AUSTRALIAN PRODUCT INFORMATION – ZIRABEV® (BEVACIZUMAB)

1. NAME OF THE MEDICINE

Bevacizumab

ZIRABEV is a biosimilar medicine to Avastin®. The evidence for comparability supports the use of ZIRABEV for the listed indications.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Bevacizumab is an immunoglobulin G (IgG) composed of two identical light chains, consisting of 214 amino acid residues and two 453 residue heavy chains containing an N-linked oligosaccharide and has a molecular weight of approximately 149,000 daltons. Bevacizumab is a recombinant humanised monoclonal antibody produced by DNA technology in Chinese Hamster Ovary cells.

Bevacizumab is available in 100 mg and 400 mg single dose vials containing 4 mL and 16 mL, respectively, of bevacizumab (25 mg/mL).

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

3. PHARMACEUTICAL FORM

Concentrated solution for injection.

Bevacizumab is a clear to slightly opalescent, colourless to pale brown, sterile solution for intravenous (IV) infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Metastatic Colorectal Cancer

ZIRABEV (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of patients with metastatic colorectal cancer.

Locally recurrent or metastatic Breast Cancer

ZIRABEV (bevacizumab) in combination with paclitaxel is indicated for the first-line treatment of metastatic breast cancer in patients in whom an anthracycline-based therapy is contraindicated. (see Section 5.1 Pharmacodynamic properties – Clinical trials).

Advanced, metastatic or recurrent non-squamous Non-Small Cell Lung Cancer (NSCLC)

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

Advanced and/or metastatic Renal Cell Cancer

ZIRABEV (bevacizumab) in combination with interferon alfa-2a is indicated for treatment of patients with advanced and/or metastatic renal cell cancer.

Grade IV Glioma

ZIRABEV (bevacizumab) as a single agent, is indicated for the treatment of patients with Grade IV glioma after relapse or disease progression after standard therapy, including chemotherapy.

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

ZIRABEV (bevacizumab) in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Recurrent Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

ZIRABEV (bevacizumab), in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, is indicated for the treatment of patients with first recurrence of **platinum-sensitive**, epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior bevacizumab or other VEGF-targeted angiogenesis inhibitors.

ZIRABEV (bevacizumab) in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin is indicated for the treatment of patients with recurrent, **platinum-resistant** epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received no more than two prior chemotherapy regimens, and have not received any prior anti-angiogenic therapy including bevacizumab.

Cervical Cancer

ZIRABEV (bevacizumab) in combination with paclitaxel and cisplatin is indicated for the treatment of persistent, recurrent or metastatic carcinoma of the cervix. ZIRABEV (bevacizumab) in combination with paclitaxel and topotecan is an acceptable alternative where cisplatin is not tolerated or not indicated.

4.2 Dose and method of administration

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

ZIRABEV should be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products.

Dosage

Metastatic Colorectal Cancer

The recommended dose of ZIRABEV, administered as an IV infusion, is as follows;

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

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

Locally recurrent or metastatic Breast Cancer

The recommended dose of ZIRABEV is 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an IV infusion.

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

Advanced, metastatic or recurrent non-squamous Non-Small Cell Lung Cancer

The recommended dose of ZIRABEV in combination with carboplatin and paclitaxel is 15 mg/kg of body weight given once every 3 weeks as an IV infusion.

ZIRABEVis administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by ZIRABEV as a single agent until disease progression.

Advanced and/or metastatic Renal Cell Cancer

The recommended dose of is ZIRABEV 10 mg/kg given once every 2 weeks as an IV infusion. It is recommended that ZIRABEV treatment be continued until progression of the underlying disease.

ZIRABEV should be given in combination with IFN alfa-2a (Roferon-A®). The recommended IFN alfa-2a dose is 9 MIU three times a week, however, if 9 MIU is not tolerated, the dosage may be reduced to 6 MIU and further to 3 MIU three times a week (see Section 5.1 Pharmacodynamic properties – Clinical trials). Please also refer to the Roferon-A Product Information.

Grade IV Glioma

The recommended dose of ZIRABEV is 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an IV infusion.

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

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

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

First line treatment

15 mg/kg of body weight given once every 3 weeks in combination with carboplatin and paclitaxel for up to 6 cycles of treatment, followed by continued use of ZIRABEV as single agent.

It is recommended that ZIRABEV treatment be continued for a total of 15 months therapy or until disease progression, whichever occurs earlier.

Treatment of recurrent disease

Platinum sensitive

15 mg/kg of body weight given once every 3 weeks in combination with carboplatin and paclitaxel for 6 cycles (up to 8 cycles) followed by continued use of ZIRABEV as a single agent until disease progression.

Alternatively, 15 mg/kg of body weight given once every 3 weeks in combination with carboplatin and gemcitabine for 6 cycles (up to 10 cycles), followed by continued use of ZIRABEV as single agent until disease progression.

Platinum resistant

10 mg/kg body weight given once every 2 weeks when administered in combination with one of the following agents – paclitaxel or topotecan (given weekly) or pegylated liposomal doxorubicin. Alternatively, 15 mg/kg every 3 weeks when administered in combination with topotecan given on days 1-5, every 3 weeks. (See Section 5.1 Pharmacodynamic properties – Clinical trials Study MO22224 for descriptions of the chemotherapy regimens).

It is recommended that treatment be continued until disease progression.

Cervical Cancer

ZIRABEV is administered in combination with paclitaxel and cisplatin or, if cisplatin is not tolerated or not indicated, paclitaxel and topotecan (see Section 5.1 Pharmacodynamic properties – Clinical trials, study GOG-0240 for further details on the chemotherapy regimens).

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

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

Preparing the Infusion

ZIRABEV should be prepared by a healthcare professional using aseptic technique. Withdraw the necessary amount of ZIRABEV and dilute to the required administration volume with 0.9% sodium chloride solution. The concentration of the final ZIRABEV solution should be kept within the range of 1.4-16.5 mg/mL.

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

ZIRABEV infusions should not be administered or mixed with dextrose or glucose solutions.

Method of Administration

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

Do not administer as an intravenous push or bolus.

ZIRABEV is not formulated for intravitreal use *(*see Section 4.4 Special warnings and precautions for use - Severe Eye Infections Following Compounding for Unapproved Intravitreal Use).

Dosage reduction

Dose reduction of ZIRABEV for adverse reactions is not recommended. If indicated, ZIRABEV should either be discontinued or temporarily suspended (see Section 4.4 Special warnings and precautions for use)**.**

Special Dosage Instructions

Children and adolescents: The safety and efficacy of ZIRABEV in patients under the age of 18 years have not been established.

Elderly: No dose adjustment is required in the elderly.

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

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

4.3 Contraindications

ZIRABEV is contraindicated in patients with:

- known hypersensitivity to any components of the product; Chinese hamster ovary cell products or other recombinant human or humanised antibodies

4.4 Special warnings and precautions for use

Gastrointestinal Perforations and Fistulae

Patients may be at increased risk for the development of gastrointestinal (GI) perforation and gallbladder perforation when treated with bevacizumab. Bevacizumab should be permanently discontinued in patients who develop GI perforation. Patients treated with

bevacizumab for persistent, recurrent, or metastatic cervical cancer may be at increased risk of fistulae between the vagina and any part of the GI tract (GI-vaginal fistulae).

Bevacizumab has been associated with serious cases of GI perforation. GI perforations have been reported in clinical trials with an incidence of < 1% in patients with metastatic breast cancer or NSCLC, up to 2% in patients with metastatic colorectal cancer or ovarian cancer, and up to 2.7% in patients with metastatic colorectal cancer (including GI fistula and abscess). Cases of GI perforations have also been observed in patients with relapsed glioblastoma. Fatal outcome was reported in approximately a third of serious cases of GI perforations, which represents between 0.2% - 1% of all bevacizumab treated patients.

Patients treated for recurrent platinum-resistant ovarian cancer should not have a history or symptoms of bowel obstruction, abdominal fistulae or clinical or radiological evidence of recto- sigmoid involvement. Patient eligibility in the pivotal study MO22224 was also limited to those with two or fewer prior chemotherapy regimens.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (Study GOG-0240), GI perforations (all Grades) were reported in 3.2% of patients, all of whom had a history of prior pelvic radiation. The incidence of GI-vaginal fistulae was 8.3% in bevacizumab treated patients and 0.9% in control patients, all of whom had a history of prior pelvic radiation. Patients who develop GI-vaginal fistulae may also have bowel obstructions and require surgical intervention as well as diverting ostomies.

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

Hypertension

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

In most cases hypertension was controlled adequately using standard anti-hypertensive treatment appropriate for the individual situation of the affected patient. 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 Section 4.8 Adverse effects - Post-marketing experience).

An increased incidence of hypertension (all grades) of up to 42.1% has been observed in patients treated with bevacizumab compared with up to 14% in the comparator arm. In clinical

trials across all indications the overall incidence of Grade 3-4 hypertension 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 compared to up to 0.2% patients treated with the same chemotherapy alone.

Hypertension was generally treated with oral anti-hypertensives such as angiotensin-converting enzyme inhibitors, diuretics and calcium-channel blockers. It rarely resulted in discontinuation of bevacizumab treatment or hospitalisation. The use of diuretics to manage hypertension is not advised in patients who receive a cisplatin-based chemotherapy regimen.

Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal (see Section 4.8 Adverse Effects - Post-marketing experience). The risk of bevacizumab associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy.

Wound Healing

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

Across metastatic colorectal cancer clinical trials there was no increased risk of post-operative bleeding or wound healing complications observed in patients who underwent major surgery between 28-60 days prior to starting bevacizumab therapy. An increased incidence of post-operative bleeding or wound healing complications 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, including anastomotic complications, have been reported, some of which had a fatal outcome.

