFOX-4 + placebo, XELOX + bevacizumab, FOLFOX-4 + bevacizumab). In Part II, treatment assignment was double-blind with respect to bevacizumab. Approximately 350 patients were randomised into each of the 4 trial arms in the Part II of the trial.

Table 4: Treatment regiments in trial NO16966 (mCRC)

	Therapy	Starting dose	Schedule
FOLFOX-4 or FOLFOX-4 + Bevacizumab	Oxaliplatin	85 mg/m^2 IV 2h	Oxaliplatin on day 1
	Leucovorin	200 mg/m^2 IV 2h	Leucovorin on day 1 and day 2
	5-Fluorouracil	400 mg/m^2 IV bolus, 600 mg/m^2 IV 22h	5-fluorouracil IV bolus/infusion, each on days 1 and 2
	Placebo or Bevacizumab	5 mg/kg IV 30-90 min	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX+Bevacizumab	Oxaliplatin	130 mg/m^2 IV 2h	Oxaliplatin on day 1
	Capecitabine	1000 mg/m^2, oral, twice a day	Oxaliplatin on day 1 Capecitabine oral bid for 2 weeks (followed by 1 week off treatment)
	Placebo or Bevacizumab	7.5 mg/kg IV 30-90 min	Day 1, prior to XELOX, q3 weeks
5-Fluorouracil: IV bolus injection immediately after leucovorin			

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

- Non-inferiority of the XELOX-containing arms compared with the FOLFOX-4-containing arms in the overall comparison was demonstrated in terms of progression-free survival and overall survival in the eligible per-protocol population.
- Superiority of the bevacizumab -containing arms versus the chemotherapy alone arms in the overall comparison was demonstrated in terms of progression-free survival in the ITT population (Table 5).

Significantly clinical benefits to patients treated with bevacizumab were confirmed by the secondary PFS analysis based on the Independent Review Committee (IRC) and efficacy evaluation of 'in-treatment' patients (subgroup analysis results were shown in Table 4), consistent with the statistically significant benefit observed in the pooled analysis.

Table 5: Key efficacy results for the superiority analysis (ITT population, trial NO16966)

Endpoint (months)	FOLFOX-4 or XELOX + placebo (n=701)	FOLFOX-4 or XELOX + bevacizumab (n=699)	P Value
Primary endpoint			
Median PFS (months) **	8.0	9.4	0.0023
Hazard ratio (97.5% CI)a	0.83 (0.72–0.95)		
Endpoint (months)			
Median PFS (on treatment) (months) **	7.9	10.4	<0.0001
Hazard ratio (97.5% CI)	0.63 (0.52-0.75)		
Median PFS (ICR assessment) (months)**	8.5	11.0	<0.0001
Hazard ratio (97.5% CI)	0.70 (0.58-0.83)		
ORR (invest. assessment, %)**	49.2%	46.5%	
ORR (ICR assessment),%)**	37.5%	37.5%	
Median overall survival (months)*	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

ECOGE 3200

This was a phase III randomized, active-controlled, open-label trial investigating bevacizumab 10 mg/kg in combination with leucovorin with 5-fluorouracil bolus and then 5-fluorouracil infusional, with IV oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule in previously-treated patients (second line) with advanced colorectal cancer. In the chemotherapy arms, the FOLFOX-4 regimen used the same doses and schedule as shown in Table 3 for trial NO16966.

The primary efficacy parameter of the trial was overall survival, defined as the time from randomisation to death from any cause. Eight hundred and twenty-nine patients were randomised (292 FOLFOX-4, 293 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 (Table 6).

Table 6: Efficacy results for trial E3200

	E3200	
	FOLFOX-4	FOLFOX-4+ bevacizumab [a]
Number of Patients	292	293
Progression-Free Survival		
Median (months)	10.8	13.0
95%CI	10.12-11.86	12.90-14.03
Hazard ratio [b]	0.751 (p =0.0012)	
Progression-free survival		
Median (months)	4.5	7.5
Hazard ratio	0.518 (p <0.0001)	
ORR(%)	8.6%	22.2%
	(p <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.

