PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# PrZIRABEV™

Bevacizumab for injection

100 mg and 400 mg vials (25 mg/mL, solution for infusion)

Antineoplastic

Pfizer Canada ULC
17300 Trans-Canada Highway
Kirkland, Quebec
H9J 2M5

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## RECENT MAJOR LABEL CHANGES

## TABLE OF CONTENTS

ZIRABEV (bevacizumab for injection) is a biosimilar biologic drug to Avastin®.

## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

Indications have been granted on the basis of similarity between ZIRABEV (bevacizumab for injection) and the reference biologic drug Avastin.

ZIRABEV (bevacizumab) is indicated for:

- **Metastatic Colorectal Cancer (mCRC)**

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

Consideration should be given to current standard of care guidelines for colorectal cancer.

See Drug-Drug Interactions for further information on the use of ZIRABEV in combination with irinotecan.

Please refer to the Product Monographs for irinotecan, 5-fluorouracil and leucovorin for additional information on these products, and specifically **DOSAGE AND ADMINISTRATION** for guidance on dose adjustments.

- **Locally Advanced, Metastatic or Recurrent Non Small Cell Lung Cancer (NSCLC)**

ZIRABEV, in combination with carboplatin/paclitaxel chemotherapy regimen, is indicated for treatment of patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer.

- **Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer**

ZIRABEV in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens. These patients should not have received prior VEGF-targeted therapy including ZIRABEV. The effectiveness of bevacizumab in platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer is based on a study in patients with disease progression within < 6 months from the most recent platinum-based chemotherapy, with a minimum of 4 platinum therapy cycles completed. A statistically significant improvement in progression-free survival was seen. No overall survival benefit was demonstrated with bevacizumab.

- **Malignant Glioma (WHO Grade IV) – Glioblastoma**

ZIRABEV, in combination with lomustine, is indicated for the treatment of patients with glioblastoma after relapse or disease progression, following prior therapy.

The efficacy of bevacizumab in relapsed glioblastoma is based on an improvement in progression free survival, while an improvement in overall survival was not demonstrated in study EORTC 26101 (see **CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG** for information).

### 1.1 Pediatrics

The safety and efficacy of ZIRABEV in pediatric patients have not been assessed (see **WARNINGS AND PRECAUTIONS**, Special Populations, Pediatrics section).

### 1.2 Geriatrics

See **WARNINGS AND PRECAUTIONS**, Special Populations, Geriatrics section.

## 2 CONTRAINDICATIONS

ZIRABEV is contraindicated in patients who are hypersensitive to this drug, Chinese hamster ovary cell products or other recombinant human or humanised antibodies or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

ZIRABEV is contraindicated in patients with untreated Central Nervous System (CNS) metastases (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).

## 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

**Serious Warnings and Precautions**

**Eye Disorders**

ZIRABEV is not formulated and has not been authorized for intravitreal use. Local and systemic adverse events have been reported in the post-market setting with unauthorized intravitreal use (see **WARNINGS AND PRECAUTIONS**, General).

**Gastrointestinal Perforations**

ZIRABEV administration can result in the development of gastrointestinal perforation in some instances resulting in fatality. Gastrointestinal perforation, sometimes associated with intra-abdominal abscess, occurred throughout treatment with ZIRABEV (i.e. was not correlated to duration of exposure). The typical presentation was reported as abdominal pain associated with symptoms such as constipation and vomiting. Gastrointestinal perforation should be included in the differential diagnosis of patients on ZIRABEV presenting with abdominal pain. The incidence of gastrointestinal perforation, some fatal, in bevacizumab treated patients ranges from 0.3 to 3.2%. Gastrointestinal perforations (including gastrointestinal fistula and abscess) have been reported in up to 2.7% in patients with metastatic colorectal cancer, and 1.7% in platinum-resistant ovarian cancer studies. The incidence of gastrointestinal perforation in patients receiving irinotecan/bolus 5-fluorouracil/leucovorin with bevacizumab was 2%. ZIRABEV therapy should be permanently discontinued in patients with gastrointestinal perforation (see **WARNINGS AND PRECAUTIONS**, Gastrointestinal and **ADVERSE REACTIONS**, Gastrointestinal).

**Wound Healing Complications**

ZIRABEV administration can result in wound dehiscence, in some instances resulting in fatality. ZIRABEV therapy should be permanently discontinued in patients with wound dehiscence requiring medical intervention. ZIRABEV should be discontinued at least 28 days prior to elective surgery. ZIRABEV therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed (see **WARNINGS AND PRECAUTIONS**, Peri-Operative Considerations, Wound Healing).

**Hemorrhage**

Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, central nervous systems (CNS) hemorrhage, epistaxis, and vaginal bleeding occurred up to five-fold more frequently in patients receiving bevacizumab. Do not administer ZIRABEV to patients with serious hemorrhage or recent hemoptysis (see **DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**).

## 4 DOSAGE AND ADMINISTRATION

### 4.1 Dosing Considerations

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

There are no recommended dose reductions. Discontinue ZIRABEV for:

- Gastrointestinal perforations (gastrointestinal perforations, fistula formation in the gastrointestinal tract, intra-abdominal abscess);
- Internal fistula not arising in the GI tract, tracheoesophageal (TE) fistula or any Grade 4 fistula;
- Wound dehiscence and wound healing complications requiring medical intervention;
- Necrotizing fasciitis;
- Serious hemorrhage or recent hemoptysis;
- Severe arterial thromboembolic events;
- Life- threatening (Grade 4) VTEs, including pulmonary embolism;
- Severe hypertension not controlled with medical management;
- Hypertensive crisis or hypertensive encephalopathy;
- Posterior Reversible Encephalopathy Syndrome (PRES);
- Nephrotic syndrome.

Temporarily suspend ZIRABEV for:

- At least 4 weeks prior to elective surgery;
- Moderate to severe proteinuria pending further evaluation;
- Severe infusion reactions.

### 4.2 Recommended Dose and Dosage Adjustment

Health Canada has not authorized an indication for pediatric use (see **WARNINGS AND PRECAUTIONS**, Special Populations, Pediatrics).

**Metastatic Colorectal Cancer**

The recommended dose of ZIRABEV is 5 mg/kg of body weight given once every 14 days as an intravenous infusion.

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

The recommended dose of ZIRABEV is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion in addition to carboplatin + paclitaxel chemotherapy regimen.

In clinical trials, bevacizumab was administered in addition to carboplatin/paclitaxel chemotherapy for up to 6 cycles of treatment followed by bevacizumab as a single agent until disease progression.

**Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer**

The recommended dose of ZIRABEV is 10 mg/kg of body weight given once every 2 weeks as an intravenous infusion when administered in combination with one of the following agents – paclitaxel, topotecan (given weekly) or pegylated liposomal doxorubicin (see **CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG** section, Study MO22224 (AURELIA) for chemotherapy regimens).

Alternatively, the recommended dose of ZIRABEV is 15 mg/kg every 3 weeks when administered in combination with topotecan given on days 1-5, every 3 weeks (see **CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG** section, Study MO22224 (AURELIA) for chemotherapy regimen).

**Malignant Glioma (WHO Grade IV) - Glioblastoma**

The recommended dose of ZIRABEV is 10 mg/kg of body weight given once every 2 weeks as an intravenous infusion in combination with lomustine every 6 weeks until disease progression. An oral dose of 90 mg/m$^2$ (maximum dose 160 mg) of lomustine is recommended for the first cycle; in the absence of Grade > 1 hematological toxicity during the first cycle, it can be escalated to 110 mg/m$^2$ (maximum dose 200 mg) from the second cycle onwards (see also **CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG** section).

### 4.3 Administration

**Do not administer as an intravenous push or bolus.**

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

**ZIRABEV INFUSIONS SHOULD NOT BE ADMINISTERED OR MIXED WITH DEXTROSE OR GLUCOSE SOLUTIONS.** A concentration-dependent degradation profile of bevacizumab was observed when diluted with dextrose solutions (5%).

No incompatibilities between ZIRABEV and polyvinyl chloride, polyolefin bags or ethylene vinyl acetate (EVA) have been observed.

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

Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

ZIRABEV is not formulated for intravitreal use (see **WARNINGS AND PRECAUTIONS**, General).

### 4.4 Missed Dose

For a missed dose of ZIRABEV, the physician will decide when the patient should receive the next one.

## 5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

In addition to the possible adverse reactions listed, the highest dose of bevacizumab tested in humans (20 mg/kg of body weight, intravenous, multiple doses) was associated with severe migraine in several patients.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table 1 – Dosage Forms, Strengths, Composition and Packaging**

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|---|---|---|
| Intravenous | 100 mg (25 mg/mL solution for injection)<br>400 mg (25 mg/mL solution for injection) | Edetate disodium dihydrate (EDTA), Polysorbate 80, Sodium hydroxide, Succinic Acid, Sucrose, Water for Injection |

**Availability:**

ZIRABEV is available as single-use, preservative-free, clear glass vials with butyl rubber stopper containing 25 mg/mL bevacizumab as either 100 mg bevacizumab in 4 mL or 400 mg bevacizumab in 16 mL. Non-medicinal ingredients: edetate disodium dihydrate (EDTA), polysorbate 80, sodium hydroxide, succinic acid, sucrose and water for injection. Packs of 1 vial.

The vial stopper is not manufactured with natural rubber latex.

## 7 DESCRIPTION

ZIRABEV (bevacizumab) is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF).

## 8 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

### General

No studies on the effects on the ability to drive and use machines have been performed.

All patients discontinuing treatment with ZIRABEV should be monitored according to medical practice.

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

### Unauthorized Intravitreal Use: Eye Disorders

Individual cases and clusters of serious ocular adverse events affecting multiple patients have been reported from unauthorized intravitreal use of bevacizumab following variable and non-validated methods in compounding, storage, and handling of bevacizumab vials authorized for intravenous administration in cancer patients. These events included infectious endophthalmitis (some cases leading to permanent blindness, one case reported extraocular extension of infection resulting in meningoencephalitis), intraocular inflammation[i] (such as sterile endophthalmitis, uveitis, and vitritis) (some cases leading to permanent blindness), retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular hemorrhage (such as vitreous hemorrhage or retinal hemorrhage), conjunctival hemorrhage.