In locally recurrent and metastatic breast cancer, National Cancer Institute-Common Toxicity Criteria (NCI-CTC) 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 Study AVF3708g, patients with relapsed GBM, the incidence of post-operative wound healing complications (craniotomy site wound dehiscence and cerebrospinal fluid leak) was 3.6% in patients treated with single-agent bevacizumab and 1.3% in patients treated with bevacizumab and irinotecan.

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

Thromboembolism

Arterial thromboembolic events

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

In clinical trials, the overall incidence ranged up to 5.9% in the bevacizumab containing arms compared with up to 1.7% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving bevacizumab in combination with chemotherapy compared to 0.5% of patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischaemic attacks) were reported in up to 2.3% of bevacizumab treated patients versus 0.5% of patients in the control group. Myocardial infarction was reported in 1.4% of bevacizumab treated versus 0.7% of patients in the observed control group. In the uncontrolled study AVF3708g, in patients with relapsed GBM, arterial thromboembolic events were observed in 6.3% (5/79) of patients who received bevacizumab in combination with irinotecan compared to 4.8% (4/84) of patients who received bevacizumab alone. Bevacizumab is approved for the treatment of relapsed GBM as a single agent. Bevacizumab, in combination with fluoropyrimidine-based chemotherapy (5-fluorouracil ± irinotecan), is indicated only for the treatment of patients with metastatic colorectal cancer.

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

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

Venous thromboembolic events

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

Patients may be at risk of developing venous thromboembolic events, including pulmonary embolism under bevacizumab treatment. Patients treated with bevacizumab for persistent, recurrent, or metastatic cervical cancer may be at increased risk of venous thromboembolic events, compared to patients receiving chemotherapy alone.

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

Grade 3-5 venous thromboembolic events have been reported in up to 10.6% of patients treated with chemotherapy plus bevacizumab compared with up to 5.4% in patients with chemotherapy alone. Patients who have experienced a venous thromboembolic event may be at higher risk for a recurrence if they receive bevacizumab in combination with chemotherapy versus chemotherapy alone.

Haemorrhage

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

In clinical trials across all indications the overall incidence of NCI-CTC Grade 3-5 bleeding events ranged from 0.4% to 6.9% in bevacizumab treated patients, compared to 0 to 4.5% of patients in the chemotherapy control group. Haemorrhagic events observed in bevacizumab clinical trials were predominantly tumour-associated haemorrhage and minor mucocutaneous haemorrhage (e.g. epistaxis).

Patients with untreated central nervous system (CNS) metastases have been routinely excluded from clinical studies with bevacizumab, based on imaging procedures or signs and symptoms. However, 2 studies of bevacizumab in ovarian cancer provide a comparison with standard carboplatin/paclitaxel therapy of the incidence of CNS and non-CNS haemorrhage in patients without cerebral metastases. In Study GOG-0218, three patients who received extended treatment with bevacizumab developed CNS haemorrhage, with 1 death, and the same number in the bevacizumab arm of Study BO17707, also with 1 death. No CNS haemorrhage occurred in the control arms. Non-CNS haemorrhages were observed in Study GOG-0218 in 15.9% of control patients vs. 35.7% and 37.0% in the short and extended duration bevacizumab arms; in B017707 they were observed in 11% of control patients and 39.4% of the bevacizumabtreated patients. Most of the non- CNS haemorrhages were Grade 3 or less (GOG-0218: three events in the bevacizumab arm were Grade 4; B017707: one patient in the bevacizumab arm had a Grade 4 event and 2 patients in the control arm had a Grade 4 or higher event, one Grade 4 event and one Grade 5 event). In a third study of ovarian cancer (MO22224) one patient in the CT + bevacizumab arm experienced a Grade 4 GI haemorrhage which was ongoing at the time of death, and one patient who had crossed over to bevacizumab monotherapy died from a Grade 5 GI haemorrhage.

Patients should be monitored for signs and symptoms of CNS bleeding, and bevacizumab treatment discontinued in case of intracranial bleeding.

There is no information on the safety profile of bevacizumab in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting bevacizumab therapy, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. However, patients who developed venous thrombosis while receiving bevacizumab therapy did not appear to have an increased rate of Grade 3 or above bleeding when treated with full dose of warfarin and bevacizumab concomitantly.

Tumour-associated haemorrhage

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

with predominant squamous cell histology were excluded from subsequent studies, while patients with unknown tumour histology were included.

In patients with NSCLC excluding predominant squamous histology, all grade events were seen with a frequency of up to 9% when treated with bevacizumab plus chemotherapy compared with 5% in the patients treated with chemotherapy alone. Grade 3-5 events have been observed in up to 2.3% of patients treated with 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.

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

Tumour-associated haemorrhages have also been seen rarely in other tumour types and locations and include cases of CNS bleeding in patients with CNS metastases and glioblastoma (GBM). 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 2 subsequent studies in patients with treated brain metastases (approx. 800 patients treated with bevacizumab), 1 case of Grade 2 CNS haemorrhage was reported. One patient in the CT + bevacizumab arm of the recurrent platinum resistant ovarian cancer study MO22224 experienced a Grade 3 haemorrhagic ascites which subsequently resolved.

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

Mucocutaneous haemorrhage

Mucocutaneous haemorrhages were seen in up to 50% of patients treated with bevacizumab, across all bevacizumab clinical trials. These were most commonly NCI-CTC Grade 1 epistaxis that lasted < 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous haemorrhage (e.g. epistaxis) may be dose-dependent. There have been less common events of minor mucocutaneous haemorrhage in other locations such as gingival bleeding or vaginal bleeding.

Pulmonary haemorrhage/haemoptysis

Patients with NSCLC treated with bevacizumab may be at risk for serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis. Patients with recent pulmonary haemorrhage/haemoptysis (> $^1/_2$ teaspoon red blood) should not be treated with bevacizumab.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been rare reports of bevacizumab treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephalopathy Syndrome (PRES) (see Section 4.8 Adverse effects - Post-marketing experience), a rare neurological 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.

Two confirmed cases (0.8%) of PRES were reported in Study AVF4095g (OCEANS). Symptoms usually resolved or improved within days, although some patients experienced neurologic sequelae.

Two confirmed cases of PRES were reported in Study MO22224 (AURELIA). One case occurred during concurrent administration of CT + bevacizumab and the other after cross-over from CT to bevacizumab monotherapy.

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.

Proteinuria

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence suggesting that all Grade proteinuria may be dose-dependent. Testing for proteinuria is recommended prior to the start of bevacizumab therapy. In most clinical studies urine protein levels of ≥ 2 g/24 h led to the holding of bevacizumab until recovery to < 2 g/24 h.

In clinical trials, the incidence of proteinuria was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone. Grade 4 proteinuria was common in patients treated with bevacizumab.

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. In the event of nephrotic syndrome or isolated Grade 4 proteinuria, bevacizumab should be permanently discontinued.

Congestive Heart Failure

Caution should be exercised when treating patients with clinically significant cardiovascular disease or pre-existing congestive heart failure (CHF).

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

Events consistent with CHF were reported in clinical trials in all cancer indications studied to date. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation. 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 phase III studies 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. Most patients who developed CHF during mBC trials showed improved symptoms and/or left ventricular function following appropriate medical therapy.

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

An increased incidence of CHF has been observed in a phase III clinical trial of patients with diffuse large B-cell lymphoma when receiving bevacizumab with a cumulative doxorubicin dose greater than 300 mg/m2. This 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.

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 (e.g. bevacizumab with platinum-or taxane based chemotherapies); (see Section 4.5 Interactions with other medicines and other forms of interactions).

Non-GI Fistulae

Patients may be at increased risk for the development of fistulae when treated with bevacizumab. bevacizumab use has been associated with serious cases of fistulae including events resulting in death. From a clinical trial in patients with persistent, recurrent or metastatic cervical cancer (GOG- 0240), 1.8% of bevacizumab treated patients and 1.4% of control patients were reported to have had non-gastrointestinal vaginal, vesical, or female genital tract fistulae.

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

Events were reported at various time points during treatment ranging from one week to greater than 1 year from initiation of bevacizumab, with most events occurring within the first 6 months of therapy. Permanently discontinue bevacizumab in patients with tracheo-oesophageal fistula or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

Hypersensitivity Reactions, Infusion Reactions

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

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.

Severe Eye Infections Following Compounding for Unapproved Intravitreal Use

Individual cases and clusters of serious ocular adverse events have been reported (including infectious endophthalmitis and other ocular inflammatory conditions) following unapproved intravitreal use of bevacizumab compounded from vials approved for intravenous administration in cancer patients. Some of these events have resulted in various degrees of visual loss, including permanent blindness (see Section 4.8 Adverse effects - Post-marketing experience).

Osteonecrosis of the Jaw (ONJ)

Cases of ONJ have been reported in cancer patients treated with bevacizumab (see Section 4.8 Adverse effects - Post-marketing experience). Most had received prior or concomitant intravenous bisphosphonates, for which ONJ is an identified risk. Invasive dental procedures are also an identified risk factor. A dental examination and appropriate preventive dentistry should be considered prior to starting bevacizumab.

Use in hepatic impairment

See Section 5.2 Pharmacokinetic properties - Pharmacokinetics in Special Populations.

Use in renal impairment

See Section 5.2 Pharmacokinetic properties - Pharmacokinetics in Special Populations.

Use in the elderly

In randomised clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic events including cerebrovascular accidents, transient ischaemic attacks and myocardial infarction, as compared to those aged ≤ 65 years when treated with bevacizumab. 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 study MO22224 alopecia, mucosal inflammation, peripheral sensory neuropathy, proteinuria and hypertension were observed at a higher incidence in elderly patients (≥ 65 years) receiving CT + bevacizumab compared to those aged < 65 years treated with CT + bevacizumab. Serious adverse events also occurred at a higher incidence in patients ≥ 65 years treated with CT + bevacizumab (38.6%) compared to patients < 65 years (26.6%).

