NEW ZEALAND DATA SHEET
VEGZELMA® (bevacizumab)

1 PRODUCT NAME

Vegzelma 25 mg/mL concentrate for solution for infusion.

Vegzelma is a biosimilar medicine.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Vegzelma 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.

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

Vegzelma is a biosimilar medicine for further information refer to http://www.medsafe.govt.nz/profs/RIss/Biosimilars.asp

Comparability of Vegzelma to the reference product can be found in Section 5.1 Clinical efficacy and safety data.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Vegzelma is a clear to slightly opalescent, colourless to pale brown, sterile solution for intravenous (IV) infusion. Vegzelma is not formulated for intravitreal use (see Section 4.4).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

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

Advanced, metastatic or recurrent non-squamous Non-Small Cell Lung Cancer (NSCLC)
Vegzelma (bevacizumab), in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable advanced, recurrent or metastatic, NSCLC.

Metastatic Breast Cancer
Vegzelma (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.

Relapsed high grade malignant glioma
Vegzelma (bevacizumab) as a single agent, is indicated for the treatment of patients with high grade relapsed malignant glioma.

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer
Vegzelma (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.

Vegzelma (bevacizumab), in combination with carboplatin and paclitaxel treatment of patients with recurrent, platinum-sensitive, epithelial ovarian, fallopian tube, or primary peritoneal cancer.

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

4.2 DOSE AND METHOD OF ADMINISTRATION

General

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

Recommended Dose

Metastatic Colorectal Cancer

The recommended dose of Vegzelma, 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 Vegzelma treatment be continued until progression of the underlying disease.

Advanced and/or Metastatic Renal Cell Cancer

The recommended dose of Vegzelma is 10 mg/kg given once every 2 weeks as an IV infusion.

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

Vegzelma 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 Clinical efficacy and safety data). Please also refer to the Roferon-A Data sheet.

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

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

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

Metastatic Breast Cancer

The recommended dose of Vegzelma 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 Vegzelma treatment be continued until progression of the underlying disease.

Relapsed high grade malignant glioma

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

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

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

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

Front- line treatment

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

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

Treatment of recurrent, platinum-sensitive disease

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 Vegzelma as a single agent until disease progression.

Treatment of recurrent, platinum-resistant disease

10 mg/kg body weight given once every 2 weeks when administered in combination with one of the following agents – paclitaxel, topotecan (given weekly) or pegylated liposomal doxorubicin. Alternatively, 15 mg/kg every 3 weeks when administered in combination with topotecan given on days 1-5, every 3 weeks. (See Section 5.4 Clinical efficacy and safety data, study MO22224 for descriptions of the chemotherapy regimens).

It is recommended that treatment be continued until disease progression.

Cervical Cancer

Vegzelma is administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin or paclitaxel and toptecan (see Section 5.1).

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

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

Dose Reduction

Dose reduction of Vegzelma for adverse reactions is not recommended. If indicated, Vegzelma should either be discontinued or temporarily suspended (see Section 4.4; Special Warnings and Precautions for Use)**.**

Special Dosage Instructions

Paediatric Use

The safety and efficacy of Vegzelma in children and adolescents (<18 years) have not been established.

Elderly

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

Renal impairment

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

Hepatic impairment

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

Method of Administration

The initial Vegzelma 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.

Vegzelma 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).

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 CONTRAINDICATIONS

Vegzelma 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
- NSCLC patients with recent pulmonary haemoptysis (see Section 4.4)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

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.

Gastrointestinal Perforations and Fistulae

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

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.

Permanently discontinue bevacizumab in patients with tracheo-oesophageal (TE) fistula or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

Hypertension

An increased incidence of hypertension was observed in patients treated with bevacizumab. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre-existing hypertension should be adequately controlled before starting Vegzelma 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 Vegzelma therapy.

In most cases hypertension was controlled adequately using standard anti-hypertensive treatment appropriate for the individual situation of the affected patient. Vegzelma 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;).

Wound Healing

Vegzelma may adversely affect the wound healing process, Serious wound healing complications, with a fatal outcome have been reported during use of bevacizumab.

Vegzelma 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 Vegzelma therapy, Vegzelma should be withheld until the wound is fully healed. Vegzelma therapy should be withheld for elective surgery.

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. Vegzelma therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated (see Section 4.8 Adverse Effects).

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.

Vegzelma 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 Vegzelma therapy. Caution should be taken when treating such patients with Vegzelma.

Venous thromboembolic events

Patients may be at risk of developing venous thromboembolic events, including pulmonary embolism under bevacizumab treatment. Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab may be at increased risk of venous thromboembolic events (see Section 4.8).

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

Haemorrhage

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.

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 16% of control patients vs. 35.6% and 36.7% in the short and extended duration bevacizumab arms; in B017707 they were observed in 11% of control patients and 39.4% of the bevacizumab -treated 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).

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 Vegzelma 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.

Pulmonary haemorrhage

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.

Aneurysms and artery dissections

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

Posterior Reversible Encephalopathy Syndrome (PRES)

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

A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known (see Section 4.8).