ML18147

This was a phase III randomized, controlled, open-label trial in patients with metastatic colorectal cancer who have progressed following first-line therapy with bevacizumab. To compare the efficacy and safety of bevacizumab 5.0 mg/kg (once every 2 weeks) or 7.5mg/kg (once every 3 weeks) combined with fluorouracil-based chemotherapy and fluorouracil-based chemotherapy alone.

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

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

Table 7: 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	409.0
Overall Survival		
Median (months)	9.8	11.2
95% confidence interval	9-11	10-12
Hazard ratio	0.81 (p –value = 0.0062)	
Progression-Free Survival		
Median (months)	4.1	5.7
Hazard ratio	0.68 (p –value < 0.0001)	
Objective Response Rate (ORR)		
Rate	3.9%	5.4%
	(p –value = 0.3113)	

a 2.5 mg/kg/week

Statistically significant improvements in progression-free survival were also observed. Objective response rate was low in both treatment arms and the difference was not significant.

Adjuvant therapy for colon cancer (aCC)

BO17920

This was a phase III randomized, open-label study in three groups to evaluate efficacy and safety of bevacizumab (a single dose of 2.5mg/kg body weight/week, every 2 weeks in combination with FolfoX-4, or every 3 weeks in combination with Xelox-4, and folfox-4 regimen alone was the control arm) as adjuvant chemotherapy in 3451 high-risk stage 2 and 3 colon cancer patients.

More recurrent and fatal cases due to disease progression were observed in the two bevacizumab groups compared with the control group. In patients with stage 3 colon cancer, the primary endpoints of prolonging progression-free survival were either failed in chemotherapy regimens combined with bevacizumab. Hazard ratio for progression-free survival was 1.17 (95%CI: 0.98-1.39) in the folfoX-4 + bevacizumab group and 1.07 (95%CI: 0.90 to 1.28) in the Xelox-4 + bevacizumab group).

Studies in China

BO20696

BO20696 was a randomized, open-label clinical trial designed to evaluate the safety and efficacy of bevacizumab (5mg/kg every 2 weeks) in the first-line treatment of Chinese patients with metastatic colorectal cancer.

The primary efficacy measures were 6-month progression-free survival and progression-free survival (PFS), which was based on the assessment of tumor from the investigators. Secondary endpoints included objective response rate (ORR, as assessed by the investigator), overall survival (OS), time to response (DoR), and safety.

A total of 214 Chinese patients were randomly divided (according to the ratio of 1:2), and were treated with irinotecan /5-FU/LV (m-IFL group) or irinotecan /5-FU/LV in combination with bevacizumab (bevacizumab + M-IFL group). Study treatment continued until disease progression or the emergence of intolerable toxicity occurred.

As defined in protocol, the final analysis was performed 10 months after the last patient was enrolled. The final efficacy analysis was performed in the full analysis set (FAS, N=203), and the results were shown in Table 8:

Table 8: Validity results of the BO20696 study（FAS）

	m-IFL group	bevacizumab + m-IFL group
Number of Patients	64	139
Progression-Free Survival		
Median (months)	4.2	83
95%CI	3.7-4.9	7.4-8.9
p value（Log-Rank）	<0.001	
Hazard ratio b	0.44	
95%CI	0.31-0.63	
Overall Survival		
Median (months)	13.4	35.3%
95%CI	9.7-17.2	15.8-19.6
p value（Log-Rank）	0.014	
Hazard ratio b	0.62	
95%CI	0.41-0.95	
Objective Response Rate（%）		
Rate	17.2%	35.3%
95%CI	8.4-27.7%	27.5-43.5%
p value（Pearson Clopper method）	0.013	

m-IFL：

Irinotecan 125 mg/m^2 was given intravenously for 90 min, followed by leucine 20mg/m^2 intravenously for 1-2 min, 5-fluorouracil intravenously 500 mg/m^2 for 6-8 h, once a week, 4 times in total every 6 weeks.