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

Paediatric use

Bevacizumab is not approved for use in patients under the age of 18 years. The safety and effectiveness of bevacizumab in this population have not been established. Addition of bevacizumab to standard of care did not demonstrate clinical benefit in paediatric patients in two phase II clinical trials: one in paediatric high grade glioma and one in paediatric metastatic rhabdomyosarcoma or non- rhabdomyosarcoma soft tissue sarcoma. In published reports, cases of osteonecrosis at sites other than the jaw have been observed in patients under the age of 18 years exposed to bevacizumab.

In a 26 week pre-clinical study in cynomolgus monkeys, physeal dysplasia was observed in young animals with open growth plates, at bevacizumab average serum concentrations below the expected human therapeutic average serum concentrations.

Also see Section 5.2 Pharmacokinetic properties - Pharmacokinetics in Special Populations.

Effects on laboratory tests

See Section 4.8 Adverse effects – Laboratory Abnormalities.

4.5 Interactions with other medicines and other forms of interactions

Effect of antineoplastic agents on bevacizumab pharmacokinetics

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

Effect of bevacizumab on the pharmacokinetics of other antineoplastic agents

Results from a drug-drug interaction study, AVF3135g, demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan and its active metabolite SN38.

Results from study NP18587 demonstrated no significant effect of bevacizumab on the pharmacokinetic of capecitabine and its metabolites, and on the pharmacokinetics of oxaliplatin, as determined by measurement of free and total platinum.

Results from study B017705 demonstrated no significant effect of bevacizumab on the pharmacokinetics of IFN alfa-2a.

Combination of bevacizumab and sunitinib malate

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

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

Combination of bevacizumab with pegylated liposomal doxorubicin (PLD), platinum or taxane-based chemotherapies

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 (eg bevacizumab with platinum- or taxane-based chemotherapies). Bevacizumab may also exacerbate other adverse reactions commonly seen with chemotherapy when combined with chemotherapeutic agents (see Section 4.8 Adverse effects).

Radiotherapy

The safety and efficacy of concomitant administration of radiotherapy and bevacizumab have not been established.

4.6 Fertility, pregnancy and lactation

Effects on fertility

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

No specific studies in animals have been performed to evaluate the effect of bevacizumab on fertility. No adverse effect on the male reproductive organ was observed in repeat dose toxicity studies in cynomolgus monkeys, but inhibition of ovarian function was observed in females. This was characterised by decreases in ovarian and/or uterine weight and the number of corpora lutea, a reduction in endometrial proliferation and an inhibition of follicular maturation in cynomolgus monkeys treated with bevacizumab. The lowest dose tested in the 26 week study (2 mg/kg weekly which corresponds to 0.6-fold the human therapeutic dose based on AUC) caused a reduction in uterine weight, however the reduction was not statistically significant. In rabbits, administration of 50 mg/kg of bevacizumab IV for 3 or 4 doses every 4 days resulted in decreases in ovarian and/or uterine weight and number of corpora lutea. The changes in both monkeys and rabbits were reversible upon cessation of treatment.

The incidence of new cases of ovarian failure (defined as amenorrhoea lasting 3 or more months, FSH level ≥30 mIU/mL and a negative serum β-HCG pregnancy test) was evaluated in a sub- study of 295 premenopausal women, treated with or without bevacizumab in adjuvant colon cancer therapy. New cases of ovarian failure were reported more frequently in patients receiving bevacizumab (39% in the bevacizumab group compared to 2.6% in the control). After discontinuation of bevacizumab, ovarian function recovered in a majority of women. Long term effects of treatment with bevacizumab on fertility are unknown, however a higher rate of long-term amenorrhoea following bevacizumab therapy was observed in patients <40 years (40% amenorrhoeic at 24 months after bevacizumab treatment compared to 6% in the control group).

Use in pregnancy – Pregnancy Category D

There are no adequate and well-controlled studies in pregnant women. IgGs are known to cross the placental barrier, and bevacizumab may inhibit angiogenesis in the foetus. Angiogenesis has been shown to be critically important to foetal development. The inhibition of angiogenesis following administration of bevacizumab could result in an adverse outcome of pregnancy. Therefore, bevacizumab should not be used during pregnancy. In the post-marketing setting, cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see Section 4.8 Adverse Effects - Post-marketing experience).

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

Bevacizumab has been shown to be embryotoxic and teratogenic when administered to rabbits. Observed effects included decreases in foetal body weights, an increased number of foetal resorptions and an increased incidence of specific gross and skeletal foetal alterations. Adverse foetal outcomes were observed at all tested doses. At the lowest dose tested, maternal serum AUC values were about 0.7-fold those observed in humans at the recommended clinical dose.

Use in lactation

Immunoglobulins are excreted in milk, although there are no data specifically for bevacizumab excretion in milk. Since bevacizumab could harm infant growth and development, women should be advised to discontinue breastfeeding during bevacizumab therapy and not to breast feed for at least 6 months following the last dose of bevacizumab.

4.7 Effects on ability to drive and use machines

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

4.8 Adverse effects (undesirable effects)

Experience from Clinical Trials

Clinical trials have been conducted in approximately 5,500 patients with various malignancies treated with bevacizumab, predominantly in combination with chemotherapy. The safety profile from the clinical trial population is presented in this section.

The most serious adverse drug reactions were:

- Gastrointestinal Perforations (see Section 4.4 Special warnings and precautions for use)
- Haemorrhage including pulmonary haemorrhage/haemoptysis, which is more common in NSCLC patients (see Section 4.4 Special warnings and precautions for

use)

- Arterial and venous thromboembolism (see Section 4.4 Special warnings and precautions for use)

Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with bevacizumab therapy are likely to be dose-dependent (see Section 4.4 Special warnings and precautions for use).

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

Table 1 lists adverse drug reactions associated with the use of bevacizumab in combination with different chemotherapy regimens in multiple indications. These reactions had occurred either with at least a 2% difference compared to the control arm (NCI-CTC Grade 3-5 reactions) or with at least a 10% difference compared to the control arm (NCI-CTC Grade 1-5 reactions), in at least one of the major clinical trials. The adverse drug reactions listed in the table below fall into the following categories: Very Common (≥ 10%) and Common (≥ 1%-< 10%). Adverse drug reactions have been included in the appropriate category according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping adverse drug reactions are presented in order of decreasing seriousness. Some of the adverse reactions are reactions commonly seen with chemotherapy however bevacizumab may exacerbate these reactions when combined with chemotherapeutic agents. Examples include palmar-plantar erythrodysaesthesia syndrome with pegylated liposomal doxorubicin or capecitabine, peripheral sensory neuropathy with paclitaxel or oxaliplatin, and nail disorders or alopecia with paclitaxel.

Table 1 Very Common and Common Adverse Drug Reactions

System Organ Class (SOC)	**NCI-CTC Grade 3-5 Reactions (≥2% difference between the study arms in at least one clinical trial)**		**All Grade Reactions*** **(≥10% difference between the study arms in at least one clinical trial)**
	Very common	**Common**	**Very common**
Infections and infestations		Sepsis Abcess Cellulitis Infection	
Blood and the lymphatic systems disorders	Febrile neutropenia Leukopenia Neutropenia Thrombocytopenia	Anemia Lymphopenia	
Metabolism and nutrition disorders		Dehydration Hyponatremia	Anorexia Hypomagnesemia Hyponatremia

System Organ Class (SOC)	**NCI-CTC Grade 3-5 Reactions (≥2% difference between the study arms in at least one clinical trial)**		**All Grade Reactions*** **(≥10% difference between the study arms in at least one clinical trial)**
	Very common	**Common**	**Very common**
Nervous system disorders	Peripheral sensory neuropathy	Cerebrovascular accident Syncope Somnolence Headache	Dysgeusia Headache Dysarthria **Peripheral sensory neuropathy
Eye disorders			Eye disorder Lacrimation increased
Cardiac disorders		Cardiac failure congestive Supraventricular tachycardia	
Vascular disorders	Hypertension Venous thromboembolism	Thromboembolism (arterial) Deep vein thrombosis Hemorrhage	Hypertension
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism Dyspnea Hypoxia Epistaxis	Dyspnoea Epistaxis Rhinitis Cough
Gastrointestinal disorders	Diarrhea Nausea Vomiting Abdominal pain	Intestinal Perforation Ileus Intestinal obstruction Recto-vaginal fistulae*** Gastrointestinal disorder Stomatits Proctalgia	Constipation Stomatitis Rectal hemorrhage Diarrhoea
Endocrine disorders			Ovarian failure
Skin and subcutaneous tissue disorders		Palmar-plantar erythrodysaesthesia syndrome	Exfoliative dermatitis Dry skin Skin discolouration
Musculoskeletal, connective tissue and bone disorders		Muscular weakness Myalgia Arthralgia Back pain	Arthralgia
Renal and urinary disorders		Proteinuria Urinary Tract Infection	Proteinuria

System Organ Class (SOC)	NCI-CTC Grade 3-5 Reactions (≥2% difference between the study arms in at least one clinical trial)		All Grade Reactions* (≥10% difference between the study arms in at least one clinical trial)
	Very common	**Common**	**Very common**
General disorders and administration site conditions	Asthenia Fatigue	Pain Lethargy Mucosal Inflammation General physical health deterioration	Pyrexia Asthenia Pain Mucosal inflammation
Reproductive System and Breast		Pelvic pain	
Investigations			Weight decreased

*Only Grade 2-5 adverse events were collected in study MO22224

**Difference of ≥ 10% was observed in study MO22224

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

Laboratory Abnormalities

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

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

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

Post-marketing experience

Table 2: Adverse reactions reported in post-marketing setting

System Organ Class (SOC)	Reactions (frequency^)
Congenital, familial and genetic disorders	Cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see Section 4.4 Special warnings and precautions for use)
Nervous system disorders	Hypertensive encephalopathy (very rare**) (see Section 4.4 Special warnings and precautions for use) Posterior Reversible Encephalopathy Syndrome (rare***) (see Section 4.4 Special warnings and precautions for use)
Vascular disorders	Renal Thrombotic Microangiopathy, clinically manifested as proteinuria (not known). (See Section 4.4 Special warnings and precautions for use).