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 $\geq$ 2 g/24 h led to the holding of bevacizumab until recovery to < 2 g/24 h.

Congestive Heart Failure (CHF)

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

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.

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.

Hypersensitivity Reactions, Infusion Reactions

Patients may be at risk of developing infusion/hypersensitivity reactions, anaphylactic reactions (including anaphylactic shock) and infusion-related reactions. Close observation of the patient during and following the administration of bevacizumab is recommended. If an anaphylactic reaction occurs, the infusion should be permanently discontinued and appropriate medical therapies should be administered.

If an infusion-related reaction occurs, treatment should be temporarily interrupted until resolution of symptoms. Permanently discontinue bevacizumab for severe (Grade $\geq$3) infusion-related reaction.

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).

Ovarian Failure

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, has been evaluated. New cases of ovarian failure were reported more frequently in patients receiving bevacizumab. After discontinuation of bevacizumab treatment, ovarian function recovered in a majority of women. Long term effects of the treatment with bevacizumab on fertility are unknown (see Section 4.8).

Paediatric Use

Vegzelma 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.

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.

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.

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.

Results from BO17704 demonstrated no significant effect of bevacizumab on the pharmacokinetics of cisplatin. Due to high inter-patient variability and limited sampling, the results from BO17704 do not allow firm conclusions on the impact of bevacizumab on gemcitabine pharmacokinetics to be drawn.

Combination of bevacizumab and sunitinib malate

In two clinical studies of metastatic renal cell carcinoma, microangiopathic haemolytic anaemia (MAHA) was reported in 7/19 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, *Hypertension, Proteinuria and PRES*).

Radiotherapy

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

4.6 FERTILITY, PREGNANCY AND LACTATION

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, Vegzelma 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).

Breastfeeding

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 Vegzelma therapy and not to breast feed for at least 6 months following the last dose of Vegzelma.

Fertility

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

Long term effects of treatment with bevacizumab on fertility are unknown. A sub-study with 295 premenopausal women, has shown a higher incidence of new cases of ovarian failure in the bevacizumab group compared to the control group (39% compared to 2.6%).

Women of childbearing potential

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

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

Summary of the safety profile

Clinical trials have been conducted in patients with various malignancies treated bevacizumab in combination with chemotherapy. The safety profile from a clinical trial population of approximately 5,500 patients 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)
- Haemorrhage including pulmonary haemorrhage/haemoptysis, which is more common in NSCLC patients (see Section 4.4)
- Arterial and venous thromboembolism (see Section 4.4)

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*)*.

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

Tabulated summary of adverse reactions

Table 1 lists adverse drug reactions associated with the use of bevacizumab in combination with different chemotherapy regimens in multiple indications, by MedDRA system organ class. The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). These reactions had occurred either with at least a 2% difference compared to the control arm (NCI-CTC [common toxicity criteria] Grade 3-5 reactions) or with at least a 10% difference compared to the control arm (NCI-CTC Grade 1-5 reactions), in at least one of the major clinical trials. Adverse drug reactions have been included in the appropriate category in Table 1 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 Abscess Cellulitis Infection	
Blood and the lymphatic systems disorders	Febrile neutropenia Leucopenia Neutropenia Thrombocytopenia	Anaemia Lymphopenia	
Immune system disorders		Hypersensitivity, anaphylactic reactions, infusion-related reactions	
Metabolism and nutrition disorders		Dehydration Hyponatraemia	Anorexia Hypomagnesaemia Hyponatraemia
Nervous system disorders	Peripheral sensory neuropathy	Cerebrovascular accident Syncope Somnolence Headache	Dysgeusia Headache Dysarthria
Eye disorders			Eye disorder Lacrimation increased
Cardiac disorders		Cardiac failure congestive Supraventricular tachycardia	
Vascular disorders	Hypertension	Thromboembolism (arterial) Deep vein thrombosis Haemorrhage	Hypertension
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism Dyspnoea Hypoxia Epistaxis	Dyspnoea Epistaxis Rhinitis Cough
Gastrointestinal disorders	Diarrhoea Nausea Vomiting Abdominal pain	Intestinal Perforation Ileus Intestinal obstruction Recto-vaginal fistulae* Gastrointestinal disorder Stomatitis Proctalgia	Constipation Stomatitis Rectal haemorrhage Diarrhoea
Endocrine disorders			Ovarian failure
Skin and subcutaneous tissue disorders		Palmar-plantar erythrodysaesthesia syndrome	Exfoliative dermatitis Dry skin Skin discolouration

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**
Musculoskeletal, connective tissue and bone disorders		Muscular weakness Myalgia Arthralgia Back Pain	Arthralgia
Renal and urinary disorders		Proteinuria Urinary Tract Infection	Proteinuria
General disorders and administration site conditions	Asthenia Fatigue	Pain Lethargy Mucosal inflammation	Pyrexia Asthenia Pain Mucosal inflammation
Reproductive System and Breast		Pelvic Pain	
Investigations			Weight Decreased