Outcomes in the FAS population were further supported by analyses in the intentional-treatment population (ITT, N=214) and in the regimen-set population (PP, N=171).

Safety results:

The final safety analysis was performed based on the safety analysis population (N=211). The addition of bevacizumab to chemotherapy was generally well tolerated, with a slight increase in the incidence of known chemotherapy-related adverse reactions. Compared with the safety data of bevacizumab from key global studies, no new safety information was observed in the Chinese population.

Adverse events of special concern in the bevacizumab combined chemotherapy group included Grade 3 hypertension, Grade 3 proteinuria, Grade 3 bleeding events, Grade 3 myocardial ischemia, Grade 1/2 phlebitis, Grade 3 rectal perforation and Grade 3 intestinal fistula.

- Almost all patients in each group had at least one adverse event (98.6% in chemotherapy alone vs. 97.2% in bevacizumab combined chemotherapy).
- The incidence of Grade 3-5 adverse events was similar between the two groups (61.4% in the chemotherapy alone group and 68.8% in the bevacizumab combined chemotherapy group).
- The proportion of patients who dropped out of all treatments due to adverse events was higher in the chemotherapy alone group (13/70, 18.6%) than in the bevacizumab combination group (14/141, 9.9%). Most of the adverse events are known adverse reactions to chemotherapy.
- Three (2.1%) patients in the bevacizumab combined chemotherapy group died of serious adverse events, compared with one (1.4%) in the chemotherapy alone group.

Overall, the safety and efficacy of bevacizumab in the Chinese population are close to the results of key studies conducted worldwide.

Non-small cell lung cancer（NSCLC）

In E4599, BO17704, and YO25404, the safety and efficacy of bevacizumab in combination with platinum-based first-line chemotherapy in patients with non-squamous cell non-small cell lung cancer (NSCLC) were studied.

Foreign research

E4599

E4599 was an open-label, randomized, active-controlled, multicenter clinical trial evaluating bevacizumab as first-line treatment of patients with locally advanced, 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 IV 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 IV infusion day 1 of every 3-week cycle. After completion of six cycles of carboplatin-paclitaxel chemotherapy or upon premature discontinuation of chemotherapy, patients on the 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 trial, 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 9.

Table 9: Efficacy results for trial E4599

	Arm 1 Carboplatin/ Paclitaxel	Arm 2 Carboplatin/ Paclitaxel + bevacizumab 15 mg/kg q 3 weeks
Number of patients	444	434
Overall survival		
Median (months)	10.3	12.3
Median (months)		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)

BO17704

BO17704 was a randomized, double-blind Phase III trial comparing bevacizumab combined cisplatin versus gemcitabine versus placebo combined cisplatin and gemcitabine in patients with locally advanced, metastatic or relapsed non-squamous cell NSCLC who have not previously received chemotherapy. The primary end point was progression-free survival, and the secondary end point included overall survival. Patients were randomized to platinum-based chemotherapy with intravenous cisplatin 80 mg/m^2 on day 1 and gemcitabine 1250 mg/m^2 on days 1 and day 8 every 3 weeks for a maximum of 6 cycles of chemotherapy (CG). Placebo or bevacizumab was given intravenously at 7.5 or 15 mg/kg on day 1 of every 3 weeks. In the bevacizumab group, patients were treated with bevacizumab monotherapy (every 3 weeks) until disease progression or intolerable toxicity.

Results showed that 94% (277/296) of patients continued to receive bevacizumab monotherapy at the 7th cycle. The majority of patients (approximately 62%) continued to receive antitumor therapy that was not prescribed in the study protocol, which may have influenced the analysis of overall survival.

The efficacy results are presented in Table 10.