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

[i] Gower et al. Adverse Event Rates Following Intravitreal Injection of AVASTIN or LUCENTIS for Treating Age-Related Macular Degeneration ARVO 2011, Poster 6644, Data on File
[ii] Ibid

### Unauthorized Intravitreal Use: Systemic Events

An observational claims database[iii] study comparing unauthorized intravitreal bevacizumab to an authorized treatment in patients treated for wet age-related macular degeneration has reported an increased risk of hemorrhagic stroke for bevacizumab (adjusted HR: 1.57; 99% CI: 1.04,

2.37) (Incidence 0.41 events per 100 patients per year; comparator 0.26 events per 100 patients per year) as well as an increased risk for overall mortality (adjusted HR: 1.11; 99% CI: 1.01, 1.23) (Incidence 6.03 events per 100 patients per year; comparator 5.51 events per 100 patients per year). A second observational study found similar results for all-cause mortality.[iv] A randomized controlled clinical trial comparing unauthorized bevacizumab to an authorized treatment for patients with wet age-related macular degeneration[v] has reported an increased risk of serious systemic adverse events for bevacizumab, most of which resulted in hospitalization (adjusted risk ratio 1.29; 95% CI: 1.01, 1.66) (Incidence 24.1%; comparator 19.0%). The most frequent serious systemic adverse events reported directly to the sponsor include myocardial infarction, cerebrovascular accident, and hypertension.

[iii] Ibid
[iv] Curtis LH, et al. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration. Arch Ophthalmol. 2010;128(10):1273-1279
[v] Comparison of Age-Related Macular Degeneration Treatment Trials (CATT) Research Group, Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration. 10.1056/NEJMoa1102673

## Selected Adverse Reactions

### Cardiovascular

### Hypertension

An increased incidence of hypertension was observed in patients treated with bevacizumab.

Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre-existing hypertension should be adequately controlled before starting ZIRABEV treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Frequently monitor of blood pressure (e.g. 2-3 weeks) during ZIRABEV therapy in order to detect potentially serious complications of therapy, including hypertensive encephalopathy and Posterior Reversible Encephalopathy Syndrome (PRES) (see Neurologic and **ADVERSE REACTIONS**).

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

### Thromboembolism (see ADVERSE REACTIONS)

#### *Arterial Thromboembolism*

In clinical trials, the incidence of Arterial Thromboembolic Events (ATEs) including cerebrovascular accident, transient ischemic attack and myocardial infarction was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone.

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

Patients receiving bevacizumab plus chemotherapy with a history of arterial thromboembolism, diabetes or age greater than 65 years have an increased risk of developing arterial thromboembolic events during bevacizumab therapy. Caution should be used when treating such patients with ZIRABEV (see **ADVERSE REACTIONS**). Regular clinical, and if necessary, special radiological investigations, should be performed to assess for signs of ATEs. Appropriate treatment, including permanent discontinuation of bevacizumab, should be carried out in case of identified ATE.

***Venous Thromboembolism***

Patients may be at risk of developing Venous Thromboembolic Events (VTEs), including pulmonary embolism under ZIRABEV treatment.

In a clinical trial, patients with persistent, recurrent, or metastatic cervical cancer who were administered bevacizumab showed an increased risk of venous thromboembolic events (see **ADVERSE REACTIONS**, Venous thromboembolism). ZIRABEV is not authorized for use in cervical cancer.

ZIRABEV should be discontinued in patients with life-threatening (Grade 4) VTEs, including pulmonary embolism. Patients with ≤ Grade 3 venous thromboembolism need to be monitored closely in accordance with local practice guidelines and receive appropriate treatment for VTEs including discontinuation of ZIRABEV therapy if their condition deteriorates.

**Congestive Heart Failure (CHF)/Cardiomyopathy**

Events consistent with congestive heart failure (CHF) were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalization.

Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with ZIRABEV. CHF was observed in all cancer indications. 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 (see **ADVERSE REACTIONS**). ZIRABEV is not authorized for the treatment of metastatic breast cancer. The signs and symptoms of CHF include unspecific symptoms such as fatigue, weakness and fainting and depending on the side of heart affected, abdominal pain, nausea, orthopnea, pulmonary and/or peripheral edema, shortness of breath, palpitations and/or irregular fast heartbeat.

If symptomatic cardiac failure develops during therapy with ZIRABEV, it should be treated with the standard medications for this purpose. Discontinuation of ZIRABEV should be strongly considered in patients who develop clinically significant congestive heart failure, taking into account a careful benefit-risk assessment.

**Driving and Operating Machinery**

Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

**Gastrointestinal (see ADVERSE REACTIONS)**

**Gastrointestinal Perforations and Fistula**

Patients may be at increased risk for the development of gastrointestinal perforation and fistulae when treated with ZIRABEV and chemotherapy (see **ADVERSE REACTIONS**). Bevacizumab use has been associated with serious and sometimes fatal cases of gastrointestinal perforation and fistula in clinical trials (see **ADVERSE REACTIONS**). In bevacizumab clinical trials, gastrointestinal fistulae have been reported with the highest incidence of around 2% in patients with metastatic colorectal cancer and ovarian cancer, but were also reported less commonly in patients with other types of cancers (e.g. breast cancer, lung cancer and others). The typical presentation may include abdominal pain, nausea, emesis, constipation, and fever. The majority of cases occurred within the first 50 days of initiation of bevacizumab.

In a clinical trial, patients with persistent, recurrent, or metastatic cervical cancer who were administered bevacizumab showed an increased risk of fistulae between the vagina and any part of the GI tract (gastrointestinal-vaginal fistulae) (see **ADVERSE REACTIONS**, Gastrointestinal Perforations and Fistula). Prior radiation is an additional important risk factor for the development of GI-vaginal fistulae. ZIRABEV is not authorized for use in cervical cancer.

ZIRABEV should be permanently discontinued in patients who develop gastrointestinal perforation. Patients may be at increased risk for the development of gallbladder perforation when treated with ZIRABEV (see **ADVERSE REACTIONS**).

**Non-Gastrointestinal Fistula (see ADVERSE REACTIONS)**

Patients may be at increased risk for the development of fistulae when treated with ZIRABEV. Bevacizumab use has been associated with serious cases of fistulae including events resulting in death.

Permanently discontinue ZIRABEV in patients with 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, ZIRABEV should be discontinued.

Serious and sometimes fatal non-gastrointestinal fistula formation involving tracheoesophageal, bronchopleural, biliary, vaginal, renal and bladder sites occurs at a higher incidence in bevacizumab -treated patients compared to controls. Uncommon (≥ 0.1% to < 1%) reports of non-gastrointestinal perforation were observed in clinical studies across various indications at any time points ranging from one week to greater than 1 year from initiation of bevacizumab treatment, with most of the events occurring within the first 6 months of bevacizumab therapy. Fistulae have also been reported in post-marketing experience. Although other risk factors (e.g. diagnosis of cancer, cancer progression, cancer treatments) are known to be associated with an increased risk of development of fistulae, a role for ZIRABEV in increasing this risk cannot be excluded.

**Tracheoesophageal (TE) Fistula**

Cases of TE fistula have been reported in lung and esophageal cancer studies of bevacizumab in combination with chemotherapy alone or with concurrent radiation treatment. TE fistulae have not to date been reported in patients with metastatic colorectal cancer, but the possibility that this is a rare adverse drug reaction associated with bevacizumab in indications other than lung or esophageal cancer cannot be excluded.

Permanently discontinue ZIRABEV in patients with tracheoesophageal (TE) fistula.

**Genitourinary**

**Ovarian Failure**

ZIRABEV may cause ovarian failure. Therefore, fertility preservation strategies and hormonal changes should be discussed with women of reproductive potential prior to starting treatment with ZIRABEV (see Special Populations, Pregnant Women and **ADVERSE REACTIONS**). Long term effects of the treatment with ZIRABEV on fertility are unknown.

**Proteinuria**

Patients with a history of hypertension are at increased risk for the development of proteinuria when treated with ZIRABEV. There is evidence suggesting that ≥ Grade 1 proteinuria may be related to bevacizumab dose. Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria with serial urinalyses during ZIRABEV therapy. Patients with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection.

Temporarily suspend ZIRABEV administration for ≥ 2 grams of proteinuria/24 hours and resume when proteinuria is <2 grams/24 hours. ZIRABEV should be permanently discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome) (see **ADVERSE REACTIONS**). Proteinuria may not completely resolve after discontinuation of ZIRABEV.

Data from a post-marketing safety study showed poor correlation between UPCR (Urine Protein/Creatinine Ratio) and 24 hour urine protein (Pearson Correlation 0.39 (95% CI 0.17, 0.57)).

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

Limited safety information is available for patients with proteinuria ≥ 0.5g/24 hr urine collection as they were excluded from clinical trials.

**Hematologic**

**Hemorrhage (see ADVERSE REACTIONS)**

Patients treated with ZIRABEV have an increased risk of hemorrhage, especially tumour-associated hemorrhage. ZIRABEV can result in gastrointestinal bleeding, hematemesis, CNS hemorrhage, hemoptysis, epistaxis or vaginal bleeding. Patients should be monitored for bleeding events. ZIRABEV should be permanently discontinued in patients who experienced

Grade 3 or 4 bleeding (i.e. bleeding requiring medical intervention) during ZIRABEV therapy, and aggressive medical management should be initiated. Routine assessment of this event should include serial complete blood counts and physical examination.

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

***CNS hemorrhage***

Cases of CNS hemorrhage, some with fatal outcome, have been observed with bevacizumab use. Patients should be monitored for signs and symptoms of CNS bleeding, and ZIRABEV treatment discontinued in case of intracranial bleeding.

The risk of CNS hemorrhage in patients with CNS metastases receiving bevacizumab could not be fully evaluated, as these patients were excluded from clinical trials (see **CONTRAINDICATIONS**).

Intracranial hemorrhage can occur in patients with relapsed glioblastoma. In study EORTC 26101, 2.5% of patients in the bevacizumab + Lomustine arm versus 0.7% in the Lomustine arm experienced intracranial hemorrhage.