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

Post-Marketing Experience

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

Table 2: Adverse Reactions Reported in Post-Marketing Experience

Adverse reactions	Frequency Category
Infections and Infestations	
Necrotising fasciitis[1, 2]	Rare
Nervous system disorders	
Hypertensive encephalopathy[2,3]	Very rare
Posterior Reversible Encephalopathy Syndrome (PRES)[2]	Rare
Vascular Disorders	
Renal Thrombotic Microangiopathy, clinically manifested as proteinuria[2,3]	Unknown
Respiratory, thoracic and mediastinal disorders	
Nasal septum perforation	Unknown
Pulmonary hypertension	Unknown
Dysphonia	Common
Gastrointestinal disorders	
Gastrointestinal ulcer	Unknown
Hepatobiliary disorders	
Gallbladder perforation	Unknown
Musculoskeletal and Connective Tissue disorders	
Osteonecrosis of the Jaw (ONJ)[4]	Unknown
Osteonecrosis at sites other than the jaw[5,6]	Unknown
Congenital, familial and genetic disorders	
Foetal abnormalities[7]	Unknown

[*] If specified, the frequency has been derived from clinical trial data

[1] Usually secondary to wound healing complications, gastrointestinal perforation or fistula formation

[2] See Section 4.4 Special Warnings and Precautions for use

[3] See Section 5.1Clinical efficacy and safety

[4] Cases of Osteonecrosis of the Jaw (ONJ) have been observed in bevacizumab -treated patients mainly in association with prior or concomitant use of bisphosphonates.

[5] Cases observed in bevacizumab -treated pediatric patients. See Section 4.4 Special Warnings and Precautions Use.

[6] Osteonecrosis observed in pediatric 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.

[7] Cases have been observed in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics. See Section 4.6 Pregnancy

Description of selected adverse drug reactions

Gastrointestinal (GI) perforations and Fistulae (see section 4.4)

Bevacizumab has been associated with serious cases of GI perforation. GI perforations have been reported in clinical trials with an incidence of less than 1% in patients with metastatic breast cancer or NSCLC, up to 2% in patients with metastatic renal cell cancer or ovarian cancer, and up to 2.7% (including gastrointestinal fistula and abscess) in patients with metastatic colorectal cancer. Cases of GI perforations have also been observed in patients with relapsed glioblastoma. From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), GI perforations (all grade) were reported in 3.2% of patients, all of whom had a history of prior pelvic radiation.

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

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.

In bevacizumab clinical trials, GI fistulae (all grade) have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer and ovarian cancer, but were also reported less commonly in patients with other types of cancer. In a trial of patients with persistent, recurrent, or metastatic cervical cancer, the incidence of GI-vaginal fistulae was 8.2% 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.

Non-GI Fistulae (see section 4.4)
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 1 week to greater than 1 year from initiation of bevacizumab, with most events occurring within the first 6 months of therapy.

Hypertension (see section 4.4)
An increased incidence of hypertension (all grades) of up to 34% 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.

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

Wound healing (see section 4.4)
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).

In locally recurrent and metastatic breast cancer trials, 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.

Thromboembolism (see section 4.4)

Arterial thromboembolism

In clinical trials, the overall incidence ranged up to 5.9% in the bevacizumab-containing arms compared to 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 glioblastoma, 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.

Venous thromboembolism (see section 4.4)

In clinical trials across all 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.

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

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

Haemorrhage (see section 4.4)

In clinical trials across all indications, the overall incidence of National Cancer Institute-Common Toxicity Criteria (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).

Tumour-associated haemorrhage (see section 4.4)

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 two subsequent studies in patients with treated brain metastases (which included around 800 patients), 1 case of Grade 2 CNS haemorrhage was reported.

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
Across all bevacizumab clinical trials, mucocutaneous haemorrhages were seen in up to 50% of patients treated with bevacizumab. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in 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.

Proteinuria (see section 4.4)
In clinical trials, the incidence of proteinuria was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone. 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 < 3% of treated patients, except in advanced and/or metastatic renal cell cancer where it was reported in up to 7% of patients. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of treated patients. In the event of nephrotic syndrome bevacizumab treatment should be permanently discontinued.

Congestive Heart Failure (see section 4.4)
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.

Hypersensitivity reactions (see section 4.4)
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).

Laboratory abnormalities
Decreased neutrophil count, decreased white blood count and presence of urine protein maybe 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after registration of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

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 National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
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

Mechanism of Action
Bevacizumab 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 and is purified by a process that includes specific viral inactivation and removal steps.

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 tumour angiogenesis, thereby inhibiting tumour growth. Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumour activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was inhibited and microvascular permeability was reduced.

Clinical efficacy and safety data

Comparability of Vegzelma® with Avastin®

The clinical comparability between Vegzelma and Avastin® in one double blind, randomized, active-controlled, parallel group study as first-line treatment for metastatic or recurrent nsNSCLC.