Table 10: Efficacy results for trial BO17704

	Cisplatin/Gemcitabine + placebo	Cisplatin/Gemcitabine + Avastin 7.5 mg/kg q 3 weeks	Cisplatin/Gemcitabine + Avastin 15 mg/kg q 3 weeks
Number of patients	347	345	351
Progression-free survival			
Median (months)	6.1	6.7 (p = 0.0026)	6.5 (p = 0.0301)
Hazard ratio		0.75 [0.62;0.91]	0.82 [0.68;0.98]
Best overall response rate	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		0.93 [0.78; 1.11]	1.03 [0.86, 1.23]

China Study

YO25404

YO25404 was a randomized, double-blind, placebo-controlled, multi-center Phase III clinical study in Chinese patients with unresectable, advanced or relapsed non-squamous cell NSCLC who previously had not received chemotherapy, the patients received bevacizumab plus carboplatin and paclitaxel (CP) or placebo combined carboplatin and paclitaxel (CP) chemotherapy. The primary endpoint was progression-free survival, and secondary endpoints included overall survival and objective response rates.

Patients were randomized to receive CP chemotherapy (carboplatin AUC = 6.0 and paclitaxel 175 mg/m^2, both intravenously) on day 1 of every 3 weeks for up to 6 cycles, or CP in combination with bevacizumab at 15 mg/kg intravenously on day 1 of every 3 weeks. After completing six cycles of carboplatin and paclitaxel chemotherapy or early discontinuation of chemotherapy, patients continued bevacizumab or placebo monotherapy every 3 weeks until disease progression or intolerable toxicity.

Bevacizumab monotherapy were continued in 78% (107/138) of patients in the bevacizumab group at cycle 7, and 57% (78/138) of patients in the placebo group continued to receive placebo monotherapy at cycle 7. Efficacy results are shown in Table 11.

Table 11: Efficacy results for trial YO25404

	Arm 1 Carboplatin/paclitaxel + placebo	Arm 2 Carboplatin/paclitaxel +bevacizumab 15 mg/kg q3W
Number of patients	138	138
Progression-free survival		
Median (months)	6.5	9.2 (p<0.0001)
Hazard ratio		0.4 [0.29, 0.54]
Overall response rate		
Rate (percent)	26.3	54.4
		(p<0.0001)
Overall survival		
Median (months)	26.3	24.3 (p=0.0154)
Hazard ratio		0.68 [0.50, 0.93]

Safety Result:

All safety analyses were based on the safety population. Overall, the safety data during the double-blind treatment period were consistent with the expected safety of CP regimen in the treatment of NSCLC and the established safety characteristics of bevacizumab.

- No new security signals were found.
- The incidence of adverse events (of any grade) and serious adverse events was similar in both treatment groups, with hematological events being reported most frequently.
- The incidence of Grade ≥3 adverse events was slightly higher in the bevacizumab +CP group (60.9% in the placebo +CP group versus 66.7% in the bevacizumab +CP group). This elevated outcome was attributable to adverse events of particular concern with bevacizumab, namely, those known to be associated with bevacizumab therapy (AE [AESI] of particular concern, primarily hypertension and proteinuria) and certain hematologic adverse events (bone marrow failure and decreased white blood cell count).
- The rate of adverse events leading to discontinuation of any study drug was similar between the two treatment groups (15.0% vs. placebo +CP group). bevacizumab +CP group 18.4%). Proteinuria is the most common cause of discontinuation of bevacizumab and hematological toxicity is the most common cause of discontinuation of chemotherapy.
- The incidence of adverse events of particular concern was higher in the bevacizumab +CP group (23.3% vs. bevacizumab +CP group 45.4%). The increased incidence was mainly due to Grade 1 and 2 hemorrhage (mostly epistaxis and hemoptysis), hypertension and proteinuria. The incidence of Grade ≥ 3 adverse events of special concern was higher in the bevacizumab +CP group (2.3% vs. placebo +CP).9.9% in bevacizumab + CP group), mainly due to Grade 3 hypertension and proteinuria.
- The incidence of adverse events leading to death was lower in both treatment groups (placebo +CP 0.8% vs. bevacizumab +CP group 2.1%).

In summary, the safety and efficacy results of bevacizumab observed in the Chinese YO25404 study are similar to those of key studies worldwide.