**Pulmonary Hemorrhage/ Hemoptysis**

Patients with non–small cell lung cancer treated with ZIRABEV may be at risk for serious, and in some cases fatal, pulmonary hemorrhage/hemoptysis. Patients with recent pulmonary hemorrhage/hemoptysis (>1/2 teaspoon red blood) should not be treated with ZIRABEV (see **ADVERSE REACTIONS**: Hemorrhage).

**Neutropenia and Infections (see ADVERSE REACTIONS)**

Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone. Patients should be closely monitored for signs of febrile neutropenia, and white blood cell count carried out according to local oncology standards. Treatment of neutropenia and febrile neutropenia should follow established oncological standards.

**Thrombocytopenia**

The incidence of thrombocytopenia was higher in patients receiving bevacizumab in combination with chemotherapy (eg.cisplatin/gemcitabine) compared to those who received chemotherapy alone.

**Hypersensitivity Reactions, Infusion Reactions**

Patients may be at risk of developing infusion/hypersensitivity reactions. Close observation of the patient during and following the administration of ZIRABEV is recommended as expected for any infusion of a therapeutic humanized monoclonal antibody. If a reaction occurs, the infusion should be interrupted and appropriate medical therapies should be administered. A systematic premedication specifically for ZIRABEV administration, in general, is not warranted; however, use of premedication should be based on clinical judgment.

Infusion reactions reported in the clinical trials and post-marketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis.

**Hepatic/Biliary/Pancreatic**

The safety and efficacy of ZIRABEV has not been studied in patients with hepatic impairment.

**Neurologic**

**Posterior Reversible Encephalopathy Syndrome (PRES) (previously known as Reversible Posterior Leukoencephalopathy Syndrome (RPLS))**

There have been rare reports of patients treated with bevacizumab 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. PRES has been reported with an incidence rate of up to 0.8% in clinical studies. The frequency of PRES was 0.5% in cervical cancer, 0.5% in glioblastoma multiforme, 0.1% in NSCLC, 0.2% in ovarian cancer, and 0.3% in renal cancer. No cases of PRES were reported in metastatic colorectal carcinoma and breast cancer trials.

The symptoms of PRES may be difficult to differentiate from those of uncontrolled hypertension, therefore neurological examination should be carried out in a patient presenting with the above signs and symptoms. Brain imaging, particularly Magnetic Resonance Imaging (MRI), confirms the diagnosis of PRES. The onset of symptoms has been reported to occur from 16 hours to 1 year after initiation of bevacizumab. Discontinue ZIRABEV in patients developing PRES, and treat patient-specific symptoms including control of hypertension. Signs and symptoms of PRES usually resolve within days, although neurologic sequelae may remain. The safety of reinitiating therapy with ZIRABEV in patients previously experiencing PRES is not known (see **ADVERSE REACTIONS**).

**Osteonecrosis of the Jaw (ONJ)**

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

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

invasive dental procedures should be avoided, if possible. Other known risk factors for ONJ include other treatments such as radiotherapy and glucocorticoids.

**Peri-Operative Considerations**

**Wound Healing**

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

ZIRABEV therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experience wound healing complications during ZIRABEV treatment, ZIRABEV should be withheld until the wound is fully healed. ZIRABEV therapy should be withheld for elective surgery (see **ADVERSE REACTIONS**).

Necrotizing fasciitis including fatal cases, has rarely been reported in patients treated with bevacizumab; usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. ZIRABEV therapy should be discontinued in patients who develop necrotizing fasciitis, and appropriate treatment should be promptly initiated (see sections Post Market Adverse Reactions and **CLINICAL TRIALS**).

**Renal**

The safety and efficacy of ZIRABEV have not been studied in patients with renal impairment (see Proteinuria and Genitourinary above).

**Hepatic**

The safety and efficacy of ZIRABEV has not been studied in patients with hepatic impairment.

## 8.1 Special Populations

### 8.1.1 Pregnant Women

There are no adequate and well controlled studies in pregnant women. IgGs are known to cross the placental barrier, and ZIRABEV may inhibit angiogenesis in the fetus. In the post-marketing setting, cases of fetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see Post Market Adverse Reactions).

Therefore, ZIRABEV should not be used during pregnancy. In women with childbearing potential, appropriate precautions must be undertaken to avoid pregnancy and at least two contraceptive methods should be used with ZIRABEV therapy and for at least 6 months following the last dose of ZIRABEV.

Angiogenesis has been shown to be critically important to fetal development. The inhibition of angiogenesis following administration of ZIRABEV could result in an adverse outcome of pregnancy.

Bevacizumab has been shown to be embryotoxic and teratogenic when administered to rabbits. Observed effects included decreases in maternal and fetal body weights, an increased number of fetal resorptions and an increased incidence of specific gross and skeletal fetal alterations. Adverse fetal outcomes were observed at all tested doses of 10-100 mg/kg.

**Women of Reproductive Potential**

Repeat dose safety studies in animals have shown that bevacizumab may have an adverse effect on female fertility (see **NON-CLINICAL TOXICOLOGY – REFERENCE BIOLOGIC DRUG**). A substudy with 295 women of reproductive potential has shown a higher incidence of new cases of ovarian failure in the bevacizumab group compared to the control group (39.0 vs. 2.6%). After discontinuation of bevacizumab treatment, ovarian function recovered in the majority (86%) of patients. Long term effects of the treatment with bevacizumab on fertility are unknown (see **ADVERSE REACTIONS**).

### 8.1.2 Breast-feeding

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

### 8.1.3 Pediatrics

ZIRABEV is not approved for use in patients under the age of 18 years. The safety and efficacy of ZIRABEV in this population has not been established. The addition of bevacizumab to standard of care did not demonstrate clinical benefit in pediatric patients in two phase II clinical trials: one in pediatric high grade glioma and one in pediatric metastatic rhabdomyosarcoma (RMS) or non-rhabdomyosarcoma soft tissue sarcoma (NRSTS). See **CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG section**; Pediatric Studies.

In published reports, cases of osteonecrosis at sites other than the jaw have been observed in patients under the age of 18 years exposed to bevacizumab (see **NON-CLINICAL TOXICOLOGY – REFERENCE BIOLOGIC DRUG**, Physeal Development).

### 8.1.4 Geriatrics

Patients receiving ZIRABEV plus chemotherapy with a history of arterial thromboembolism, diabetes and age greater than 65 years have a higher risk of arterial thromboembolic events. Caution should be used when treating these patients with ZIRABEV (see **ADVERSE REACTIONS**). In randomised clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic events (including cerebrovascular accidents, transient ischemic attacks, myocardial infarction), Grade 3-4 leukopenia, neutropenia, thrombocytopenia, proteinuria, diarrhea and fatigue as compared to those aged ≤ 65 years when treated with bevacizumab (see **WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**). The risk and benefit of ZIRABEV administration in patients > 65 should be carefully evaluated prior to initiating therapy.

In study E4599, patients aged >65 years receiving carboplatin, paclitaxel, and bevacizumab had a greater relative risk for proteinuria as compared to younger patients.

## 9 ADVERSE REACTIONS

The adverse drug reaction profiles reported in clinical studies that compared ZIRABEV to the reference biologic drug were comparable. The description of adverse reactions in this section is based on clinical experience with the reference biologic drug.

### 9.1 Adverse Reaction Overview

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

The most serious adverse drug reactions were:

- Gastrointestinal Perforations (see **WARNINGS AND PRECAUTIONS**)
- Hemorrhage including pulmonary hemorrhage/hemoptysis, which is more common in NSCLC patients (see **WARNINGS AND PRECAUTIONS**)
- Arterial Thromboembolism (see **WARNINGS AND PRECAUTIONS**)
- Non-gastrointestinal Fistula
- Hypertensive Crises
- Posterior Reversible Encephalopathy Syndrome (PRES)
- Neutropenia and Infections
- Nephrotic Syndrome
- Congestive Heart Failure

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

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

### 9.2 Clinical Trial Adverse Reactions

*Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

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

palmar-plantar erythrodysaesthesia syndrome with capecitabine or pegylated liposomal doxorubicin and peripheral sensory neuropathy with paclitaxel or oxaliplatin and nail disorders or alopecia with paclitaxel.

**Table 2 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 (≥10%) | Common (≥1% - ≥10%) | Very common (≥10%) |
| **Infections and infestations** | | Sepsis<br>Abcess<br>Cellulitis<br>Infection | |
| **Blood and the lympthatic systems disorders** | Febrile neutropenia<br>Leukopenia<br>Neutropenia<br>Thrombocytopenia | Anemia<br>Lymphopenia | |
| **Metabolism and nutrition disorders** | | Dehydration<br>Hyponatremia | Anorexia<br>Hypomagnesemia<br>Hyponatremia |
| **Nervous system disorders** | Peripheral sensory neuropathy | Cerebrovascular accident<br>Syncope<br>Somnolence Headache | Dysgeusia Headache |
| **Eye disorders** | | | Eye disorder<br>Lacrimation increased |
| **Cardiac disorders** | | Cardiac failure congestive<br>Supraventricular tachycardia | |
| **Vascular disorders** | Hypertension | Thromboembolism (arterial)<br>Deep vein thrombosis<br>Hemorrhage | Hypertension |
| **Respiratory, thoracic and mediastinal disorders** | | Pulmonary embolism<br>Dyspnea Hypoxia<br>Epistaxis | Dyspnea<br>Epistaxis<br>Rhinitis<br>Cough |

| 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 (≥10%)** | **Common (≥1% - ≥10%)** | **Very common (≥10%)** |
| **Gastrointestinal disorders** | Diarrhea<br>Nausea<br>Vomiting<br>Abdominal pain | Intestinal Perforation<br>Ileus<br>Intestinal obstruction<br>Recto-vaginal fistulae*<br>Gastrointestinal disorder<br>Stomatits<br>Proctalgia | Constipation<br>Stomatitis<br>Rectal hemorrhage |
| **Endocrine disorders** | | | Ovarian failure** |
| **Skin and subcutaneous tissue disorders** | | Palmar-plantar erythrodysaesthesia syndrome | Exfoliative dermatitis<br>Dry skin<br>Skin discolouration |
| **Musculoskeletal, connective tissue and bone disorders** | | Muscular weakness<br>Myalgia<br>Back pain | Arthralgia |
| **Renal and urinary disorders** | | Proteinuria<br>Urinary Tract Infection | Proteinuria |
| **General disorders and administration site conditions** | Asthenia<br>Fatigue | Pain<br>Lethargy<br>Mucosal Inflammation | Pyrexia<br>Asthenia<br>Pain<br>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

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

**Metastatic Colorectal Cancer (mCRC) (Studies AVF 2107g, AVF 0780g, and AVF 2192g)**

Data presented in Table 3 are based on the experience with the recommended dose of bevacizumab in 788 patients treated with IFL in Study AVF2107g.