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)

Three additional studies were conducted in mCRC patients: first-line (NO16966), second-line with no previous bevacizumab treatment (E3200) and second-line with previous treatment following progression in first-line (ML18147). In these studies, bevacizumab was administered at the following dosing regimens, in combination with FOLFOX-4 (FU/LV/Oxaliplatin) and XELOX (Capecitabine/Oxaliplatin), and fluoroprymidine/irinotecan and fluropyrmidine/oxiplatin:

- **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) in bevacizumab naïve patients.
- **ML18147**: Bevacizumab 5.0 mg/kg of body weight every 2 weeks or bevacizumab 7.5 mg/kg of body weight every 3 weeks in combination with fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin in patients with disease progression following first-line treatment with bevacizumab. Use of irinotecan- or oxaliplatin-containing regimen was switched depending on first-line usage of either oxaliplatin or irinotecan.

† The New Zealand Approved Name for leucovorin is calcium foliante

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

Fluorouracil: IV bolus injection immediately after Leucovorin
Leucovorin: 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.

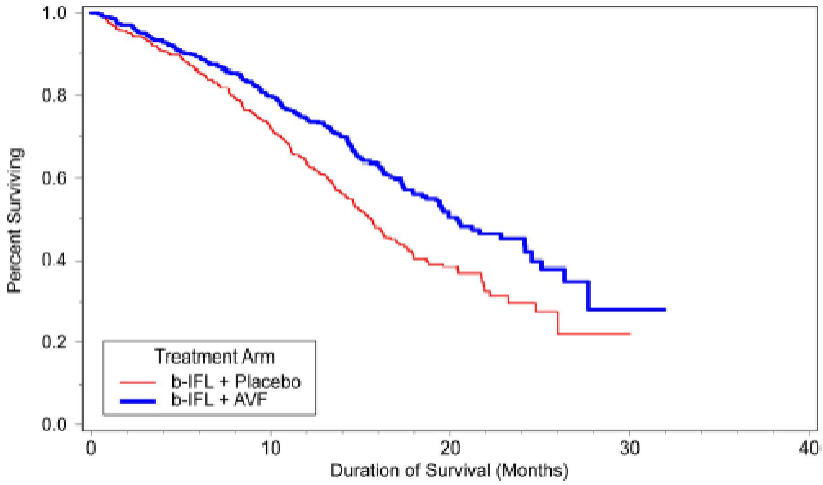
Table 4: Efficacy Results for Study AVF2107g

	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])
<u>Overall Survival</u>			
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		-
<u>Progression-Free Survival</u>			
Median (months)	6.2	10.6	8.8
Hazard ratio (95% CI)	0.54 (0.45, 0.66)		
p-value (log rank)	<0.0001		-
<u>Overall Response Rate</u>			
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

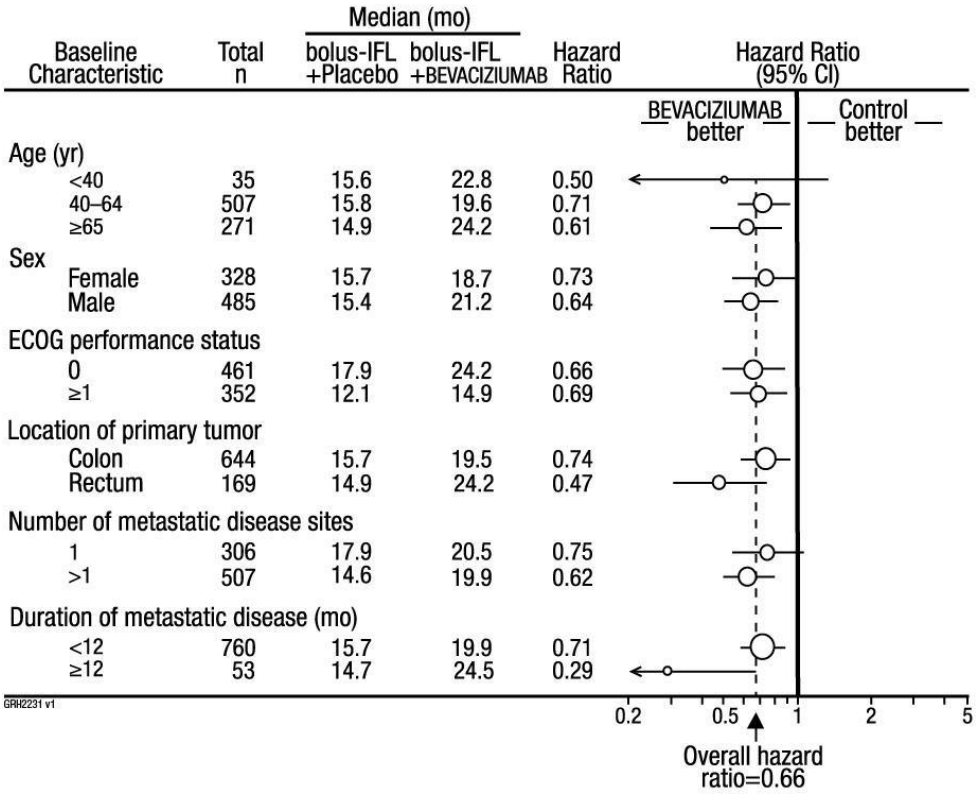
[a] 5 mg/kg every 2 weeks; [b] Recruitment stopped as per protocol; [c] Relative to control arm
CI = confidence interval; IFL = irinotecan/fluorouracil/leucovorin (calcium folinate); FU/LV=fluorouracil/leucovorin (calcium folinate)