Malignant glioma (WHO standard classification: class IV) – glioblastoma

In the AVF3708g and EORTC 26101 studies, the safety and efficacy of bevacizumab in the treatment of patients with relapsed glioblastoma were studied.

AVF3708g

The efficacy and safety of bevacizumab in patients with glioblastoma have been investigated in an open-label, multicenter, randomized, noncomparative study (AVF3708g).

Patients with glioblastoma who had received prior radiotherapy (at least eight weeks prior to the start of bevacizumab) and temozolomide were randomly arranged to receive bevacizumab (intravenously at 10 mg/kg doses every two weeks) or bevacizumab plus irinotecan (125 mg/m^2 intravenously) after first or second recurrence. The dosages were adjusted to 340 mg/m^2 intravenously every two weeks for patients treated with enzyme-induced antiepileptics until the disease progresses or unacceptable toxicity.The primary endpoints of this study were six-month progression-free survival (PFS) and objective response rate (ORR) based on independent review committee (IRF) assessments, and the other endpoints for efficacy assessment were progression-free survival, duration of remission, and overall survival. A summary of the findings can be found in Table 12.

Table 12: Efficacy results of AVF3708g

	Bevacizumab		Bevacizumab + Irinotecan	
Number of patients	85		82	
	Inv	**IRF**	**Inv**	**IRF**
Progression-free survival				
Progression-free survival of 6 months	43.6%	42.6%	57.9%	50.3%
95% CI (Inv)	(33.0, 54.3)	-	(46.6, 69.2)	-
97.5% CI (IRF)	-	(29.6, 55.5)	-	(36.8, 63.9)
objective response rate	41.2%	28.2%	51.2%	37.8%
95% CI (Inv)	(30.6, 52.3)	-	(39.9, 62.4)	-
97.5% CI (IRF)	-	(18.5, 40.3)	-	(26.5, 50.8)
Secondary endpoints				
progress free survival（months）				
Median	4.2	4.2	6.8	5.6
（95% CI)	(3.0, 6.9)	(18.5, 40.3)	(5.0, 8.2)	(4.4, 6.2)
Duration of objective remission（months）				
Median	8.1	5.6	8.3	4.3
（95% CI)	(5-5,*)	(3.0, 5.8)	(5.5, *)	(4.2,*)
overall survival（months				
Median	9.3		8.8	
（95% CI)	(8.2,*)		(7.8, *)	

The ORR is determined by the modified Mcdonald standard; Inv = Investigator Assessment; IRF = Independent Review Committee
* The upper bound data for the confidence interval cannot be obtained

In AVF3708g study, the PFSs of the two treatment arms, based on the evaluation of an independent review committee, were significantly higher than that of historical controls (p< 0.0001): bevacizumab (42.6%) vs bevacizumab + irinotecan (50.3%); or bevacizumab (43.6%) vs bevacizumab + irinotecan (57.9%), assessed by investigators. The objective response rates reported in both treatment arms were also significantly higher than those of historical controls (p<0.0001): bevacizumab (28.2%) vs bevacizumab + irinotecan (37.8%); or bevacizumab (41.2%) vs bevacizumab + irinotecan (51.2%), assessed by investigators.

Patients treated with corticosteroids at baseline (including remission and non-remission) were mostly able to reduce their corticosteroid doses during bevacizumab therapy. Patients with objective remission or prolonged progression-free survival (week 24) were more likely to maintain neurocognitive function during the study period compared to baseline. Karnofsky performance status (KPS) remained stable in patients who remained in the study and had not progressed at week 24.

EORTC 26101

The safety and efficacy of bevacizumab were evaluated in a multicenter, randomized (2:1), open-ended study in patients with recurrent glioblastoma (EORTC 26101, NCT01290939). Patients with first progression following radiotherapy and temozolomide were randomized (2:1) to receive bevacizumab (10 mg/kg every 2 weeks) with lomustine (90 mg/m^2 every 6 weeks) or lomustine (110 mg/m^2 every 6 weeks) alone until disease progression or unacceptable toxicity. Randomization was stratified by World Health Organization performance status (0 vs >0), steroid use (yes vs no), largest tumor diameter (≤40 vs >40 mm), and institution. The main outcome measure was OS. Secondary outcome measures were investigator-assessed PFS and ORR per the modified Response Assessment in Neuro-oncology (RANO) criteria, health related quality of life (HRQoL), cognitive function, and corticosteroid use.