**Table 3 NCI-CTC Grade 3 and 4 Adverse Events (Events with ≥ 2% Higher Incidence in Arm 2) in Study AVF2107g**

| **Adverse Event**<br>**System Organ Class (MedDRA)** | **Arm 1**<br>**IFL* + Placebo**<br>**(n = 396)** | **Arm 2**<br>**IFL* + bevacizumab**<br>**(n = 392)** |
|---|---|---|
| Patients with at least one adverse event | 293 (74.0%) | 333 (84.9%) |
| **Cardiac Disorders** | 9 (2.3%) | 43 (11.0%) |
| Hypertension | | |
| **Blood & Lymphatic System Disorders** | 123 (31.1%) | 145 (37.0%) |
| Leukopenia | | |
| **Gastrointestinal Disorders** | | |
| Abdominal pain NOS | 20 (5.1%) | 28 (7.1%) |
| Diarrhoea NOS | 98 (24.7%) | 127(32.4%) |
| **General Disorders & Administration Site Conditions** | | |
| Pain NOS | 12 (3.0%) | 20 (5.1%) |
| **Vascular Disorders** | | |
| Thromboembolism (Arterial )** | 3 (0.8%) | 12 (3.1%) |
| Deep Vein Thrombosis | 25 (6.3%) | 35 (8.9%) |

* IFL = irinotecan/5-fluorouracil/leucovorin (see Table 4 for treatment regimen)
** This represents a pooled list of thromboembolic events of arterial origin including myocardial infarction, cerebrovascular accident, transient ischaemic attack and other arterial thromboembolism.
Data are unadjusted for the differential time on treatment
Median duration of safety observation was 28 weeks for Arm 1 and 40 weeks for Arm 2
NOS = Not otherwise specified

The safety profile of 5-FU/LV + bevacizumab combination (Arm 3) and concurrently enrolled patients in IFL + placebo arm (Arm 1) and IFL + bevacizumab arm (Arm 2) is shown in Table 4.

**Table 4 Adverse Events of all Grades during Randomised Therapy (Events with ≥10% Higher Incidence in Arms 2 or 3 Compared to Arm 1) in Study AVF2107g: Patients Enrolled in Arm 3 and Concurrently Enrolled Patients in Arms 1 and 2**

| MedDRA System Organ Class Adverse Event | Arm 1 IFL + Placebo (n = 98) | Arm 2* IFL + bevacizumab (n = 102) | Arm 3 Bolus 5-FU/LV + bevacizumab (n = 109) |
|---|---|---|---|
| **Cardiac Disorders** | | | |
| Hypertension | 14 (14.3%) | 22 (21.6%) | 37 (33.9%) |
| **General Disorders & Administration Site Conditions** | | | |
| Pain NOS | 34 (34.7%) | 51 (50.0%) | 43 (39.4%) |
| **Gastrointestinal Disorders** | | | |
| Constipation | 28 (28.6%) | 41 (40.2%) | 32 (29.4%) |
| Rectal Hemorrhage | 2 (2.0%) 13 (13.3%) | 17 (16.7%) 24 (23.5%) | 9 (8.3%) 19 (17.4%) |
| **Metabolism & Nutrition Disorders** | | | |
| Anorexia | 29 (29.6%) | 44 (43.1%) | 37 (33.9%) |
| **Respiratory, Thoracic & Mediastinal Disorders** | | | |
| Epistaxis | 10 (10.2%) | 36 (35.3%) | 35 (32.1%) |
| Dyspnoea | 15 (15.3%) | 26 (25.5%) | 27 (24.8%) |
| Rhinitis NOS | 12 (12.2%) | 26 (25.5%) | 23 (21.1%) |
| **Skin & Subcutaneous Tissue Disorders** | | | |
| Dry Skin | 7 (7.1%) | 7 (6.9%) | 22 (20.2%) |
| Exfoliative Dermatitis | 3 (3.1%) | 3 (2.9%) | 21 (19.3%) |
| Skin Discolouration | 3 (3.1%) | 2 (2.0%) | 17 (15.6%) |
| **Nervous System Disorders** | | | |
| Dysgeusia | 8 (8.2%) | 12 (11.8%) | 21 (19.3%) |
| **Eye Disorders** | | | |
| Eye Disorders NOS | 2 (2.0%) | 6 (5.9%) | 20 (18.3%) |

*Showed the safety profile at the time of the decision that the combination of IFL + bevacizumab (Arm 2) was sufficiently safe, and subsequently enrollment in the 5-FU/LV + bevacizumab arm (Arm 3) was discontinued.
NOS = Not otherwise specified

NCI-CTC Grade 3 or 4 events were experienced by 71.2% of patients in the 5 FU/LV + placebo arm and 87% of patients in the 5-FU/LV + bevacizumab arm (see Table 5). Common adverse events of any Grade with a higher incidence of ≥10% in the 5 FU/LV + bevacizumab arm compared to the 5-FU/LV + placebo arm are displayed in Table 5.

**Table 5 NCI-CTC Grade 3 or 4 Adverse Events during Randomized Therapy (Events with ≥ 2% Higher Incidence in Arm 2) in Study AVF2192g**

| MedDRA System Organ Class Adverse Event | Arm 1 5-FU/LV + Placebo (n = 104) | Arm 2 5-FU/LV + bevacizumab (n = 100) |
|---|---|---|
| Subjects with at least one adverse event | 74 (71.2%) | 87 (87.0%) |
| **Cardiac Disorders** | | |
| Hypertension | 3 (2.9%) | 16 (16.0%) |
| **General Disorders & Administration Site Conditions** | | |
| Asthenia | 12 (11.5%) | 17 (17.0%) |
| Pain NOS | 2 (1.9%) | 6 (6.0%) |
| **Infections & Infestations** | | |
| Abcess | 1 (1.0%) | 3 (3.0%) |
| Sepsis | 3 (2.9%) | 8 (8.0%) |
| **Nervous System Disorders** | | |
| Syncope | 2 (1.9%) | 4 (4.0%) |
| Cerebral ischemia | 1 (1.0%) | 3 (3.0%) |
| **Vascular Disorders** | | |
| Thromboembolism (Arterial)* | 5 (4.8%) | 9 (9.0%) |

*This represents a pooled list of thromboembolic events of arterial origins including myocardial infarction, cerebrovascular accident, cerebral ischaemia and infarct, and other arterial thromboembolism.
Note: Data are unadjusted for the differential time on treatment.
Median duration of safety observation was 23 weeks for Arm 1 and 31 weeks for Arm 2.

**Table 6 Adverse Events of all Grades (NCI-CTC) during Randomized Therapy (Events with ≥10% Higher Incidence in Arm 2 compared to Arm 1) in Study AVF2192g**

| MedDRA System Organ Class Adverse Event | Arm 1 5-FU/LV + Placebo (n = 104) | Arm 2 5-FU/LV + bevacizumab (n = 100) |
|---|---|---|
| Total | 102 (98.1%) | 100 (100%) |
| **Cardiac Disorders** | | |
| Hypertension | 5 (4.8%) | 32 (32.0%) |
| **Gastrointestinal Disorders** | | |
| Stomatitis | 13 (12.5%) | 25 (25.0%) |
| **Central Disorders & Administration Site Conditions** | | |
| Asthenia | 63 (60.6%) | 76 (76.0%) |
| Pain NOS | 21 (20.2%) | 34 (34.0%) |
| Pyrexia | 11 (10.6%) | 24 (24.0%) |

Note: Data are unadjusted for the differential time on treatment.
Median duration of safety observation was 23 weeks for Arm 1 and 31 weeks for Arm 2.

**Locally Advanced, Metatstatic or Recurrent Non Small Cell Lung Cancer (NSCLC) (Studies E4599 and AVF0757g)**

**Table 7 All NCI-CTC Grade 3-5 Non-Hematologic* and Grade 4-5 Hematologic* Adverse Events (i.e. regardless of drug relationship) occurring in ≥ 1% of Patients in Study E4599 (NSCLC)**