Respiratory, thoracic and mediastinal disorders	Nasal septum perforation (not known) Pulmonary hypertension (not known) Dysphonia (common[****])
Gastrointestinal disorders	Gastrointestinal ulcer (not known)
Hepatobiliary disorders	Gallbladder perforation (not known)
Immune system disorders	Hypersensitivity, infusion reactions; possibly associated with the following co- manifestations: dyspnoea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting
Eye disorders (reported from unapproved intravitreal use)	Infectious endophthalmitis[1,5] (some cases leading to permanent blindness) (not known) Intraocular inflammation[1,2] (some cases leading to permanent blindness) such as sterile endophthalmitis, uveitis, and vitritis (see Section 4.4 Special warnings and precautions for use) Retinal detachment (not known) Retinal pigment epithelial tear (not known) Intraocular pressure increased (not known) Intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage (not known) Conjunctival haemorrhage (not known)
Systemic events (reported from unapproved intravitreal use)	Increased risk for haemorrhagic stroke[1,2] (see Section 4.4 Special warnings and precautions for use) Increased risk for overall mortality[1,2,3] Increased risk for serious systemic adverse events, most of which resulted in hospitalization (adjusted risk ratio 1.29; 95% CI: 1.01, 1.66) (Incidence 24.1%; comparator 19.0%)[1,4]
Musculoskeletal and Connective Tissue disorders	Cases of osteonecrosis of the jaw (ONJ) have been observed in bevacizumab treated patients mainly in association with prior or concomitant use of bisphosphonates. Cases of osteonecrosis at sites other than the jaw, have been observed in bevacizumab treated paediatric patients (see Section 4.4 Special warnings and precautions for use, Paediatric Use)[6].
Infections and Infestations	Necrotising fasciitis, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation (rare) (see Section 4.4 Special warnings and precautions for use)

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

[1] As compared to an approved treatment in patients treated for wet age-related macular degeneration

[2] Gower et al. Adverse Event Rates Following Intravitreal Injection of bevacizumab or Lucentis for Treating Age-Related Macular Degeneration ARVO 2011, Poster 6644, Data on file

[3] Curtis LH, et al. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration. Arch Ophthalmol. 2010;128(10):1273-1279

[4] CATT Research Group, Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration. 10.1056/NEJMoa1102673

[5] One case reported extraocular extension of infection resulting in meningoencephalitis

[6] Osteonecrosis observed in paediatric population in non-company clinical trials was identified through post-marketing surveillance and has therefore been added to the post-marketing section as neither CTC grade nor reporting rate were available from published data.

** very rare (≤1/10,000)

*** rare (≥1/10,000 to <1/1,000)

**** common (≥1/100 to <1/10)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

The highest dose tested in humans (20 mg/kg body weight, IV) was associated with severe migraine in several patients.

Treatment of overdose should consist of general supportive measures.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

ZIRABEV is an antineoplastic agent containing the active ingredient, bevacizumab. Bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab contains human framework regions with antigen binding regions of a humanised murine antibody that binds to VEGF. Bevacizumab is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin and is purified by a process that includes specific viral inactivation and removal steps. Gentamicin is detectable in the final product at $\leq$ 0.35 ppm.

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

Clinical trials

Metastatic Colorectal Cancer

The safety and efficacy of bevacizumab in metastatic colorectal cancer were studied in two randomised, active-controlled clinical trials. Bevacizumab was combined with two chemotherapy regimens:

- **AVF2107g**: A weekly schedule of irinotecan/bolus fluorouracil/leucovorin† (IFL) for

a total of 4 weeks of each 6 week cycle

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

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

- **NO16966:** Bevacizumab 7.5 mg/kg of body weight every 3 weeks in combination with oral capecitabine and IV oxaliplatin (XELOX) or bevacizumab 5 mg/kg every 2 weeks in combination with leucovorin† plus fluorouracil bolus, followed by fluorouracil infusion, with IV oxaliplatin (FOLFOX-4).
- **E3200:** Bevacizumab 10 mg/kg of body weight every 2 weeks in combination with leucovorin† and fluorouracil bolus, followed by fluorouracil infusion, with IV oxaliplatin (FOLFOX- 4).

† The Australian Approved Name for leucovorin is folinic acid

Study 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 colorectal cancer. Eight hundred and thirteen patients were randomised to receive IFL plus placebo (Arm 1) or IFL plus bevacizumab (Arm 2), see Table 3. A third group of 110 patients received FU/LV plus 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 median age of patients was 60 years (range 21-88), 60% were male.

Table 3: Treatment regimens in study AVF2107g

	Treatment	Starting Dose	Schedule
Arm 1	Irinotecan Fluorouracil Folinic acid	125 mg/m^2 IV 500 mg/m^2 IV 20 mg/m^2 IV	Given once weekly for 4 weeks every 6 weeks
	Placebo	IV	Every 2 weeks
Arm 2	Irinotecan Fluorouracil Folinic acid	125 mg/m^2 IV 500 mg/m^2 IV 20 mg/m^2 IV	Given once weekly for 4 weeks every 6 weeks
	Bevacizumab	5 mg/kg IV	Every 2 weeks
Arm 3	Fluorouracil Folinic acid	500 mg/m^2 IV 500 mg/m^2 IV	Given once weekly for 6 weeks every 8 weeks
	Bevacizumab	5 mg/kg IV	Every 2 weeks

Fluorouracil: IV bolus injection immediately after folinic acid

Folinic acid: IV bolus injection (over 1- 2 minutes) immediately after each irinotecan dose

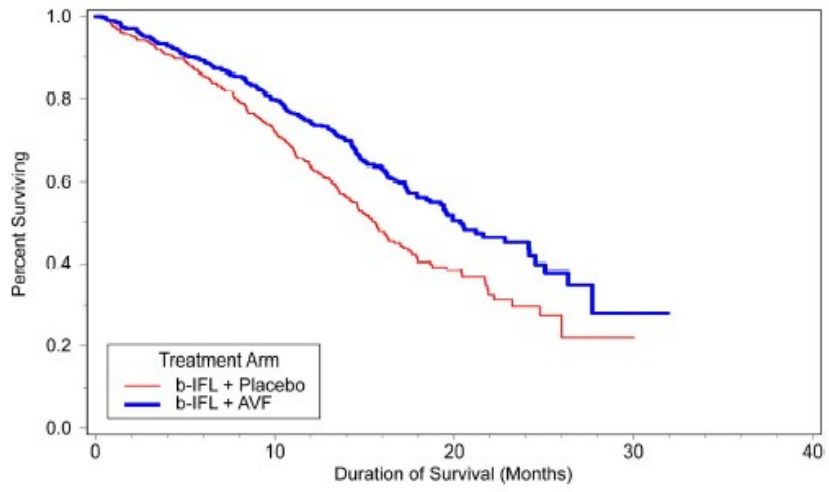
The primary efficacy endpoint of the trial was overall survival. At the time of data cut-off, 399 deaths had occurred in patients randomised to Arm 1 (n = 225) and Arm 2 (n = 174). The addition of bevacizumab to IFL resulted in a statistically significant increase in overall survival. Results are presented in Table 4 and Figure 1. The clinical benefit of , bevacizumab as measured by survival, progression-free survival and objective response, was seen in all pre-specified patient subgroups, see Figure 2.

Table 4: Efficacy results for study AVF2107g

	Arm 1 IFL plus placebo (*n* = 411)	**Arm 2 IFL plus bevacizumab[a] (*n* = 402)**	**Arm 3 FU/LV plus bevacizumab[a] (*n* = 110[b])**
Overall Survival			
Median (months)	15.6	20.3	18.3
Hazard ratio[c] (95% CI)	0.660 (0.54, 0.81)		
p-value (log rank)	0.00004		-
Progression-Free Survival			
Median (months)	6.2	10.6	8.8
Hazard ratio (95% CI)	0.54 (0.45, 0.66)		
p-value (log rank)	<0.0001		-
Overall Response Rate			
Rate (percent)	34.8	44.8	40.0
Between-arm difference (%) (95% CI)	10 (3.3, 16.7)		–
p-value (log rank)	0.0036		-
Duration of Response			
Median (months)	7.1	10.4	8.5
25–75 percentile (months)	4.7-11.8	6.7-15.0	5.5-11.9

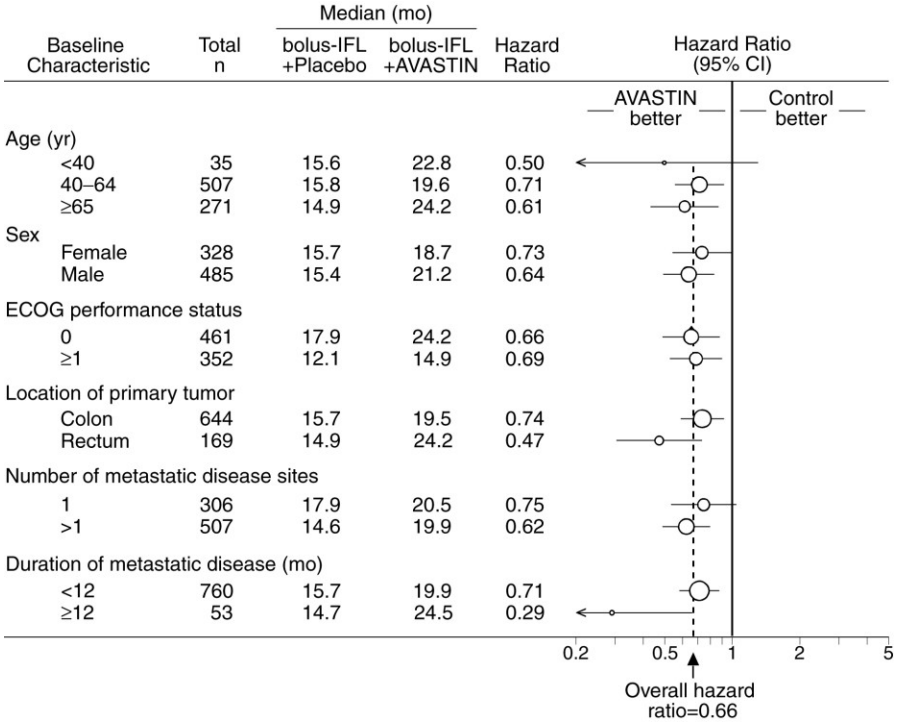
[a] 5 mg/kg every 2 weeks; [b] Recruitment stopped as per protocol; [c] Relative to control arm