A total of 432 patients were randomized to receive lomustine alone (N = 149) or bevacizumab with lomustine (N = 283). The median age was 57 years; 24.8% of patients were ≥ 65 years. The majority of patients were male (61%); 66% had a performance status score >0; and in 56% the largest tumor diameter was ≤40 mm. Approximately 33% of patients randomized to receive lomustine received bevacizumab following documented progression.

No difference in OS (HR 0.91, p-value 0.4578) was observed between arms; therefore, all secondary outcome measures are descriptive only. PFS was longer in the bevacizumab + lomustine arm [HR 0.52 (95% CI: 0.41 to 0.64) with median PFS of 4.2 months in the bevacizumab + lomustine arm and 1.5 months in the lomustine arm.

In patients receiving corticosteroid at the time of randomization, the percentage of patients with 50% reduction in corticosteroid use in the bevacizumab + lomustine arm was higher than those in lomustine arm (51% vs 25.7%); and the proportion of patients in the bevacizumab + lomustine arm discontinued corticosteroids was also higher (23% vs 12%).

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer（OC）

GOG-0218

The safety and efficacy of bevacizumab was evaluated in Study GOG-0218 (NCT00262847), a multicenter, randomized, double-blind, placebo-controlled, three arm study, which evaluated the addition of bevacizumab to carboplatin and paclitaxel for the treatment of patients with stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer (N = 1873) following initial surgical resection. Patients were randomized (1:1:1) to the following three arms:

- CPP arm: Five cycles of placebo (started cycle 2) in combination with carboplatin (AUC 6) and paclitaxel (175mg/m^2) for 6 cycles followed by placebo alone q3w, for a total of up to 22 cycles (n = 625) 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 q3w, for a total of up to 22 cycles (n = 625) 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 22 cycles (n = 625) of therapy.

The median age of patients included in the study was 60 years (range 22-89 years), 28% of patients were > 65 years old. Overall approximately 50% of patients had a GOG PS of 0 at baseline, 43% a GOG PS score of 1. Patients had epithelial ovarian cancer (83%), primary peritoneal cancer (15%), or fallopian tube cancer (2%). Serous adenocarcinoma is the most common histological type (85% in the CPP and CPB15, 86% in CPB15+). Overall approximately 34% of patients were FIGO Stage III optimally debulked with gross residual disease (residual lesions < 1 cm), 40% Stage III sub-optimally debulked(residual lesions > 1 cm), and 26% were Stage IV patients.

Most patients in all 3 treatment arms received follow-up antineoplastic therapy: 78.1% in CPP, 78.6% in CPB15, and 73.2% in CPB15+. The proportion of patients, who received at least once anti-angiogenesis (including bevacizumab) treatment after the study, in the CPP (25.3%) and CPB15 (26.6%) arms were higher than CPB15+ (15.6%) arm.

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

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (carboplatin and paclitaxel) alone in the front-line setting, patients who received bevacizumab at a dose of 15 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab alone (CPB15+), had a clinically meaningful and statistically significant improvement in PFS. The results of this study are summarised in Table 13.

Table 13 Efficacy results from study GOG-0218

Progression-free survival[1]			
	CPP (n = 625)	CPB 15 (n = 625)	CPB 15+ (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)	CPB 15 (n = 396)	CPB 15+ (n = 403)
% pts with objective response	63.4	66.2	66.0
p-value		0.2341	0.2041
Overall survival [6]			
	CPP (n = 625)	CPB 15 (n = 625)	CPB 15+ (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 Final overall survival analysis performed when 46.9% of the patients had died.

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

- The protocol specified analysis of investigator-assessed PFS (without censoring for CA-125 progression or non-protocol therapy [NPT]) shows a stratified hazard ratio of 0.71 (95% CI: 0.61-0.83, 1-sided 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.