| Toxicity Category and Term | Control Arm | Treatment Arm |
|---|---|---|
| | Carboplatin/Paclitaxel | Bevacizumab + Carboplatin/Paclitaxel |
| | (n=441) | (n=427) |
| **Blood/Bone Marrow** | | |
| Neutrophils | 76 (17.2%) | 113 (26.5%) |
| Leukocytes | 11 (2.5%) | 19 (4.4%) |
| Platelets | 1 (0.2%) | 7 (1.6%) |
| **Cardiovascular (Arrhythmia)** | | |
| Sinus Tachycardia | 4 (0.9%) | 7 (1.6%) |
| Supraventricular Arrhythmias | 7 (1.6%) | 2 (0.5%) |
| **Cardiovascular (General)** | | |
| Hypertension | 3 (0.7%) | 33 (7.7%) |
| Thrombosis/Embolism | 14 (3.2%) | 24 (5.6%) |
| Hypotension | 11 (2.5%) | 14 (3.3%) |
| Cardiac-Ischemia | 3 (0.7%) | 7 (1.6%) |
| **Constitutional Symptoms** | | |
| Fatigue | 57 (12.9%) | 67 (15.7%) |
| Constitutional | 1 (0.2%) | 19 (4.4%) |
| Fever | 6 (1.4%) | 7 (1.6%) |
| **Dermatology/Skin** | | |
| Rash/Desquamation | 4 (0.9%) | 10 (2.3%) |
| **Gastrointestinal** | | |
| Nausea | 25 (5.7%) | 27 (6.3%) |
| Vomiting | 20 (4.5%) | 25 (5.9%) |
| Anorexia | 17 (3.9%) | 24 (5.6%) |
| Dehydration | 18 (4.1%) | 23 (5.4%) |
| Constipation | 15 (3.4%) | 13 (3.0%) |
| Diarrhea | 9 (2.0%) | 15 (3.5%) |
| Stomatitis | 5 (1.1%) | 2 (0.5%) |
| **Hemorrhage** | | |
| Hemoptysis | 2 (0.5%) | 9 (2.1%) |
| Melena/GI Bleeding | 2 (0.5%) | 5 (1.2%) |
| **Hepatic** | | |
| SGPT | 3 (0.7%) | 5 (1.2%) |
| **Infection/Febrile Neutropenia** | | |
| Infection w/o Neutropenia | 12 (2.7%) | 30 (7.0%) |
| Febrile Neutropenia | 8 (1.8%) | 23 (5.4%) |
| Infection w/ Grade 3 or 4 | 9 (2.0%) | 19 (4.4%) |
| Infection-Other | 1 (0.2%) | 5 (1.2%) |
| **Neurology** | | |
| Neuropathy−Sensory | 48 (10.9%) | 39 (9.1%) |
| Dizziness/ Lightheadedness | 8 (1.8%) | 14 (3.3%) |
| Confusion | 10 (2.3%) | 11 (2.6%) |

| Toxicity Category and Term | Control Arm | Treatment Arm |
|---|---|---|
| | Carboplatin/Paclitaxel | Bevacizumab + Carboplatin/Paclitaxel |
| | (n=441) | (n=427) |
| Syncope | 9 (2.0%) | 8 (1.9%) |
| Neuropathy−Motor | 8 (1.8%) | 7 (1.6%) |
| Cerebrovascular Ischemia | 3 (0.7%) | 6 (1.4%) |
| Anxiety/Agitation | 6 (1.4%) | 1 (0.2%) |
| **Metabolic/Laboratory** | | |
| Hyperglycemia | 17 (3.9%) | 17 (4.0%) |
| Hyponatremia | 5 (1.1%) | 16 (3.7%) |
| Hypokalemia | 5 (1.1%) | 8 (1.9%) |
| **Muscoloskeletal** | | |
| Muscle Weakness | 15 (3.4%) | 17 (4.0%) |
| Musculoskeletal-Other | 0 (0.0%) | 6 (1.4%) |
| **Allergy/Immunology** | | |
| Allergic Reaction | 13 (2.9%) | 17 (4.0%) |
| **Pain** | | |
| Bone Pain | 18 (4.1%) | 18 (4.2%) |
| Myalgia | 21 (4.8%) | 17 (4.0%) |
| Arthralgia | 16 (3.6%) | 18 (4.2%) |
| Abdominal Pain | 6 (1.4%) | 14 (3.3%) |
| Headache | 2 (0.5%) | 13 (3.0%) |
| Chest Pain | 4 (0.9%) | 9 (2.1%) |
| Pain-Other | 8 (1.8%) | 6 (1.4%) |
| Tumour Pain | 5 (1.1%) | 5 (1.2%) |
| **Pulmonary** | | |
| Dyspnea | 66 (15.0%) | 56 (13.1%) |
| Pneumonitis/Pulmonary Infiltrates | 11 (2.5%) | 21 (4.9%) |
| Hypoxia | 15 (3.4%) | 14 (3.3%) |
| Cough | 8 (1.8%) | 10 (2.3%) |
| Pulmonary−Other | 5 (1.1%) | 7 (1.6%) |
| Pleural Effusion | 3 (0.7%) | 5 (1.2%) |
| **Renal/Genitourinary** | | |
| Proteinuria | 0 (0.0%) | 13 (3.0%) |

*Grade 1-2 non-hematologic and Grade 1-3 hematologic adverse events were not assessed in the clinical trial.

Table 8 below includes adverse events that occurred with ≥ 2% increased frequency in the bevacizumab group over the control arm.

**Table 8 Adverse Events That Occurred with ≥ 2% Difference in Rates between Treatment Arms: Treated Patients, Study E4599 (NSCLC)**

| | No. (%) of Patients | |
|---|---|---|
| **NCI-CTC Category Term[a]** | **Control Arm** | **Treatment Arm** |
| | **Carboplatin Paclitaxel (n = 441)** | **bevacizumab + Carboplatin Paclitaxel (n = 427)** |
| Any event | 286 (64.9%) | 327 (76.6%) |
| **Blood/bone marrow** | | |
| Neutropenia | 76 (17.2%) | 112 (26.2%) |
| **Constitutional symptoms** | | |
| Fatigue | 57 (12.9%) | 67 (15.7%) |
| **Infection/febrile neutropenia** | | |
| Infection without neutropenia | 12 (2.7%) | 22 (5.2%) |
| Febrile neutropenia | 8 (1.8%) | 19 (4.4%) |
| **Cardiovascular (general)** | | |
| Hypertension | 3 (0.7%) | 32 (7.5%) |
| **Metabolic/laboratory** | | |
| Hyponatremia | 5 (1.1%) | 15 (3.5%) |
| **Pain** | | |
| Headache | 2 (0.5%) | 13 (3.0%) |
| **Renal/genitourinary** | | |
| Proteinuria | 0 (0.0%) | 13 (3.0%) |

BV/CP = bevacizumab + carboplatin/paclitaxel; CP = carboplatin/paclitaxel.

Note: Events were sorted by highest relative frequency across all treatment groups combined.

[a] Events were reported and graded according to NCI-CTC, Version 2.0. Per protocol, investigators were required to report only Grade 3–5 non- hematologic and Grade 4–5 hematologic events.

**Table 9 Adverse Events (i.e. regardless of drug relationship) occurring in ≥ 4%* of Patients in Study AVF0757g (NSCLC)**

| Body System/Preferred Term | Control Arm | Treatment Arm | Treatment Arm |
|---|---|---|---|
| | Carboplatin Paclitaxel | Bevacizumab 7.5 mg/kg + Carboplatin Paclitaxel | Bevacizumab 15 mg/kg + Carboplatin Paclitaxel |
| | (N=32) | (N=32) | (N=34) |
| **Body as a Whole** | | | |
| Asthenia | 22 (68.80%) | 24 (75.00%) | 26 (76.50%) |
| Headache | 3 (9.40%) | 10 (31.30%) | 16 (47.10%) |
| Pain | 13 (40.60%) | 13 (40.60%) | 14 (41.20%) |
| Chest Pain | 9 (28.10%) | 6 (18.80%) | 12 (35.30%) |
| Infection | 8 (25.00%) | 10 (31.30%) | 12 (35.30%) |
| Fever | 4 (12.50%) | 11 (34.40%) | 11 (32.40%) |
| Abdominal Pain | 3 (9.40%) | 4 (12.50%) | 8 (23.50%) |
| Back Pain | 2 (6.30%) | 5 (15.60%) | 4 (11.80%) |
| Chills | 3 (9.40%) | 4 (12.50%) | 4 (11.80%) |
| Reaction Unevaluable | 1 (3.10%) | 4 (12.50%) | 0 (0.00%) |
| Moniliasis | 0 (0.00%) | 0 (0.00%) | 3 (8.80%) |
| Cellulitis | 0 (0.00%) | 2 (6.30%) | 2 (5.90%) |
| Abscess | 0 (0.00%) | 0 (0.00%) | 2 (5.90%) |
| Accidental Injury | 1 (3.10%) | 1 (3.10%) | 2 (5.90%) |
| Mucous Membrane Disorder | 2 (6.30%) | 1 (3.10%) | 2 (5.90%) |
| Allergic Reaction | 2 (6.30%) | 1 (3.10%) | 0 (0.00%) |
| **Cardiovascular** | | | |
| Hypertension | 1 (3.10%) | 5 (15.60%) | 6 (17.60%) |
| Hemorrhage | 0 (0.00%) | 4 (12.50%) | 0 (0.00%) |
| Hypotension | 1 (3.10%) | 4 (12.50%) | 3 (8.80%) |
| Vasodilatation | 3 (9.40%) | 4 (12.50%) | 4 (11.80%) |
| Syncope | 2 (6.30%) | 2 (6.30%) | 4 (11.80%) |
| Cerebrovascular Accident | 0 (0.00%) | 0 (0.00%) | 2 (5.90%) |
| Deep Thrombophlebitis | 0 (0.00%) | 1 (3.10%) | 2 (5.90%) |
| Phlebitis | 1 (3.10%) | 0 (0.00%) | 2 (5.90%) |
| Tachycardia | 1 (3.10%) | 1 (3.10%) | 2 (5.90%) |
| Thrombosis | 0 (0.00%) | 0 (0.00%) | 2 (5.90%) |
| Heart Arrest | 2 (6.30%) | 0 (0.00%) | 0 (0.00%) |
| **Digestive** | | | |
| Nausea | 15 (46.90%) | 16 (50.00%) | 17 (50.00%) |
| Anorexia | 8 (25.00%) | 9 (28.10%) | 14 (41.20%) |
| Constipation | 13 (40.60%) | 13 (40.60%) | 14 (41.20%) |
| Diarrhea | 6 (18.80%) | 9 (28.10%) | 14 (41.20%) |
| Dyspepsia | 7 (21.90%) | 8 (25.00%) | 6 (17.60%) |