Figure 1: Plot of Kaplan Meier estimates for survival in study AVF2107g



IFL =irinotecan/ fluorouracil/ leucovorin (folinic acid); AVF = bevacizumab

Figure 2: Duration of survival by baseline risk factor in study AVF2107g



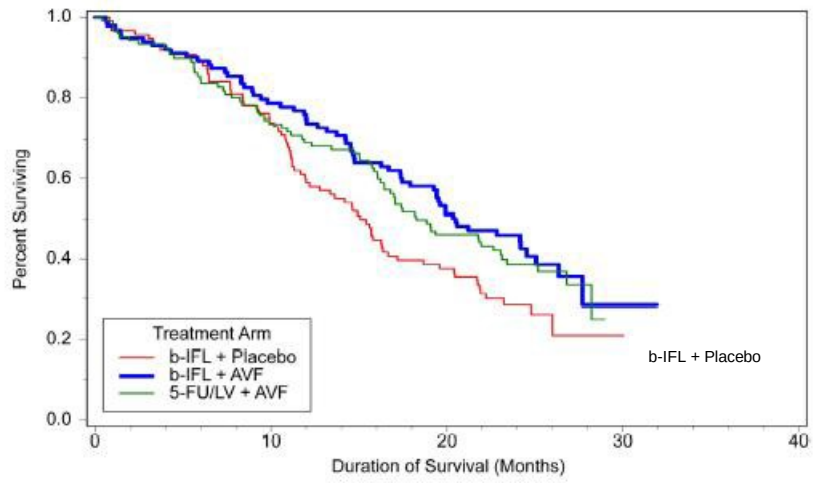
CI= interval; IFL= irinotecan/fluorouracil/ leucovorin (folinic acid);.

Hazard ratio <1 indicates a lower hazard of death in the IFL plus bevacizumab arm compared with the IFL plus placebo arm. Size of circle is proportional to the number of patients in the subgroup.

Confidence interval is indicated by the horizontal line.

Results for the 110 patients in Arm 3 were compared to the first 100 patients enrolled in Arm 1 and Arm 2. There was a trend towards prolonged survival in the bevacizumab plus FU/LV arm as compared to the IFL plus placebo arm in this subset of patients, see Figure 3. Although the results did not show a statistical difference, the results were consistently better for the bevacizumab plus FU/LV arm than for IFL plus placebo arm for all efficacy parameters measured.

Figure 3: Plot of Kaplan Meier Estimates for survival in study AVF2107g: Patients enrolled in Arm 3 and concurrently enrolled patients in Arms 1 and 2



IFL = irinotecan/ fluorouracil/ leucovorin (folinic acid); AVF = bevacizumab

Study AVF0780g

This was a phase II randomised, active-controlled, open-labelled clinical trial investigating bevacizumab in combination with FU/LV as first-line treatment of metastatic colorectal cancer. Seventy one patients were randomised to receive bolus FU/LV or FU/LV plus bevacizumab (5 mg/kg every 2 weeks). A third group of 33 patients received bolus FU/LV plus bevacizumab (10 mg/kg every 2 weeks). Patients were treated until disease progression. The median age was 64 years (range 23-85), 57% were male. The primary efficacy endpoints of the trial were objective response rate and progression-free survival. The addition of bevacizumab (5 mg/kg every two weeks) to FU/LV resulted in higher objective response rates, longer progression-free survival and a trend in longer survival, compared with FU/LV chemotherapy alone, see Table 5. This efficacy data is consistent with the results from study AVF2107g.

Table 5: Efficacy results for study AVF0780g

	FU/LV (*n* = 36)	**FU/LV plus bevacizumab[a] (*n* = 35)**	**FU/LV plus bevacizumab[b] (*n* = 33)**
Overall Survival			
Median (months)	13.6	17.7	15.2
Hazard ratio[c]	-	0.52	1.01
p-value (log-rank)	-	0.073	0.978
Progression-Free Survival			
Median (months)	5.2	9.0	7.2
Hazard ratio[c]	-	0.44	0.69
p-value (log-rank)	-	0.005	0.217
Overall Response Rate			
Rate[d] (percent) (95% CI)	16.7 (7.0-33.5)	40.0 (24.4-57.8)	24.2 (11.7-42.6)
p-value (log-rank)	-	0.03	0.43
Duration of Response			
Median (months)	NR	9.3	5.0
25–75 percentile (months)	5.5 - NR	6.1 - NR	3.8–7.8

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

Study 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 fluorouracil bolus, followed by fluorouracil infusional, with IV oxaliplatin (FOLFOX-4), administered on a 2 weekly schedule. The study contained two parts (see Table 6): 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 four study arms in Part II of the trial.

Table 6: Treatment Regimens in Study N016966

	Treatment	Starting Dose	Schedule
FOLFOX-4 or FOLFOX-4 + bevacizumab	Oxaliplatin Leucovorin† Fluorouracil	85 mg/m^2 IV 2 h 200 mg/m^2 IV 2 h 400 mg/m^2 IV bolus, 600 mg/ m^2 IV 22 h	Oxaliplatin on Day 1 Leucovorin† on Day 1 and 2 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 Capecitabine	130 mg/m^2 IV 2 h 1000 mg/m^2 oral bid	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, q 3 weeks
Fluorouracil: IV bolus injection immediately after leucovorin			

† The Australian Approved Name for leucovorin is folinic acid

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

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 (see Table 7).

Secondary PFS analyses, based on Independent Review Committee and 'on-treatment'-based response assessments, confirmed the significantly superior clinical benefit for patients treated with bevacizumab.

Table 7: Key efficacy results for the superiority analysis (ITT population, Study NO16966)

Endpoint (months)	**FOLFOX-4 or XELOX + Placebo (*n* = 701)**	**FOLFOX-4 or XELOX + bevacizumab (*n* = 699)**	***p* value**
Primary endpoint			
Median PFS^^	8.0	9.4	0.0023
Hazard ratio (97.5% CI)[a]	0.83 (0.72 - 0.95)		
Secondary endpoints			

Median PFS (on treatment)^^[b]	7.9	10.4	<0.0001
Hazard ratio (97.5% CI)	0.63 (0.52 - 0.75)		
Overall response rate (Investigator Assessment)^^	49.2%	46.5%	
Median overall survival^	19.9	21.2	0.0769
Hazard ratio (97.5% CI)	0.89 (0.76 - 1.03)		

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

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

[a] relative to control arm: [b] PFS on-treatment: based on investigator tumour assessments and death events that occurred no later than 28 days after the last confirmed intake of any study medication in the primary study treatment phase (5-FU, oxaliplatin, capecitabine, or bevacizumab/placebo, which ever was taken last)

Overall response rate was similar in the chemotherapy plus bevacizumab arm (46.5%) and in chemotherapy alone arm (49.2%).

Study ECOG E3200

This was a phase III randomised, active-controlled, open-label study investigating bevacizumab 10 mg/kg in combination with leucovorin with fluorouracil bolus and then 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 6 for Study 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 (see Table 8).

Table 8: Efficacy Results for Study E3200

	FOLFOX-4	**FOLFOX-4 + bevacizumab[a]**
Number of Patients	*292*	*293*
Overall Survival		
Median (months)	10.8	13.0
95% confidence interval	10.12 – 11.86	12.09 – 14.03
Hazard ratio[b] 95% confidence interval	0.751 (0.632, 0.893) (*p*-value = 0.0012)	
Progression-Free Survival		
Median (months)	4.5	7.5
Hazard ratio 95% confidence interval	0.518 (0.416, 0.646) (*p*-value < 0.0001)	
Objective Response Rate		
Rate	8.6 %	22.2 %
	(*p*-value < 0.0001)	

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

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

Adjuvant Colon Cancer

Study BO17920
This was a phase III randomised open-label, 3-arm study evaluating the efficacy and safety of bevacizumab administered at a dose equivalent to 2.5 mg/kg/week either every two weeks in combination with FOLFOX4, or every three weeks schedule in combination with XELOX versus FOLFOX4 alone as adjuvant chemotherapy in 3451 patients with high-risk stage II and stage III colon carcinoma.

More relapses and deaths due to disease progression were observed in both bevacizumab arms compared to the control arm. The primary objective of prolonging disease free survival (DFS) in patients with stage III colon cancer (n = 2867) by adding bevacizumab to either chemotherapy regimen was not met. The hazard ratios for DFS were 1.17 (95% CI: 0.98-1.39) for the FOLFOX4 + bevacizumab arm and 1.07 (95% CI: 0.90-1.28) for the XELOX + bevacizumab arm.

At the time of an exploratory interim analysis of overall survival in patients with stage III disease, 12.0% of FOLFOX4 (control arm) patients and 15.2-15.7% of patients in the two bevacizumab containing arms had died.

Bevacizumab is not indicated for adjuvant treatment of colon cancer.