Cervical Cancer（CC）

GOG-0240

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

A total of 452 patients were randomised to receive either:

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

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

The median age was 48 years (range:20 - 85). Of the 452 patients randomized at baseline, 78% of patients were White, 80% had received prior radiation, 74% had received prior chemotherapy concurrent with radiation and 32% had a platinum-free interval <6 months. Patients had a GOG performance status is 0 (58%) or 1 (42%). Demographics and disease characteristics were balanced across arms.

The primary efficacy endpoint was overall survival. Secondary efficacy endpoints included progression-free survival (PFS) and objective response rate (ORR). Results from the primary analysis and the follow-up analysis are shown in Table14 and Table 15.

Table14 Efficacy results from study GOG-0240 by bevacizumab treatment

	Paclitaxel/Cisplatin Paclitaxel / Topotecan (n=225)	Paclitaxel / Cisplatin + bevacizumab Paclitaxel / Topotecan + 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		
Responders [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 and percentage of patients with best overall response of confirmed CR or PR; percentage calculated on patients with measurable disease at baseline
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)

Table15 Efficacy results from study GOG-0240 by chemotherapy treatment

	Paclitaxel / Topotecan ± bevacizumab (N =223)	**Paclitaxel / Cisplatin ± bevacizumab (N =229)**
overall survival		
Median (months) a	13.3	15.5
Hazard ratio [95% CI]	1.15（0.91，1.46）	
p-value	0.23	

a Kaplan-Meier estimates

[NONCLINICAL TOXICOLOGY]

Mechanism of Action

Bevacizumab binds VEGF and prevents the interaction of VEGF to its receptors (Flt-1 and KDR) on the surface of endothelial cells. The interaction of VEGF with its receptors leads to endothelial cell proliferation and new blood vessel formation in in vitro models of angiogenesis. Administration of bevacizumab to xenotransplant models of colon cancer in nude (athymic) mice caused reduction of microvascular growth and inhibition of metastatic disease progression.

Toxicology Research

General toxicity: Rabbits dosed with bevacizumab exhibited reduced wound healing capacity. Using full-thickness skin incision and partial thickness circular dermal wound models, bevacizumab dosing resulted in reductions in wound tensile strength, decreased granulation and re-epithelialization, and delayed time to wound closure.

Juvenile cynomolgus monkeys with open growth plates exhibited physeal dysplasia following 4 to 26 weeks exposure at 0.4 to 20 times the recommended human dose (based on mg/kg and exposure). The incidence and severity of physeal dysplasia were dose-related and were partially reversible upon cessation of treatment.

Genotoxicity: The genotoxicity of bevacizumab has not been studied.

Reproductive toxicity: Bevacizumab may impair fertility. Female cynomolgus monkeys treated with 0.4 to 20 times the recommended human dose of bevacizumab exhibited arrested follicular development or absent corpora lutea, as well as dose-related decreases in ovarian and uterine weights, endometrial proliferation, and the number of menstrual cycles. Following a 4-or 12-week recovery period, there was a trend suggestive of reversibility. After the 12-week recovery period, follicular maturation arrest was no longer observed, but ovarian weights were still moderately decreased. Reduced endometrial proliferation was no longer observed at the 12-week recovery time point; however, decreased uterine weight, absent corpora lutea, and reduced number of menstrual cycles remained evident.

Pregnant rabbits dosed with 10 mg/kg to 100 mg/kg bevacizumab (approximately 1 to 10 times the clinical dose of 10 mg/kg) every three days during the period of organogenesis (gestation day 6−18) exhibited decreases in maternal and fetal body weights and increased number of fetal resorptions. There were dose-related increases in the number of litters containing fetuses with any type of malformation (42% for the 0 mg/kg dose, 76% for the 30 mg/kg dose, and 95% for the 100 mg/kg dose) or fetal alterations (9% for the 0 mg/kg dose, 15% for the 30 mg/kg dose, and 61% for the 100 mg/kg dose). Skeletal deformities were observed at all dose levels, with some abnormalities including meningocele observed only at the 100 mg/kg dose level. Teratogenic effects included: reduced or irregular ossification in the skull, jaw, spine, ribs, tibia and bones of the paws; fontanel, rib and hindlimb deformities; corneal opacity; and absent hindlimb phalanges. Animal models showed that angiogenesis, VEGF and VEGFR2 were involved in key aspects of female reproduction, embryo fetal development, and postnatal development.