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



IFL =irinotecan/ fluorouracil/ leucovorin (calcium folinate); AVF = bevacizumab

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



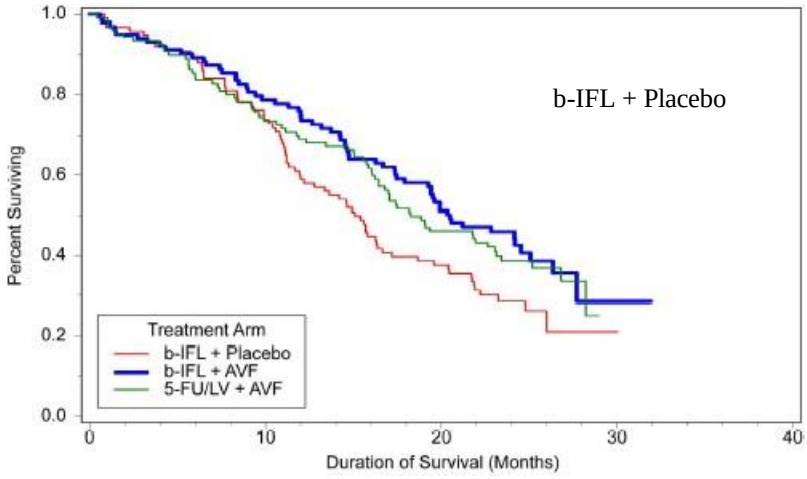
CI= interval; IFL=irinotecan/fluorouracil/ leucovorin (calcium folinate);

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 (calcium folinate); AVF = Bevacizumab

5-FU/LV = fluorouracil/leucovorin (calcium folinate)

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; FU/LV = fluorouracil/leucovorin (calcium folinate)

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	85 mg/m^2 IV 2 h	Oxaliplatin on Day 1
	Leucovorin[†]	200 mg/m^2 IV 2 h	Leucovorin[†] on Day 1 and 2
	Fluorouracil	400 mg/m^2 IV bolus, 600 mg/ m^2 IV 22 h	Fluorouracil IV bolus/infusion, each on Days 1 and 2
	Placebo or bevacizumab	5 mg/kg IV 30-90 min	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX+ bevacizumab	Oxaliplatin	130 mg/m^2 IV 2 h	Oxaliplatin on Day 1
	Capecitabine	1000 mg/m^2 oral bid	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 New Zealand Approved Name for leucovorin is calcium folinate

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:

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

ii. Superiority of the bevacizumab containing arms versus the chemotherapy alone arms in the overall comparison was demonstrated in terms of PFS 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 (subgroup analyses shown in Table 7), consistent with the statistically significant benefit observed in the pooled analysis.

Table 7: Key Efficacy Results for the Superiority Analysis (ITT population, 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)		
Median PFS (Independent review)^^	8.5	11.0	< 0.0001
Hazard ratio (97.5% CI)	0.70 (0.58-0.83)		
Overall response rate (Investigator Assessment)^^	49.2%	46.5%	
Overall response rate (Independent Review)^^	37.5%	37.5%	

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*

CI = confidence interval; PFS = progression-free survival; [a] relative to control arm: [b] On--treatment analysis includes only tumour assessments and death events occurring no later than 28 days after the last confirmed intake of any study medication in the primary study treatment phase .

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]
	(n= 292)	(n= 293)
Overall Survival		
Median (months)	10.8	13.0
95% CI	10.12 – 11.86	12.09 – 14.03
Hazard ratio[b]	0.751	
95% CI	(0.632, 0.893)	
	(*p*-value = 0.0012)	
Progression-Free Survival Median (months)	4.5	7.5
Hazard ratio	0.518	
95% CI	(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; CI = confidence interval

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.

Study ML18147

This was a Phase III randomised, controlled, open-label trial investigating bevacizumab 5.0 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks in combination with fluoropyrimidine-based

chemotherapy versus fluoropyrimidine-based chemotherapy alone in patients with metastatic colorectal cancer who have progressed on a first-line bevacizumab-containing regimen.

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

A total of 820 patients were randomised. The addition of bevacizumab to fluoropyrimidine-based chemotherapy resulted in a statistically significant prolongation of survival in patients with metastatic colorectal cancer who have progressed on a first-line bevacizumab-containing regimen (ITT = 819) (see Table 9).

Table 9: Efficacy Results for Study ML18147

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

[a] *dose equivalent to 2.5 mg/kg/week*

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

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 on either a 2-weekly schedule in combination with FOLFOX4, or on a 3-weekly 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.

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 10.