| Body System/Preferred Term | Control Arm | Treatment Arm | Treatment Arm |
|---|---|---|---|
| | Carboplatin Paclitaxel | Bevacizumab 7.5 mg/kg + Carboplatin Paclitaxel | Bevacizumab 15 mg/kg + Carboplatin Paclitaxel |
| | (N=32) | (N=32) | (N=34) |
| Stomatitis | 3 (9.40%) | 5 (15.60%) | 8 (23.50%) |
| Vomiting | 6 (18.80%) | 6 (18.80%) | 8 (23.50%) |
| Oral Moniliasis | 0 (0.00%) | 3 (9.40%) | 1 (2.90%) |
| Dysphagia | 2 (6.30%) | 1 (3.10%) | 3 (8.80%) |
| Flatulence | 2 (6.30%) | 1 (3.10%) | 3 (8.80%) |
| Rectal Disorder | 0 (0.00%) | 0 (0.00%) | 3 (8.80%) |
| Nausea And Vomiting | 0 (0.00%) | 2 (6.30%) | 0 (0.00%) |
| Cheilitis | 0 (0.00%) | 0 (0.00%) | 2 (5.90%) |
| Liver Function Tests Abnormal | 1 (3.10%) | 1 (3.10%) | 2 (5.90%) |
| Rectal Hemorrhage | 1 (3.10%) | 1 (3.10%) | 2 (5.90%) |
| Ulcerative Stomatitis | 0 (0.00%) | 0 (0.00%) | 2 (5.90%) |
| **Hemic and Lymphatic** | | | |
| Leukopenia | 10 (31.30%) | 15 (46.90%) | 19 (55.90%) |
| Anemia | 7 (21.90%) | 6 (18.80%) | 10 (29.40%) |
| Thrombocytopenia | 5 (15.60%) | 2 (6.30%) | 7 (20.60%) |
| Ecchymosis | 0 (0.00%) | 0 (0.00%) | 4 (11.80%) |
| Hypochromic Anemia | 1 (3.10%) | 1 (3.10%) | 2 (5.90%) |
| **Metabolic/Nutrition** | | | |
| Peripheral Edema | 6 (18.80%) | 7 (21.90%) | 5 (14.70%) |
| Hyperglycemia | 3 (9.40%) | 4 (12.50%) | 7 (20.60%) |
| Weight Loss | 0 (0.00%) | 2 (6.30%) | 6 (17.60%) |
| Alkaline Phosphatase Increased | 1 (3.10%) | 0 (0.00%) | 3 (8.80%) |
| Dehydration | 2 (6.30%) | 1 (3.10%) | 3 (8.80%) |
| Hypocalcemia | 1 (3.10%) | 2 (6.30%) | 1 (2.90%) |
| Edema | 0 (0.00%) | 1 (3.10%) | 2 (5.90%) |
| SGOT Increased | 1 (3.10%) | 0 (0.00%) | 2 (5.90%) |
| SGPT Increased | 2 (6.30%) | 0 (0.00%) | 2 (5.90%) |
| **Musculoskeletal** | | | |
| Arthralgia | 16 (50.00%) | 17 (53.10%) | 14 (41.20%) |
| Myalgia | 16 (50.00%) | 9 (28.10%) | 9 (26.50%) |
| Arthritis | 2 (6.30%) | 4 (12.50%) | 0 (0.00%) |
| Bone Pain | 0 (0.00%) | 3 (9.40%) | 2 (5.90%) |
| Leg Cramps | 1 (3.10%) | 1 (3.10%) | 3 (8.80%) |
| Myasthenia | 2 (6.30%) | 1 (3.10%) | 3 (8.80%) |
| **Nervous** | | | |
| Peripheral Neuritis | 9 (28.10%) | 8 (25.00%) | 13 (38.20%) |
| Paresthesia | 7 (21.90%) | 9 (28.10%) | 12 (35.30%) |
| Insomnia | 14 (43.80%) | 8 (25.00%) | 5 (14.70%) |

| Body System/Preferred Term | Control Arm | Treatment Arm | Treatment Arm |
|---|---|---|---|
| | Carboplatin Paclitaxel | Bevacizumab 7.5 mg/kg + Carboplatin Paclitaxel | Bevacizumab 15 mg/kg + Carboplatin Paclitaxel |
| | (N=32) | (N=32) | (N=34) |
| Depression | 2 (6.30%) | 5 (15.60%) | 8 (23.50%) |
| Anxiety | 4 (12.50%) | 3 (9.40%) | 7 (20.60%) |
| Confusion | 0 (0.00%) | 2 (6.30%) | 5 (14.70%) |
| Dizziness | 4 (12.50%) | 4 (12.50%) | 5 (14.70%) |
| Neuropathy | 9 (28.10%) | 4 (12.50%) | 5 (14.70%) |
| Somnolence | 1 (3.10%) | 0 (0.00%) | 4 (11.80%) |
| Agitation | 0 (0.00%) | 2 (6.30%) | 0 (0.00%) |
| Nervousness | 2 (6.30%) | 2 (6.30%) | 2 (5.90%) |
| Amnesia | 0 (0.00%) | 0 (0.00%) | 2 (5.90%) |
| Ataxia | 1 (3.10%) | 0 (0.00%) | 2 (5.90%) |
| Emotional Lability | 0 (0.00%) | 1 (3.10%) | 2 (5.90%) |
| **Respiratory** | | | |
| Cough Increased | 8 (25.00%) | 12 (37.50%) | 17 (50.00%) |
| Epistaxis | 2 (6.30%) | 10 (31.30%) | 15 (44.10%) |
| Dyspnea | 11 (34.40%) | 14 (43.80%) | 14 (41.20%) |
| Hemoptysis | 2 (6.30%) | 9 (28.10%) | 4 (11.80%) |
| Pharyngitis | 3 (9.40%) | 5 (15.60%) | 9 (26.50%) |
| Rhinitis | 0 (0.00%) | 8 (25.00%) | 7 (20.60%) |
| Voice Alteration | 0 (0.00%) | 5 (15.60%) | 8 (23.50%) |
| Sinusitis | 1 (3.10%) | 3 (9.40%) | 7 (20.60%) |
| Lung Disorder | 3 (9.40%) | 6 (18.80%) | 6 (17.60%) |
| Bronchitis | 1 (3.10%) | 3 (9.40%) | 4 (11.80%) |
| Hiccup | 1 (3.10%) | 2 (6.30%) | 2 (5.90%) |
| Pleural Effusion | 0 (0.00%) | 2 (6.30%) | 0 (0.00%) |
| Pneumonia | 2 (6.30%) | 2 (6.30%) | 1 (2.90%) |
| Asthma | 2 (6.30%) | 1 (3.10%) | 2 (5.90%) |
| **Skin and Appendages** | | | |
| Alopecia | 17 (53.10%) | 20 (62.50%) | 22 (64.70%) |
| Rash | 3 (9.40%) | 11 (34.40%) | 8 (23.50%) |
| Pruritus | 0 (0.00%) | 5 (15.60%) | 2 (5.90%) |
| Sweating | 3 (9.40%) | 4 (12.50%) | 4 (11.80%) |
| Acne | 1 (3.10%) | 0 (0.00%) | 4 (11.80%) |
| **Special Senses** | | | |
| Taste Perversion | 1 (3.10%) | 3 (9.40%) | 2 (5.90%) |
| Amblyopia | 2 (6.30%) | 0 (0.00%) | 3 (8.80%) |
| Ear Pain | 2 (6.30%) | 1 (3.10%) | 3 (8.80%) |
| Tinnitus | 1 (3.10%) | 2 (6.30%) | 1 (2.90%) |
| **Urogenital** | | | |

| Body System/Preferred Term | Control Arm | Treatment Arm | Treatment Arm |
|---|---|---|---|
| | Carboplatin Paclitaxel | Bevacizumab 7.5 mg/kg + Carboplatin Paclitaxel | Bevacizumab 15 mg/kg + Carboplatin Paclitaxel |
| | (N=32) | (N=32) | (N=34) |
| Urinary Tract Infection | 0 (0.00%) | 1 (3.10%) | 5 (14.70%) |
| Cystitis | 0 (0.00%) | 0 (0.00%) | 3 (8.80%) |
| Urinary Incontinence | 1 (3.10%) | 0 (0.00%) | 2 (5.90%) |
| Urinary Frequency | 3 (9.40%) | 0 (0.00%) | 0 (0.00%) |

*Due to the size of the trial and rates, the table of adverse events occurring in ≥ 1% patients was condensed to the table of adverse events occurring in ≥4 % of patients (1 patients per group equals <4%).

**Table 10 Summary of Adverse Events that Occurred with ≥4%* Difference in Incidence Rate between Treatment Arms in Study AVF0757g**

| Body System/Preferred Term | Control Arm | Treatment Arm | Treatment Arm |
|---|---|---|---|
| | Carboplatin Paclitaxel | Bevacizumab 7.5 mg/kg + Carboplatin Paclitaxel | Bevacizumab 15 mg/kg + Carboplatin Paclitaxel |
| | (N=32) | (N=32) | (N=34) |
| **Body as a Whole** | | | |
| Asthenia | 22 (68.80%) | 24 (75.00%) | 26 (76.50%) |
| Headache | 3 (9.40%) | 10 (31.30%) | 16 (47.10%) |
| Chest Pain | 9 (28.10%) | 6 (18.80%) | 12 (35.30%) |
| Infection | 8 (25.00%) | 10 (31.30%) | 12 (35.30%) |
| Fever | 4 (12.50%) | 11 (34.40%) | 11 (32.40%) |
| Abdominal Pain | 3 (9.40%) | 4 (12.50%) | 8 (23.50%) |
| Back Pain | 2 (6.30%) | 5 (15.60%) | 4 (11.80%) |
| Reaction Unevaluable | 1 (3.10%) | 4 (12.50%) | 0 (0.00%) |
| Moniliasis | 0 (0.00%) | 0 (0.00%) | 3 (8.80%) |
| Cellulitis | 0 (0.00%) | 2 (6.30%) | 2 (5.90%) |
| Abscess | 0 (0.00%) | 0 (0.00%) | 2 (5.90%) |
| **Cardiovascular** | | | |
| Hypertension | 1 (3.10%) | 5 (15.60%) | 6 (17.60%) |
| Hemorrhage | 0 (0.00%) | 4 (12.50%) | 0 (0.00%) |
| Hypotension | 1 (3.10%) | 4 (12.50%) | 3 (8.80%) |
| Syncope | 2 (6.30%) | 2 (6.30%) | 4 (11.80%) |
| Cerebrovascular Accident | 0 (0.00%) | 0 (0.00%) | 2 (5.90%) |
| Deep Thrombophlebitis | 0 (0.00%) | 1 (3.10%) | 2 (5.90%) |