Carcinogenicity: No studies have been conducted on the carcinogenicity of bevacizumab.

[PHARMACOKINETICS]

The pharmacokinetic parameters of bevacizumab were assessed by analyzing the total serum bevacizumab concentration (i.e., the assay could not distinguish between free bevacizumab and VEGF-bound bevacizumab). The pharmacokinetic data for bevacizumab are available from ten clinical trials in patients with solid tumours. In all clinical trials, bevacizumab was administered as an IV infusion. The rate of infusion was based on tolerability, with an initial infusion duration of 90 minutes. The pharmacokinetics of bevacizumab was linear at doses ranging from 1 to 10 mg/kg.

Absorption

Not Applicable.

Distribution

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

Metabolism

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

Binding of the IgG to the FcRn receptor results in protection from cellular metabolism and the long terminal half-life.

Elimination

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

Pharmacokinetics in special populations

The population pharmacokinetics were analyzed in adult and pediatric patients 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 children, adolescents and young adults (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 volume of distribution of bevacizumab were comparable between paediatric and young adult patients when normalized by body weight, with exposure trending lower as body weight decreased. Age was not associated with the pharmacokinetics of bevacizumab when body weight was taken into account.

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

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

Pharmacokinetics in Chinese patients

BP20689 was a phase I study on the safety and pharmacokinetic characteristics of bevacizumab in Chinese patients with advanced malignant tumors. Bevacizumab was evaluated at three dose levels (5mg/kg, 10mg/kg, and 15mg/kg). A total of 39 subjects participated in the trial.

The results showed that the pharmacokinetics of bevacizumab was linear in the range of 5 - 15mg / kg.

The pharmacokinetic parameters of bevacizumab after multiple administration were similar to those of single administration. The mean ratio of clearance rate, central distribution volume and steady-state distribution volume between multiple administration and single administration were 0.85, 1.01 and 1.21 with 5mg/kg, respectively; 0.97, 1.01 and 1.02 with 10mg/kg, respectively; 1.01, 1.01 and 1.01 with 15mg/kg, respectively.

In this study, serum PK parameters of bevacizumab in Chinese subjects, after repeated administration at 5mg/kg and 10mg/kg were closely to those obtained in the phase I study (AVF0737g) at 3mg/kg and 10mg/kg conducted in the United States (Table 16).

Table 16: Comparison of PK results between western subjects (AVF0737g) and Chinese subjects (BP20689)

Studies	Dose (mg/kg)	Clearance (ml/day/kg)	Central distribution volume (ml/kg)
America AVF0737g	3	1.65	41.4
	10	2.75	43.5
China BP20689	5	3.14	41.1
	10	3.16	41.0

No racial difference was found in bevacizumab according to the comparison of the results of this pharmacokinetic study and the results of overseas clinical trials.

[STORAGE]

Do not use this medicine after the expiry date which is stated on the outer carton and on the vial label after the abbreviation EXP.
Store and distribute refrigerated at 2°C to 8°C in the original carton in order to protect from light.

Do not freeze and shake the vial or carton.

Bevacizumab does not contain any antimicrobial preservatives, so care must be taken to ensure the sterility of the prepared solution.
Bevacizumab should be prepared using aseptic technique to ensure the sterility of the prepared solution, as the product contains no preservatives.

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.

[NATURE AND CONTENTS OF CONTAINER]

Neutral borosilicate glass tube-type vial for injection, 1 vial / small box.

[SHELF LIFE]

24 months

[APPROVED NUMBER]

[MARKETING AUTHORISATION HOLDER]

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