Locally recurrent or metastatic Breast Cancer

(Note that the efficacy and safety of the combination of bevacizumab and paclitaxel have not been compared with anthracycline-based therapies for first-line therapy in metastatic breast cancer. The efficacy of the combination of bevacizumab and paclitaxel in second and third line treatment of metastatic breast cancer has not been demonstrated.)

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

Patients were randomised to paclitaxel alone (90 mg/m2 IV over 1 hour once weekly for three out of four weeks) or in combination with bevacizumab (10 mg/kg IV infusion every two weeks). Patients were to continue assigned study treatment until disease progression. In cases where patients discontinued chemotherapy prematurely, treatment with bevacizumab as a single agent was continued until disease progression. The primary endpoint was progression free survival (PFS), as assessed by investigators. In addition, an independent review of the primary endpoint was also conducted.

Of the 722 patients in the study, the majority of patients (90%) had HER2-negative disease. A small number of patients had HER-2 receptor status that was either unknown (8%) or positive (2%). Patients who were HER2-positive had either received previous treatment with

trastuzumab or were considered unsuitable for trastuzumab. The majority (65%) of patients had received adjuvant chemotherapy including 19% who had prior taxanes and 49% who had prior anthracyclines. The patient characteristics were similar between the study arms.

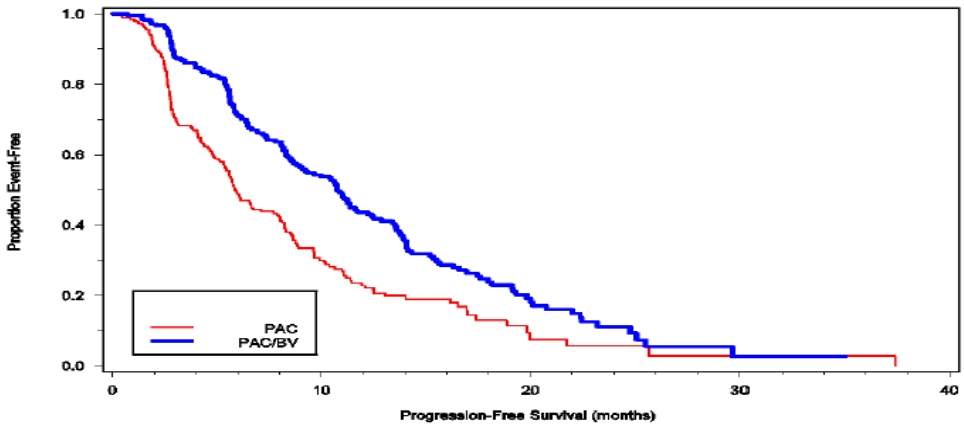
The results of this study are presented in Table 9 and Figure 4. The addition of bevacizumab to paclitaxel chemotherapy resulted in a significant reduction of risk of disease progression or death, as measured by PFS (HR = 0.42; p < 0.0001). The resulting median PFS in -bevacizumab containing arm was 11.4 months compared with 5.8 months in the control arm. The small improvement in overall survival was not statistically significant.

Table 9: Study E2100 Efficacy Results: Eligible Patients

Progression-Free Survival				
	Investigator Assessment^		**IRF Assessment**	
	Paclitaxel (*n* = 354)	Paclitaxel/bevacizumab (*n* = 368)	Paclitaxel (*n* = 354)	Paclitaxel/bevacizumab (*n* = 368)
Median PFS (months)	5.8	11.4	5.8	11.3
Hazard Ratio (95% CI)	0.421 (0.343 ; 0.516)		0.483 (0.385 ; 0.607)	
p-value	< 0.0001		< 0.0001	
Response Rates (for patients with measurable disease)				
	Investigator Assessment		IRF Assessment	
	Paclitaxel (*n* = 273)	Paclitaxel/bevacizumab (*n* = 252)	Paclitaxel (*n* = 243)	Paclitaxel/bevacizumab (*n* = 229)
% pts with objective response	23.4	48.0	22.2	49.8
p-value	< 0.0001		< 0.0001	
Overall Survival (Investigator assessment)				
	Paclitaxel (*n* = 354)		Paclitaxel/bevacizumab (*n* = 368)	
Median OS (months)	24.8		26.5	
Hazard Ratio (95% CI)	0.869 (0.722 ; 1.046)			
p-value	0.1374			

^ primary analysis; IRF = independent review facility

Figure 4: Kaplan-Meier curves for progression free survival in study E2100



The efficacy and safety of bevacizumab in combination with anthracycline-based therapies have not been studied for first-line therapy in metastatic breast cancer.

Advanced, metastatic or recurrent Non-Small Cell Lung Cancer

The safety and efficacy of bevacizumab in the first-line treatment of patients with non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology, was studied in addition to carboplatin/paclitaxel-based chemotherapy in study E4599 (n = 878). E4599 was an open-label, randomised, active-controlled, multicentre clinical trial evaluating bevacizumab as first-line treatment of patients with locally advanced (Stage IIIB with malignant pleural effusion), metastatic or recurrent NSCLC other than predominantly squamous cell histology.

Patients were randomised 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. Patients with predominant squamous histology (mixed cell type tumours only), central nervous system (CNS) metastasis, gross haemoptysis (≥ ½ tsp of red blood), clinically significant cardiovascular disease and medically uncontrolled hypertension were excluded. Other exclusion criteria were: therapeutic anticoagulation, regular use of aspirin (> 325 mg/day, NSAIDs or other agents known to inhibit platelet function, radiation therapy within 21 days of enrolment and major surgery within 28 days before enrolment.

Among 878 patients randomised to the two arms, the median age was 63, 46% were female, 43% were ≥ age 65, and 28% had ≥ 5% weight loss at study entry. 11% had recurrent disease and of the remaining 89% with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had Stage IV disease. 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.

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

The primary endpoint was overall survival (OS). The secondary endpoints, PFS (progression free survival) and ORR (overall response rate), were based on investigator assessment and were not independently verified.

Overall survival was statistically significantly higher for patients receiving bevacizumab + PC chemotherapy compared with those receiving PC alone. Results are presented in Table 10.

Table 10: Efficacy results for study 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

Hazard ratio		0.80 95% CI (0.69, 0.93)
p-value[a]		*p* = 0.003
Progression-Free Survival		
Median (months)	4.8	6.4
Hazard ratio		0.65 95% CI (0.56, 0.76)
p-value[a]		*p* < 0.0001
Overall Response Rate		
Rate (percent)	12.9	29.0
p-value[b]		*p* < 0.0001

[a]stratified logrank test; [b]stratified χ^2 test includes patients with measurable disease at baseline.

Advanced and/or metastatic Renal Cell Cancer

Study BO17705

BO17705 was a multicentre, randomised, double-blind phase III trial conducted to evaluate the efficacy and safety of bevacizumab in combination with interferon (IFN) alfa-2a (Roferon-A®) versus IFN alfa-2a alone as first-line treatment in metastatic renal cell cancer (mRCC). The 649 randomised patients (641 treated) had clear cell mRCC, Karnofsky Performance Status (KPS) of ≥ 70%, no CNS metastases and adequate organ function. IFN alfa-2a (9 MIU three times a week) plus bevacizumab (10mg/kg q2w) or placebo was given until disease progression. For patients who were unable to tolerate IFN alfa-2a treatment, treatment with bevacizumab was permitted to continue in the absence of progressive disease. A lower starting IFN alfa-2a dose (3 or 6 MIU) was permitted as long as the recommended 9MIU dose was reached within the first 2 weeks of treatment. If 9 MIU was not tolerated, IFN alfa-2a dosage reduction to a minimum of 3 MIU three times a week was also permitted. Patients were stratified according to country and Motzer score and the treatment arms were shown to be well balanced for the prognostic factors.

The primary endpoint was overall survival, with secondary endpoints for the study including progression free survival (PFS). The addition of bevacizumab to IFN alfa-2a significantly increased PFS and objective tumour response rate. These results have been confirmed through an independent radiological review. However, the increase in the primary endpoint of overall survival by 2 months was not significant (HR = 0.91). A high proportion of patients (approximately 63% IFN/placebo; 55% bevacizumab /IFN) received a variety of non-specified post-protocol anti-cancer therapies, including anti-neoplastic agents, which may have impacted the analysis of overall survival. The efficacy results are presented in Table 11.

Table 11: Efficacy Results for Study BO17705

	IFN + Placebo	**IFN + bevacizumab**
Number of Patients	*322*	*327*
Progression-Free Survival Median (months) Hazard ratio [95% CI]	5.4	10.2 0.63 [0.52; 0.75] (*p*-value < 0.0001)

Objective Response Rate (%) in Patients with Measurable Disease		
n	289	306
Response rate	12.8 %	31.4 %
	(*p*-value < 0.0001)	
Overall Survival		
Median (months) Hazard ratio [95% CI]	21.3	23.3
	0.91 [0.76; 1.10]	
	(*p*-value = 0.3360)	

Ninety seven patients in the IFN arm and 131 patients in the bevacizumab/IFN arm reduced the dose of IFN alfa-2a from 9 MIU to either 6 or 3 MIU, three times a week as pre-specified in the protocol.

Grade IV Glioma

Study AVF3708g

The efficacy and safety of bevacizumab as treatment for patients with glioblastoma (GBM) was studied in an open-label, multicentre, randomised, non-comparative study (AVF3708g).

Patients in first or second relapse after prior radiotherapy (completed at least 8 weeks prior to receiving bevacizumab) and temozolomide, were randomised (1:1) to receive bevacizumab (10mg/kg IV infusion every 2 weeks) or bevacizumab plus irinotecan (125 mg/m2 IV or 340 mg/m2 IV for patients on enzyme-inducing anti-epileptic drugs every 2 weeks) until disease progression or until unacceptable toxicity. The primary endpoints of the study were 6-month progression-free survival (PFS) and objective response rate (ORR) as assessed by an independent review facility. Other outcome measures were duration of PFS, duration of response and overall survival. Results are summarised in Table 12.