| Body System/Preferred Term | Control Arm | Treatment Arm | Treatment Arm |
|---|---|---|---|
| | Carboplatin Paclitaxel | Bevacizumab 7.5 mg/kg + Carboplatin Paclitaxel | Bevacizumab 15 mg/kg + Carboplatin Paclitaxel |
| | (N=32) | (N=32) | (N=34) |
| Thrombosis | 0 (0.00%) | 0 (0.00%) | 2 (5.90%) |
| **Digestive** | | | |
| Anorexia | 8 (25.00%) | 9 (28.10%) | 14 (41.20%) |
| Diarrhea | 6 (18.80%) | 9 (28.10%) | 14 (41.20%) |
| Stomatitis | 3 (9.40%) | 5 (15.60%) | 8 (23.50%) |
| Vomiting | 6 (18.80%) | 6 (18.80%) | 8 (23.50%) |
| Oral Moniliasis | 0 (0.00%) | 3 (9.40%) | 1 (2.90%) |
| Rectal Disorder | 0 (0.00%) | 0 (0.00%) | 3 (8.80%) |
| Nausea And Vomiting | 0 (0.00%) | 2 (6.30%) | 0 (0.00%) |
| Cheilitis | 0 (0.00%) | 0 (0.00%) | 2 (5.90%) |
| Ulcerative Stomatitis | 0 (0.00%) | 0 (0.00%) | 2 (5.90%) |
| **Hemic and Lymphatic** | | | |
| Leukopenia | 10 (31.30%) | 15 (46.90%) | 19 (55.90%) |
| Anemia | 7 (21.90%) | 6 (18.80%) | 10 (29.40%) |
| Thrombocytopenia | 5 (15.60%) | 2 (6.30%) | 7 (20.60%) |
| Ecchymosis | 0 (0.00%) | 0 (0.00%) | 4 (11.80%) |
| **Metabolic/Nutrition** | | | |
| Hyperglycemia | 3 (9.40%) | 4 (12.50%) | 7 (20.60%) |
| Weight Loss | 0 (0.00%) | 2 (6.30%) | 6 (17.60%) |
| Alkaline Phosphatase | 1 (3.10%) | 0 (0.00%) | 3 (8.80%) |
| Edema | 0 (0.00%) | 1 (3.10%) | 2 (5.90%) |
| **Musculoskeletal** | | | |
| Arthritis | 2 (6.30%) | 4 (12.50%) | 0 (0.00%) |
| Bone Pain | 0 (0.00%) | 3 (9.40%) | 2 (5.90%) |
| Leg Cramps | 1 (3.10%) | 1 (3.10%) | 3 (8.80%) |
| **Nervous** | | | |
| Peripheral Neuritis | 9 (28.10%) | 8 (25.00%) | 13 (38.20%) |
| Paresthesia | 7 (21.90%) | 9 (28.10%) | 12 (35.30%) |
| Depression | 2 (6.30%) | 5 (15.60%) | 8 (23.50%) |
| Anxiety | 4 (12.50%) | 3 (9.40%) | 7 (20.60%) |
| Confusion | 0 (0.00%) | 2 (6.30%) | 5 (14.70%) |
| Somnolence | 1 (3.10%) | 0 (0.00%) | 4 (11.80%) |
| Agitation | 0 (0.00%) | 2 (6.30%) | 0 (0.00%) |
| Amnesia | 0 (0.00%) | 0 (0.00%) | 2 (5.90%) |
| Emotional Lability | 0 (0.00%) | 1 (3.10%) | 2 (5.90%) |
| **Respiratory** | | | |
| Cough Increased | 8 (25.00%) | 12 (37.50%) | 17 (50.00%) |

| Body System/Preferred Term | Control Arm | Treatment Arm | Treatment Arm |
|---|---|---|---|
| | Carboplatin Paclitaxel | Bevacizumab 7.5 mg/kg + Carboplatin Paclitaxel | Bevacizumab 15 mg/kg + Carboplatin Paclitaxel |
| | (N=32) | (N=32) | (N=34) |
| Epistaxis | 2 (6.30%) | 10 (31.30%) | 15 (44.10%) |
| Dyspnea | 11 (34.40%) | 14 (43.80%) | 14 (41.20%) |
| Hemoptysis | 2 (6.30%) | 9 (28.10%) | 4 (11.80%) |
| Pharyngitis | 3 (9.40%) | 5 (15.60%) | 9 (26.50%) |
| Rhinitis | 0 (0.00%) | 8 (25.00%) | 7 (20.60%) |
| Voice Alteration | 0 (0.00%) | 5 (15.60%) | 8 (23.50%) |
| Sinusitis | 1 (3.10%) | 3 (9.40%) | 7 (20.60%) |
| Lung Disorder | 3 (9.40%) | 6 (18.80%) | 6 (17.60%) |
| Bronchitis | 1 (3.10%) | 3 (9.40%) | 4 (11.80%) |
| Pleural Effusion | 0 (0.00%) | 2 (6.30%) | 0 (0.00%) |
| **Skin and Appendages** | | | |
| Alopecia | 17 (53.10%) | 20 (62.50%) | 22 (64.70%) |
| Rash | 3 (9.40%) | 11 (34.40%) | 8 (23.50%) |
| Pruritus | 0 (0.00%) | 5 (15.60%) | 2 (5.90%) |
| Acne | 1 (3.10%) | 0 (0.00%) | 4 (11.80%) |
| **Special Senses** | | | |
| Taste Perversion | 1 (3.10%) | 3 (9.40%) | 2 (5.90%) |
| **Urogenital** | | | |
| Urinary Tract Infection | 0 (0.00%) | 1 (3.10%) | 5 (14.70%) |
| Cystitis | 0 (0.00%) | 0 (0.00%) | 3 (8.80%) |

*Due to the size of the trial and rates (1 patients per group equals <4%), the table is condensed to the table of adverse events occurring with ≥4% increased frequency in AVASTIN groups over the active control group.

**Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer**

**Table 11 All Treatment-Related Adverse Events with a Frequency of ≥1% in Either Treatment Arms in Study M022224**

| System Organ Class/ Preferred Term | Control Arm | Treatment Arm |
|---|---|---|
| | Chemotherapy | Chemotherapy + Bevacizumab |
| | (n=181) | (n=179) |
| **Blood And Lymphatic System Disorders** | | |
| Neutropenia | 46 (25.4%) | 52 (29.1%) |
| Anemia | 40 (22.1%) | 29 (16.2%) |
| Leukopenia | 25 (13.8%) | 21 (11.7%) |
| Thrombocytopenia | 12 (6.6%) | 10 (5.6%) |
| Lymphopenia | 7 (3.9%) | 1 (0.6%) |
| **Eye Disorders** | | |
| Lacrimation Increased | 0 (0.0%) | 3 (1.7%) |
| **Gastrointestinal Disorders** | | |
| Nausea | 8 (4.4%) | 14 (7.8%) |
| Diarrhea | 8 (4.4%) | 11 (6.1%) |
| Vomiting | 13 (7.2%) | 8 (4.5%) |
| Constipation | 9 (5.0%) | 6 (3.4%) |
| Abdominal Pain Upper | 1 (0.6%) | 4 (2.2%) |
| Abdominal Pain | 3 (1.7%) | 3 (1.7%) |
| Aphthous Stomatitis | 1 (0.6%) | 3 (1.7%) |
| Dyspepsia | 1 (0.6%) | 2 (1.1%) |
| Oesophagitis | 2 (1.1%) | 2 (1.1%) |
| Stomatitis | 0 (0.0%) | 2 (1.1%) |
| **General Disorders And Administration Site Conditions** | | |
| Fatigue | 38 (21.0%) | 41 (22.9%) |
| Mucosal Inflammation | 10 (5.5%) | 20 (11.2%) |
| Pyrexia | 2 (1.1%) | 3 (1.7%) |
| General Physical Health Disorder | 1 (0.6%) | 2 (1.1%) |
| Edema Peripheral | 1 (0.6%) | 2 (1.1%) |
| Asthenia | 5 (2.8%) | 1 (0.6%) |
| **Immune System Disorders** | | |
| Hypersensitivity | 3 (1.7%) | 2 (1.1%) |
| **Infections And Infestations** | | |
| Tooth Abscess | 0 (0.0%) | 4 (2.2%) |

| System Organ Class/ Preferred Term | Control Arm | Treatment Arm |
|---|---|---|
| | Chemotherapy | Chemotherapy + Bevacizumab |
| | (n=181) | (n=179) |
| Infection | 2 (1.1%) | 3 (1.7%) |
| Localised Infection | 0 (0.0%) | 2 (1.1%) |
| Paronychia | 1 (0.6%) | 2 (1.1%) |
| Tooth Infection | 0 (0.0%) | 2 (1.1%) |
| Urinary Tract Infection | 3 (1.7%) | 2 (1.1%) |
| Nail Infection | 2 (1.1%) | 1 (0.6%) |
| Bronchitis | 2 (1.1%) | 0 (0.0%) |
| Oral Fungal Infection | 2 (1.1%) | 0 (0.0%) |
| **Investigations** | | |
| Weight Decreased | 4 (2.2%) | 6 (3.4%) |
| Gamma-Glutamyl transferase | 1 (0.6%) | 2 (1.1%) |
| Platelet Count Decreased | 4 (2.2%) | 2 (1.1%) |
| **Metabolism And Nutrition Disorders** | | |
| Decreased Appetite | 10 (5.5%) | 8 (4.5%) |
| Hypomagnesemia | 0 (0.0%) | 2 (1.1%) |
| **Musculoskeletal And Connective Tissue Disorders** | | |
| Pain In Extremity | 1 (0.6%) | 3 (1.7%) |
| Musculoskeletal Pain | 3 (1.7%) | 1 (0.6%) |
| **Nervous System Disorders** | | |
| Peripheral Sensory Neuropathy | 11 (6.1%) | 30 (16.8%) |
| **Renal And Urinary Disorders** | | |
| Proteinuria | 0 (0.0%) | 18 (10.1%) |
| **Respiratory, Thoracic And Mediastinal Disorders** | | |
| Epistaxis | 0 (0.0%) | 9 (5.0%) |
| Dyspnoea | 0 (0.0%) | 3 (1.7%) |
| Pulmonary Embolism | 2 (1.1%) | 3 (1.7%) |
| **Skin And Subcutaneous Tissue Disorders** | | |
| Palmar−Plantar Erythrodysaesthesia Syndrome | 8 (4.4%) | 19 (10.6%) |
| Alopecia | 11 (6.1%) | 15 (8.4%) |
| Nail Disorder | 1 (0.6%) | 7 (3.9%) |
| Nail Toxicity | 0 (0.0%) | 7 (3.9%) |
| Onycholysis | 3 (1.7%) | 7 (3.9%) |
| Erythema | 1 (0.6%) | 4 (2.2%) |

| System Organ Class/ Preferred Term | Control Arm | Treatment Arm |
|---|---|---|
| | Chemotherapy | Chemotherapy + Bevacizumab |
| | (n=181) | (n=179) |
| Rash | 1 (0.6%) | 4 (2.2%) |
| Nail Dystrophy | 1 (0.6%) | 3 (1.7%) |
| Skin Lesion | 1 (0.6%) | 2 (1.1%) |
| Skin Ulcer | 0 (0.0%) | 2 (1.1%) |
| Dermatitis | 2 (1.1%) | 0 (0.0%) |
| **Vascular Disorders** | | |
| Hypertension | 0 (0.0%) | 31 (17.3%) |
| Venous Thrombosis | 0 (0.0%) | 2 (1.1%) |