Table 10: Efficacy Results for Study BO17705

	IFN + Placebo	**IFN + bevacizumab**
Number of Patients	*322*	*327*
Progression-Free Survival		
Median (months)	5.4	10.2
Hazard ratio [95% CI]	0.63 [0.52; 0.75]	
	(*p*-value < 0.0001)	
Objective Response Rate (%) in **Patients with Measurable Disease**		
Number of Patients	289	306
Response rate (%)	12.8	31.4
	(*p*-value < 0.0001)	
Overall Survival		
Median (months)	21.3	23.3
Hazard ratio [95% CI]	0.91 [0.76; 1.10]	
	(*p*-value = 0.3360)	

An exploratory multivariate Cox regression model using backward selection indicated that the following baseline prognostic factors were strongly associated with survival independent of treatment: gender, white blood cell count, platelets, body weight loss in the 6 months prior to study entry, number of metastatic sites, sum of longest diameter of target lesions and Motzer score. Adjustment for these baseline factors resulted in a treatment hazard ratio of 0.78 (95% CI [0.63;0.96], p = 0.0219), indicating a 22% reduction in the risk of death for patients in the bevacizumab + IFN arm compared to IFN arm.

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. Dose-reduction of IFN alfa-2a did not appear to affect the efficacy of the combination of bevacizumab and IFN alfa-2a, based on PFS event free rates over time, as shown by a sub-group analysis. The 131 patients in the bevacizumab + IFN alfa-2a arm who reduced and maintained the IFN alfa-2a dose at 6 or 3 MIU during the study, exhibited at 6, 12 and 18 months, PFS event free rates of 73, 52 and 21% respectively, as compared to 61, 43 and 17% in the total population of patients receiving bevacizumab + IFN alfa-2a.

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

The safety and efficacy of bevacizumab in the first-line treatment of patients with NSCLC other than predominantly squamous cell histology, were studied in addition to platinum-based chemotherapy in studies E4599 and BO17704.

Study E4599

E4599 was an open-label, randomised, active-controlled, multicentre clinical trial evaluating bevacizumab as first-line treatment of patients with locally advanced, metastatic or recurrent NSCLC other than predominantly squamous cell histology.

Patients were 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. After completion of six cycles of PC chemotherapy or upon premature discontinuation of chemotherapy, patients in bevacizumab +PC arm continue to receive bevacizumab as a single agent every 3 weeks until disease progression. 878 patients were randomized to the two arms.

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

The primary endpoint was overall survival (OS). Results are presented in Table 11.

Table 11: 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[a]		
Median (months)	10.3	12.3
Hazard ratio		0.80
		95% CI (0.69, 0.93)
Progression-Free Survival[b]		
Median (months)	4.8	6.4
Hazard ratio		0.65
		95% CI (0.56, 0.76)
Overall Response Rate[c]		
Rate (%)	12.9	29.0

[a] *p = 0.003 by stratified log rank test*

[b] *p< 0.0001 by stratified log rank test,*

[c] *stratified χ^2 test includes patients with measurable disease at baseline.*

q3w: every 3 weeks

Study BO17704

Study BO17704 was a randomised, double-blind phase III study of bevacizumab in addition to cisplatin and gemcitabine versus placebo, cisplatin and gemcitabine in patients with locally advanced, metastatic or recurrent non-squamous NSCLC who had not received prior chemotherapy. The primary endpoint was progression free survival; secondary endpoints included overall survival.

Patients were randomised to platinum-based chemotherapy (cisplatin 80 mg/m2 IV infusion on day 1 and gemcitabine 1250 mg/m2 IV infusion on days 1 and 8 of every 3-week cycle for up to 6 cycles) (CG) with placebo or CG with bevacizumab at a dose of 7.5 or 15 mg/kg IV infusion day 1 of every 3-week cycle. In the bevacizumab-containing arms, patients could receive bevacizumab as a single agent every 3 weeks until disease progression or unacceptable toxicity.

Study results showed that 94% (277/296) of eligible patients went on to receive single agent bevacizumab at cycle 7. A high proportion of patients (approximately 62%) went on to receive a variety of non-protocol specified anti-cancer therapies, which may have impacted the analysis of overall survival. The efficacy results are presented in Table 12.

Table 12: Efficacy results for study BO17704

	Cisplatin/Gemcitabine + placebo	**Cisplatin/Gemcitabine + bevacizumab 7.5 mg/kg q3w**	**Cisplatin/Gemcitabine + bevacizumab 15 mg/kg q3w**
Number of Patients	347	345	351
Progression-Free Survival			
Median (months)	6.1	6.7 (p = 0.0026)	6.5 (p = 0.0301)
Hazard ratio		0.75 [0.62;0.91]	0.82 [0.68;0.98]
Best Overall Response Rate[a]	20.1%	34.1% (p<0.0001)	30.4% (p=0.0023)
[a] patients with measurable disease at baseline; q3w: every 3 weeks			
Overall Survival			
Median (months)	13.1	13.6 (p=0.4203)	13.4 (p=0.7613)
Hazard ratio		0.93 [0.78; 1.11]	1.03 [0.86; 1.23]

Metastatic Breast Cancer

Study E2100

(*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/m^2 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 13 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.