Table 12: Efficacy Results from Study AVF3708g

	Bevacizumab		Historical controls[#]
Number of patients	85		225
	IRF	Inv	-
Primary endpoints			
6-month progression-free survival (97.5% CI)	42.6% (29.6, 55.5)	43.6% (33.0, 54.3)	15% (p < 0.0001)
Objective Response Rate (ORR) (97.5% CI)	28.2% (18.5, 40.3)	41.2% (30.6, 52.3)	5% (p < 0.0001)
Secondary endpoints			
Progression-free survival (months) Median (95% CI)	4.2 (2.9, 5.8)	4.2 (3.0, 6.9)	2.1
Duration of objective response (months) Median (95% CI)	5.6 (3.0, 5.8)	8.1 (5.5, ^)	-
Overall survival (months)			
Median (95% CI)	9.3 (8.2, ^)	9.3 (8.2, ^)	5.7

ORR and progression were determined using modified Macdonald criteria; CI = confidence interval; Inv = Investigator's assessment; IRF = Independent Review Facility [#] protocol-defined statistical comparison with the integrated analysis of Wong et al(1999).[^] Upper limit of the CI could not be obtained

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

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer First-line Ovarian Cancer

Study GOG-0218

The GOG-0218 trial was a phase III multicentre, randomised, double-blind, placebo controlled, three arm study evaluating the effect of adding bevacizumab to an approved chemotherapy regimen (carboplatin and paclitaxel) in patients with optimally or sub-optimally debulked Stage III or Stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer. Patients had a Gynecologic Oncology Performance Status of 0-2 at baseline.

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

Carboplatin/Paclitaxel/Placebo (CPP) arm: Placebo in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles followed by placebo alone, for a total of 15 months of therapy.

Carboplatin/Paclitaxel/Bevacizumab (CPB15) arm: Five cycles of bevacizumab (15 mg/kg q3w) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles (

bevacizumab commenced at cycle 2 of chemotherapy) followed by placebo alone, for a total of 15 months of therapy.

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

The primary endpoint was progression-free survival (PFS) based on investigator's assessment of radiological scans. In addition, an independent review of the primary endpoint was also conducted.

The results of this study are summarised in Table 13 (the p-value boundary for primary treatment comparisons was 0.0116).

Table 13: Efficacy Results from Study GOG-0218

Progression-Free Survival						
	Investigator Assessment[1]			IRC Assessment		
	CPP (*n* = 625)	**CPB15** (*n* = 1248)[2]	**CPB15+** (*n* =1248)[2]	**CPP** (*n* = 625)	**CPB15** (*n* = 1248)[2]	**CPB15+** (*n* = 1248)[2]
Median PFS (months)	12.0	12.7	18.2	13.1	13.2	19.1
Hazard ratio (95% CI)[3]		0.842 [0.714, 0.993]	0.644 [0.541, 0.766]		0.941 [0.779, 1.138]	0.630 (0.513, 0.773)
p–value[4]		0.0204[5]	< 0.0001[5]		0.2663	< 0.0001
Objective Response Rate[6]						
	Investigator Assessment			IRC Assessment		
	CPP (*n* = 396)	**CPB15** (*n* = 393)	**CPB15+** (*n* = 403)	**CPP** (*n* = 474)	**CPB15** (*n* = 460)	**CPB15+** (*n* = 499)
% pts with objective response	63.4	66.2	66.0	68.8	75.4	77.4
p–value[4]		0.2341	0.2041		0.0106	0.0012

Overall Survival[7]			
	CPP (*n* = 625)	**CPB15** (*n* = 625)	**CPB15+** (*n* = 623)
Median OS (months)	40.6	38.8	43.8
Hazard Ratio (95% CI)[3]		1.07 (0.91, 1.25)	0.88 (0.75, 1.04)
p-value[4]		0.2197	0.0641

IRC: Independent Review Committee;

[1] primary PFS analysis;

[2] events prior to cycle 7 from the CPB15 and CPB15+ arms were pooled for the analysis;

[3] stratified hazard ratio relative to the control arm;

[4] one-sided log-rank p-value;

[5] subject to a p-value boundary of 0.0116;

[6] patients with measurable disease at baseline;

[7] final overall survival analysis performed when 46.9% of the patients had died

The trial met its primary objective of PFS improvement. Compared with patients treated with chemotherapy (carboplatin and paclitaxel) alone, patients who received first-line

bevacizumab at a dose of 15 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab alone had a clinically meaningful and statistically significant improvement in PFS.

Although there was an improvement in PFS for patients who received first-line bevacizumab in combination with chemotherapy and did not continue to receive bevacizumab alone, the improvement was not statistically significant compared with patients who received chemotherapy alone.

The incidence of patients with any Grade 5 adverse event (AE) was higher in patients in the bevacizumab treated arms (2.5% CPB15+ arm and 1.6% in the CPB15 arm vs. 0.7% in the CPP arm).

Recurrent Ovarian Cancer

GOG-0213

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

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

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

The primary efficacy endpoint was overall survival (OS). The main secondary efficacy endpoint was progression-free survival (PFS). Objective response rates (ORR) were also examined. Results are presented in Table 14.

Table 14: Efficacy results from study GOG-0213

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

p-value	0.0683	
Secondary Endpoints		
Progression-free survival (PFS)	**CP** (n = 336)	**CPB** (n = 337)
Median PFS (months)	10.2	13.8
Hazard ratio [95% CI]	0.613 (CI: 0.521, 0.721)	
p-value	< 0.0001	
Objective response rate	**CP**[c] (n = 286)	**CPB**[c] (n = 274)
No. (%) of pts with objective response (CR, PR)	159 (55.6%)	213 (77.7%)
p–value	< 0.0001	

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

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

[c]Intent-to-treat population with measureable disease at baseline

Treatment with bevacizumab at 15 mg/kg every 3 weeks in combination with chemotherapy (carboplatin+paclitaxel) for 6 and up to 8 cycles then followed by bevacizumab as a single agent resulted, when data were derived from eCRF, in a clinically meaningful and statistically significant improvement in OS compared to treatment with carboplatin+paclitaxel alone.

Study AVF4095g (OCEANS)

The safety and efficacy of bevacizumab as treatment for patients with platinum-sensitive (defined as greater than 6 months following previous platinum therapy), recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who have not received prior chemotherapy in the recurrent setting, or prior bevacizumab treatment or other VEGF-targeted angiogenesis inhibitors, were studied in a phase III randomized, double blind, placebo-controlled trial (AVF4095g). The study compared the effect of adding bevacizumab to a carboplatin and gemcitabine chemotherapy followed by bevacizumab as a single agent to progression versus carboplatin and gemcitabine alone.

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

- Carboplatin (AUC4 mg/mL/min, Day 1) and gemcitabine (1000 mg/m2 on Days 1 and 8) and concurrent placebo until disease progression or unacceptable toxicity.
- Carboplatin (AUC4 mg/mL/min, Day 1) and gemcitabine (1000 mg/m2 on Days 1 and 8) and concurrent bevacizumab (15 mg/kg every 3 weeks) until disease progression or unacceptable toxicity.

At randomisation, patients were stratified by platinum free interval (PFI) (recurrence 6-12 months from last platinum-based treatment vs recurrence > 12 months from last platinum-based treatment) and whether they had undergone cytoreductive surgery for recurrent disease.

The primary endpoint was progression-free survival (PFS) based on investigator assessment using RECIST criteria. Additional endpoints included objective response, duration of response, safety and overall survival. An independent review of the primary endpoint was also conducted. The results of this study are summarized in Table 15.

Table 15: Efficacy Results from Study AVF4095g

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

C = carboplatin; G = gemcitabine; PFS = progression free survival; CI = confidence interval; OS = overall survival

Results of the unstratified analysis were similar to those of the stratified analysis (above table)

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

Study MO22224 (AURELIA)

Study MO22224 evaluated the efficacy and safety of bevacizumab in combination with chemotherapy for platinum-resistant recurrent ovarian cancer. The majority of patients had not previously received bevacizumab or other anti-angiogenic therapies. This study was designed as an open-label, randomised, 2-arm phase III evaluation of bevacizumab plus chemotherapy versus chemotherapy alone.

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

- CT arm (chemotherapy alone):

- Paclitaxel 80 mg/m^2 as a 1-hour IV infusion on Days 1, 8, 15, and 22 every 4 weeks.
- Topotecan 4 mg/m^2 as a 30 minute IV infusion on Days 1, 8, and 15 every 4 weeks. Alternatively, a 1.25 mg/m^2 dose could be administered over 30 minutes on Days 1–5 every 3 weeks.
- PLD 40 mg/m^2 as a 1 mg/min IV infusion on Day 1 only every 4 weeks. After cycle 1, the drug could be delivered as a 1 hour infusion.

- CT + bevacizumab arm (chemotherapy plus bevacizumab):
  - The chosen chemotherapy was combined with bevacizumab 10 mg/kg every 2 weeks or, bevacizumab 15 mg/kg every 3 weeks if used in combination with topotecan (1.25 mg/m^2 on Days 1–5 on a every 3 weeks schedule).

Eligible patients had epithelial ovarian, fallopian tube or primary peritoneal cancer that progressed within 6 months of previous platinum therapy consisting of a minimum of 4 platinum therapy cycles. Patients had a life expectancy of ≥ 12 weeks, no prior radiotherapy to the pelvis or abdomen and an ECOG status ≤ 2. Exclusion criteria included patients whose disease was refractory to their previous platinum treatment, patients with previous treatment with > 2 prior anti-cancer regimens, and patients with history or symptoms of bowel obstruction, abdominal fistula, or evidence of bowel wall or recto-sigmoid involvement.