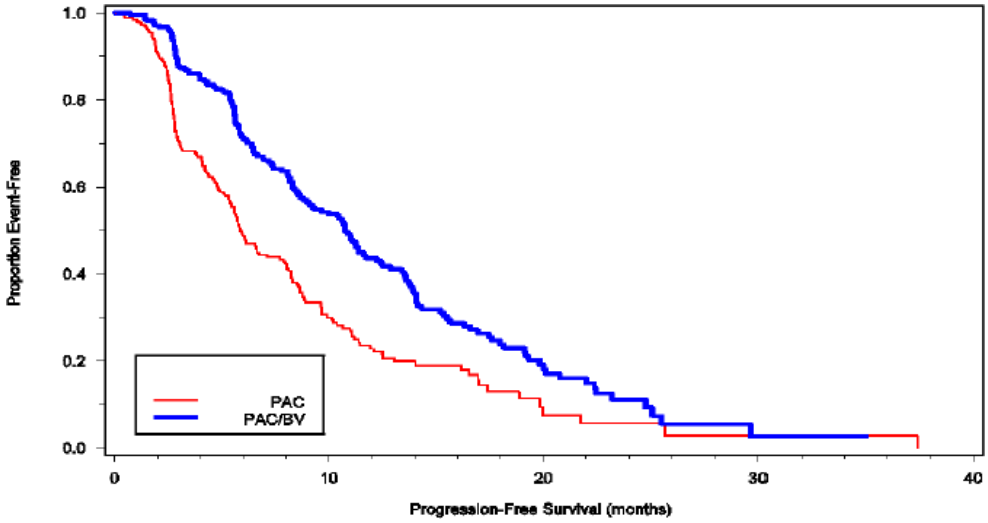
Table 13: Study E2100 Efficacy Results: Eligible Patients

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	

^ *primary analysis; IRF = independent review facility*

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	

Figure 4: Kaplan-Meier Curves for Progression Free Survival in Study E2100



Relapsed malignant glioma (WHO Grade IV) - Glioblastoma (GBM)
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/m^2 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 14.

Table 14: Efficacy Results from Study AVF3708g

	Bevacizumab		Bevacizumab + Irinotecan	
Number of patients	85		82	
	Inv	IRF	Inv	IRF
Primary endpoints				
6-month progression-free survival 95% CI (Inv) 97.5% CI (IRF)	43.6% (33.0, 54.3) -	42.6% - (29.6, 55.5)	57.9% (46.6, 69.2) -	50.3% - (36.8, 63.9)
Objective Response Rate (ORR) 95% CI (Inv) 97.5% CI (IRF)	41.2% (30.6, 52.3) -	28.2% - (18.5, 40.3)	51.2% (39.9, 62.4) -	37.8% - (26.5, 50.8)
Secondary endpoints				
Progression-free survival (months) Median (95% CI)	4.2 (3.0, 6.9)	4.2 (2.9, 5.8)	6.8 5.0, 8.2)	5.6 (4.4, 6.2)
Duration of objective response (months) Median (95% CI)	8.1 (5.5, *)	5.6 (3.0, 5.8)	8.3 (5.5, *)	4.3 (4.2, *)
Overall survival (months) Median (95% CI)	9.3 (8.2, *)		8.8 (7.8,*)	

ORR was determined using modified MacDonald criteria; CI = confidence interval;
** Upper limit of the CI could not be obtained*

In study AVF3708g, six-month PFS based on IRF assessments was significantly higher ($p < 0.0001$) compared with historical controls for both treatment arms: 42.6% in the bevacizumab arm and 50.3% in the bevacizumab plus irinotecan arm (investigator assessment: 43.6% in the bevacizumab arm and 57.9% in the bevacizumab plus irinotecan arm). Objective response rates were also significantly higher ($p < 0.0001$) compared with historical controls for both treatment arms: 28.2% in the bevacizumab arm and 37.8% in the bevacizumab plus irinotecan arm (investigator assessment: 41.2% in the bevacizumab arm and 51.2% in the bevacizumab plus irinotecan arm).

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 treatment. The majority of patients experiencing an objective response or prolonged PFS (at week 24) were able to maintain or improve their neurocognitive functions while on study treatment compared to baseline. The majority of patients that remained in the study and were progression free at 24 weeks, had a Karnofsky performance status (KPS) that remained stable.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

Front-line Ovarian Cancer

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.

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 15 (the p-value boundary for primary treatment comparisons was 0.0116).

Table 15: 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

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.

Study BO17707 (ICON7)
BO17707 was a Phase III, two arm, multicenter, randomised, controlled, open-label study comparing the effects of adding bevacizumab to carboplatin plus paclitaxel in patients with FIGO Stage I or IIA (Grade 3 or clear cell histology only), or FIGO Stage IIB - IV (all grades and all histological types) epithelial ovarian, fallopian tube or primary peritoneal cancer following surgery, and in whom no further surgery was planned before progression. A total of 1528 patients were randomised in equal proportions to the following two arms:

- CP arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m2) for 6 cycles
- CPB7.5+ arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m2) for 6 cycles plus bevacizumab (7.5 mg/kg q3w) for up to 18 cycles.