% (n=27) of enrolled patients had received prior anti-angiogenic therapy. If a patient had been previously included in a blinded trial with an anti-angiogenic agent, the patient was enrolled in the same stratum as those patients who were known to have previously received an anti-angiogenic agent.

The primary endpoint was progression-free-survival (PFS), with secondary endpoints including objective response rate and overall survival. Results are presented in Table 16. PFS results for each chemotherapy cohort by Investigator and IRC assessment are presented in Table 17.

Table 16: Investigator-assessed efficacy outcomes for Study MO22224 (AURELIA)

Primary Endpoint		
Progression-Free Survival		
	CT (*n*=182)	**CT + bevacizumab (*n*=179)**
Median PFS (months)	3.4	6.7
Hazard ratio (95% CI)	0.379 [0.296, 0.485]	
p-value	<0.0001	
Secondary Endpoints		
Objective Response Rate[a]		
	CT (*n*=144)	**CT + bevacizumab (*n*=142)**
% pts with objective response	18 (12.5%)	40 (28.2%)

Difference in objective response rates	15.7% (95% CI = 6.5%, 24.8%)	
p –value	0.0007	
Overall Survival (OS) (final analysis)[b]		
	CT (*n*=182)	**CT + bevacizumab (*n*=179)**
Median OS (months)	13.3	16.6
Hazard Ratio (95% CI)	0.870 [0.678, 1.116]	
p-value	0.2711	
HRQoL EORTC QLQ-OV28 Abdominal/GI Symptom Scale		
No. of patients who completed questionnaire at baseline and Week 8/9	84	122
No. of responders (response rate, %) (95% CI)	16 (19.0%) (11.3%, 29.1%)	34 (27.9%) (20.1%, 36.7%)
Difference in response rate, relative to CT (95% CI) p-value (unstratified)[c]	8.8% (-3.8%, 21.4%) 0.1859	

All analyses presented in this table are stratified analyses

[a] Randomized Patients with Measurable Disease at Baseline

[b] the final analysis of OS was performed when 266 deaths had occurred, which account for 73.7% of enrolled patients, were observed

[c] Fisher's Exact Test

Table 17: PFS Outcomes from Study MO22224 (AURELIA) by chemotherapy cohort

	CT	**CT + bevacizumab**
Paclitaxel	n=115	
Investigator-assessed		
Median PFS (months)	3.9	9.6
Hazard Ratio (95% CI)	0.46 [0.30, 0.71]	
IRC-assessed		
Median PFS (months)	4.2	9.6
Hazard Ratio (95% CI)	0.50 [0.31, 0.78]	
Topotecan	n=120	
Investigator-assessed		
Median PFS (months)	2.1	6.2
Hazard Ratio (95% CI)	0.28 [0.18, 0.44]	
IRC-assessed		
Median PFS (months)	2.3	7.1
Hazard Ratio (95% CI)	0.35 [0.22, 0.56]	
PLD	n=126	
Investigator-assessed		
Median PFS (months)	3.5	5.1
Hazard Ratio (95% CI)	0.55 [0.38, 0.80]	
IRC-assessed		
Median PFS (months)	3.9	7.5
Hazard Ratio (95% CI)	0.71 [0.48, 1.06]	

The overall rates of discontinuation due to AEs were 8.8% in the CT arm and 43.6% in the CT + bevacizumab arm (mostly due to Grade 2-3 AEs) and the median time to discontinuation in the CT + BV arm was 5.2 months compared with 2.4 months in the CT arm. The incidence of Grade 2–5 serious AEs was 31.1% in the CT + bevacizumab arm compared with 27.1% in the CT arm. Grade 5 AEs occurred in 5 patients in the CT arm and 6 patients in the CT + bevacizumab arm with a further Grade 5 AE occurring after cross-over to bevacizumab.

Cervical Cancer

Study GOG-0240

The efficacy and safety of bevacizumab in combination with chemotherapy (paclitaxel and cisplatin or paclitaxel and topotecan) as a treatment for patients with persistent, recurrent, or Stage IVB carcinoma of the cervix (excluding patients with craniospinal metastases) was evaluated in study GOG-0240, a randomised, four-arm, 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/m2 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 and 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 Stage IVB squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which was not amenable to curative treatment with surgery and/or radiation therapy.

The primary efficacy endpoint was overall survival (OS). Secondary efficacy endpoints included progression-free survival (PFS) and objective response rate (ORR). Results are presented in Table 18.

Table 18: Overall Efficacy by bevacizumab Treatment (ITT Population) from Study GOG- 0240

	Chemotherapy (n=225)	Chemotherapy + bevacizumab (n=227)

Primary Endpoint		
Overall Survival		
Median (months)[1]	12.9	16.8
Hazard ratio [95% CI]	0.74 [0.58;0.94] (p-value[5] = 0.0132)	
Secondary Endpoints		
Progression-free survival		
Median PFS (months)[1]	6.0	8.3
Hazard ratio [95% CI]	0.66 [0.54;0.81] (p-value[5] = <0.0001)	
Best Overall Response		
Response rate[2]	76 (33.8 %)	103 (45.4 %)
95% CI for Response Rates[3]	[27.6; 40.4]	[38.8; 52.1]
Difference in Response Rates	11.60	
95% CI for Difference in Response	[2.4; 20.8]	
p-Value (Chi-squared Test)	0.0117	

[1]Kaplan-Meier estimates

[2]Patients with best overall response of confirmed CR or PR

[3]95% CI for one sample binomial using Pearson-Clopper method

[4]Approximate 95% CI for difference of two rates using Hauck-Anderson method

[5] log-rank test (stratified)

Interim overall efficacy results by chemotherapy backbone favoured paclitaxel and cisplatin with or without bevacizumab over paclitaxel and topotecan with or without bevacizumab, although this was not statistically significant for the primary endpoint. Median OS was 15.5 months compared to 13.3 months respectively, hazard ratio (HR) 1.15 (95% CI: 0.91, 1.46, log-rank p-value=0.2326), median PFS was 7.9 months compared to 5.8 months respectively, HR 1.26 (95% CI: 1.02, 1.54; log-rank p-value = 0.0290), and the difference between ORR for the two groups was 10.9% (95% CI: 1.7, 20.1; p-value [chi-squared] = 0.0179). An exploratory subgroup analysis for OS showed HRs for histology subgroups other than squamous-cell carcinoma that were greater than 1 (i.e., adenocarcinoma [HR = 1.17] and adenosquamous [HR = 1.03] (clinical cut-off 7 March 2014)). However the analysis was exploratory and the patient numbers in each of the histology subgroups were relatively small (adenocarcinoma n = 94 and adenosquamous carcinoma n = 44).

5.2 Pharmacokinetic properties

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

As observed with other antibodies, the pharmacokinetics of bevacizumab are well described by a two-compartment model. Overall, in all clinical trials, bevacizumab disposition was characterised by a low clearance, a limited volume of the central compartment (Vc), and a long elimination half-life. This enables target therapeutic bevacizumab plasma levels to be

maintained with a range of administration schedules (such as one administration every 2 or 3 weeks).

In the population pharmacokinetics analysis there was no significant difference in the pharmacokinetics of bevacizumab in relation to age (no correlation between bevacizumab clearance and patient age [the median age was 59 years with 5th and 95th percentiles of 37 and 76 years]).

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

Absorption and Bioavailability

Not applicable.

Distribution

The typical value for central volume (V_c) was 2.73 L and 3.28 L for female and male patients, respectively, which is in the range that has been described for IgGs and other monoclonal antibodies. After correcting for body weight, male patients had a larger V_c (+20%) than female patients.

Metabolism

Assessment of bevacizumab metabolism in rabbits following a single IV dose of 125I-bevacizumab suggested that its metabolic profile was similar to that expected for a native IgG molecule which does not bind VEGF.

Elimination

The pharmacokinetics of bevacizumab are linear at doses ranging from 1.5 to 10 mg/kg/wk.

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

Children and adolescents: The pharmacokinetics of bevacizumab were evaluated in 152 patients (7 months to 21 years; 5.9 to 125 kg) across 4 clinical studies using a population pharmacokinetic model. The pharmacokinetic results show that the clearance and the volume of distribution of bevacizumab were comparable between paediatric and adult patients when normalised by body-weight. Age was not associated with the pharmacokinetics of bevacizumab when bodyweight was taken into account.

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

***Hepatic impairment*:** No studies 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.

***Patients with ascites*:** No studies have examined the effect of ascites on the pharmacokinetic parameters of bevacizumab.

5.3 Preclinical safety data

Genotoxicity

Studies to evaluate the mutagenic potential of bevacizumab has not been performed.

Carcinogenicity

Studies to evaluate the carcinogenic potential of bevacizumab has not been performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Succinic acid
Disodium edetate
Polysorbate 80
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

ZIRABEV infusions should not be administered or mixed with dextrose orglucose solutions.

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 4.2 Dose and method of administration.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

ZIRABEV does not contain any antimicrobial agent; therefore care must be taken to ensure the sterility of the prepared solution. Product is for single use in one patient only. Discard any residue. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C to 30°C in sodium chloride 9 mg/mL (0.9%) solution for injection. To reduce microbiological hazard, use as soon as practicable after preparation. If storage is necessary, hold at 2-8°C for not more than 24 hours.

6.4 Special precautions for storage

Store vials at 2 - 8°C. (Refrigerate. Do not freeze.) Do not shake.

Protect from light. Keep vial in outer carton due to light sensitivity until use.

For storage conditions after dilution of the medicinal product, see Section 6.3 Shelf life.

6.5 Nature and contents of container

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

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

Pack of 1 vial.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

CAS number

CAS 216974-75-3

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

Pfizer Australia Pty Ltd
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Toll Free Number: 1800 675 229
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9. DATE OF FIRST APPROVAL

21 November 2019

10. DATE OF REVISION

Not applicable

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