The primary endpoint was PFS as assessed by the investigator. The results of this study are summarised in Table 16.

Table 16: Efficacy Results from Study BO17707 (ICON7)

Progression-Free Survival		
	CP (n= 764)	CPB7.5+ (n=764)
Median PFS (months)	16.0	18.3
Hazard ratio [95% CI]	0.79 [0.68; 0.91] (p-value = 0.0010)	
Objective Response Rate[1]		
	CP (n=277)	CPB7.5+ (n=272)
Response rate	41.9 %	61.8 %
	(p-value <0.0001)	
Overall Survival[2]		
	CP (n= 764)	CPB7.5+ (n=764)
Median (months)	58.0	57.4
Hazard ratio [95% CI]	0.99 [0.85; 1.15]	

[1] *in patients with measurable disease at baseline*
[2] *Final OS analysis when 46.7% of patients died*

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

Recurrent Ovarian Cancer
Study 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 17.

Table 17: 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]	0.823 (CI: 0.680, 0.996)	
p-value	0.0447	
Hazard ratio [95% CI]	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**[*] (n = 286)	**CPB**[*] (n = 274)
No. (%) of pts with objective response (CR, PR)	159 (55.6%)	213 (77.7%)
p–value	< 0.0001	

[*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 MO22224 (AURELIA)

Study MO22224 evaluated the efficacy and safety of bevacizumab in combination with chemotherapy for platinum-resistant recurrent ovarian cancer. This study was designed as an open-label, randomised, 2-arm Phase III evaluation of bevacizumab plus chemotherapy (CT +BV) versus chemotherapy alone (CT).

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

The primary endpoint was progression-free-survival (PFS), with secondary endpoints including objective response rate and overall survival. Results are presented in Table 18.

Table 18: Efficacy Results from Study MO22224 (AURELIA)

Primary Endpoint		
Progression-Free Survival		
	CT (*n*=182)	**CT + bevacizumab (*n*=179)**
Median (months)	3.4	6.7
Hazard ratio (95% CI)	0.379 [0.296, 0.485]	
p-value	<0.0001	
Secondary Endpoints		
Objective Response Rate*		
	CT (*n*=144)	**CT + bevacizumab (*n*=142)**
% pts with objective response	18 (12.5%)	40 (28.2%)
p –value	0.0007	
Overall Survival (OS) (final analysis)**		
	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	

All analyses presented in this table are stratified analyses

* Randomized Patients with Measurable Disease at Baseline

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

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

The primary efficacy endpoint was overall survival (OS). Secondary efficacy endpoints included progression-free survival (PFS) and objective response rate (ORR). Results are presented in Table 19.

Table 19: Overall Efficacy by Bevacizumab Treatment (ITT Population) from Study GOG-0240

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

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

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 (V_c), 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 5^{th} and 95^{th} 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

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. The typical value for peripheral volume (Vp) was 1.69 L and 2.35 L for female and male patients respectively, when bevacizumab is co-administered with anti-neoplastic agents. After correcting for body weight, male patients had a larger V_c (+20%) than female patients.

Biotransformation

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

Elimination

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

Paeadiatric Population:

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

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.

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 inhibition of angiogenesis following administration of bevacizumab is likely to result in an adverse effect on female fertility.

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.

Carcinogenesis and Mutagenesis

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

dibasic sodium phosphate

monobasic sodium phosphate monohydrate

polysorbate 20

trehalose dihydrate

water for injections

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 6.6.

6.3 SHELF LIFE

Unopened vial

4 years (100 mg/ 4 mL).

4 years (400 mg/ 16 mL).

Diluted medicinal product

Vegzelma 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.

Chemical and physical in-use stability has been demonstrated for 48 hours at 2-30°C in 0.9% sodium chloride solution. To reduce microbiological hazard, the product should be used as soon as practicable after preparation. If storage is necessary, in-use storage times and conditions are the responsibility of the user and would not be longer than 24 hours at 2-8°C.

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.

6.5 NATURE AND CONTENTS OF CONTAINER

Vegzelma is available as:

- 100 mg pack containing one or ten 4 mL single-dose vial(s)*
- 400 mg pack containing one or ten 16 mL single-dose vial(s)*

* Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Preparing the Infusion

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

No incompatibilities between Vegzelma and polypropylene (PP) or polyethylene (PE) or polyolefin bags have been observed.

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

The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

Celltrion Healthcare New Zealand Limited
103 Carlton Gore Road,
New Market,
Auckland 1023,
New Zealand

Phone: 0800 838 899

9 DATE OF FIRST APPROVAL

25 January 2024

10 DATE OF REVISION

03 October 2024

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
6.3	Shelf-life extended to 4 years for 100 mg/4mL