The most frequent (≥ 20%) all grade adverse events occurring in the bevacizumab plus paclitaxel arm were neutropenia, fatigue, peripheral sensory neuropathy, alopecia, and hypertension. The most frequent events occurring in the paclitaxel only arm were neutropenia, fatigue, and peripheral sensory neuropathy.

The most frequent (≥ 20%) events occurring in the bevacizumab plus PLD arm were mucosal inflammation, fatigue, proteinuria, palmar-plantar erythrodysaesthesia syndrome, and hypertension. The most frequent events occurring in the PLD only arm were fatigue.

The most frequent (≥ 20%) events occurring in the bevacizumab plus topotecan group were neutropenia, anemia, and fatigue. The most frequent events occurring in the topotecan only arm were neutropenia, anemia, and leukopenia.

In the bevacizumab plus paclitaxel group 45.0% of patients discontinued treatment due to adverse events compared to 16.4% in the paclitaxel group. The most common (≥ 2%) Grade 2–5 adverse events that led to study treatment discontinuation and occurred in the bevacizumab plus paclitaxel arm were neutropenia (5.0%), fatigue (6.7%), peripheral sensory neuropathy (11.7%), nail disorder (5.0%), nail dystrophy (3.3%), and nail toxicity (3.3%). In the bevacizumab plus PLD group 21.0% of patients discontinued treatment due to adverse events compared to 3.2% in the PLD group. The most common events that led to study treatment discontinuation and occurred in the bevacizumab plus PLD arm were palmar-plantar erythrodysaesthesia syndrome (8.1%) and hypertension (3.2%). In the bevacizumab plus topotecan group 21.1% of patients discontinued treatment due to adverse events compared to 7.9% in the topotecan group. The most common event that led to study treatment discontinuation and occurred in the bevacizumab plus topotecan arm was fatigue (3.5%).

Among patients initially randomized to chemotherapy alone, 72 (40%) crossed over to receive single-agent bevacizumab after progression of disease. Median duration of bevacizumab monotherapy in this subgroup was 11.6 weeks (0-55 week range). Grade 3–5 adverse events occurred in 19 / 72 patients (26.4%). Sixteen patients (22.2%) experienced Grade 3 adverse events. Two patients (2.8%) experienced Grade 4 adverse

events (transient ischemic attack and PRES). One patient (1.4%) experienced a Grade 5 GI hemorrhage.

**Table 12 Treatment-Emergent Adverse Events Occurring in ≥2% of Platinum-Resistant Recurrent Ovarian Cancer Patients Treated with Bevacizumab+Chemotherapy Compared to Those Treated with Chemotherapy Alone (by chemotherapy cohort) in Study M022224**

| System Organ Class / Preferred Term | Control Arm | Treatment Arm |
|---|---|---|
| | Paclitaxel + Placebo | Paclitaxel + Bevacizumab |
| | (n=55) | (n=60) |
| **Blood And Lymphatic System Disorders** | | |
| Neutropenia | 12 (21.8%) | 24 (40.0%) |
| Leukopenia | 6 (10.9%) | 9 (15.0%) |
| Anemia | 10 (18.2%) | 7 (11.7%) |
| Thrombocytopenia | 0 (0.0%) | 2 (3.3%) |
| **Eye Disorders** | | |
| Lacrimation Increased | 0 (0.0%) | 3 (5.0%) |
| Conjunctivitis | 0 (0.0%) | 2 (3.3%) |
| **Gastrointestinal Disorders** | | |
| Abdominal Pain | 8 (14.5%) | 7 (11.7%) |
| Abdominal Pain Upper | 1 (1.8%) | 4 (6.7%) |
| Aphthous Stomatitis | 0 (0.0%) | 3 (5.0%) |
| Dyspepsia | 0 (0.0%) | 2 (3.3%) |
| Subileus | 0 (0.0%) | 2 (3.3%) |
| Vomiting | 7 (12.7%) | 2 (3.3%) |
| Ascites | 4 (7.3%) | 0 (0.0%) |
| **General Disorders And Administration Site Conditions** | | |
| Fatigue | 21 (38.2%) | 20 (33.3%) |
| Pyrexia | 3 (5.5%) | 6 (10.0%) |
| Mucosal Inflammation | 0 (0.0%) | 4 (6.7%) |
| General Physical Health Deterioration | 0 (0.0%) | 2 (3.3%) |
| Asthenia | 2 (3.6%) | 0 (0.0%) |
| **Hepatobiliary Disorders** | | |
| Hyperbilirubinaemia | 0 (0.0%) | 2 (3.3%) |
| **Infections And Infestations** | | |
| Infection | 2 (3.6%) | 9 (15.0%) |
| Urinary Tract Infection | 4 (7.3%) | 6 (10.0%) |
| Cystitis | 2 (3.6%) | 4 (6.7%) |

| System Organ Class / Preferred Term | Control Arm | Treatment Arm |
|---|---|---|
| | Paclitaxel + Placebo | Paclitaxel + Bevacizumab |
| | (n=55) | (n=60) |
| Bronchitis | 0 (0.0%) | 2 (3.3%) |
| Device Related Infection | 0 (0.0%) | 2 (3.3%) |
| Sinusitis | 0 (0.0%) | 2 (3.3%) |
| Respiratory Tract Infection | 2 (3.6%) | 0 (0.0%) |
| **Investigations** | | |
| Weight Decreased | 0 (0.0%) | 2 (3.3%) |
| **Metabolism And Nutrition Disorders** | | |
| Decreased Appetite | 6 (10.9%) | 3 (5.0%) |
| Hypomagnesemia | 0 (0.0%) | 2 (3.3%) |
| **Musculoskeletal And Connective Tissue Disorders** | | |
| Musculoskeletal Pain | 4 (7.3%) | 3 (5.0%) |
| Bone Pain | 2 (3.6%) | 0 (0.0%) |
| **Nervous System Disorders** | | |
| Peripheral Sensory Neuropathy | 12 (21.8%) | 22 (36.7%) |
| Headache | 3 (5.5%) | 2 (3.3%) |
| Paraesthesia | 2 (3.6%) | 0 (0.0%) |
| **Psychiatric Disorders** | | |
| Anxiety | 2 (3.6%) | 0 (0.0%) |
| **Renal And Urinary Disorders** | | |
| Proteinuria | 0 (0.0%) | 7 (11.7%) |
| Vesical Fistula | 0 (0.0%) | 2 (3.3%) |
| **Respiratory, Thoracic And Mediastinal Disorders** | | |
| Epistaxis | 0 (0.0%) | 5 (8.3%) |
| Dyspnoea | 0 (0.0%) | 3 (5.0%) |
| Pulmonary Embolism | 3 (5.5%) | 0 (0.0%) |
| **Skin And Subcutaneous Tissue Disorders** | | |
| Alopecia | 8 (14.5%) | 12 (20.0%) |
| Nail Disorder | 0 (0.0%) | 7 (11.7%) |
| Onycholysis | 3 (5.5%) | 7 (11.7%) |
| Nail Toxicity | 0 (0.0%) | 6 (10.0%) |
| Nail Dystrophy | 1 (1.8%) | 3 (5.0%) |
| **Vascular Disorders** | | |
| Hypertension | 3 (5.5%) | 12 (20.0%) |
| Embolism Venous | 0 (0.0%) | 2 (3.3%) |

| System Organ Class / Preferred Term | Control Arm | Treatment Arm |
|---|---|---|
| | Paclitaxel + Placebo | Paclitaxel + Bevacizumab |
| | (n=55) | (n=60) |
| **Blood And Lymphatic System Disorders** | | |
| Anemia | 8 (12.7%) | 11 (17.7%) |
| Lymphopenia | 4 (6.3%) | 0 (0.0%) |
| **Gastrointestinal Disorders** | | |
| Abdominal Pain Upper | 1 (1.6%) | 3 (4.8%) |
| Subileus | 5 (7.9%) | 1 (1.6%) |
| **General Disorders And Administration Site Conditions** | | |
| Mucosal Inflammation | 7 (11.1%) | 18 (29.0%) |
| Asthenia | 3 (4.8%) | 1 (1.6%) |
| Pyrexia | 3 (4.8%) | 1 (1.6%) |
| **Infections and Infestations** | | |
| Urinary Tract Infection | 3 (4.8%) | 5 (8.1%) |
| Tooth Abscess | 0 (0.0%) | 4 (6.5%) |
| Cystitis | 1 (1.6%) | 3 (4.8%) |
| Bronchitis | 2 (3.2%) | 0 (0.0%) |
| **Investigations** | | |
| Weight Decreased | 4 (6.3%) | 6 (9.7%) |
| **Metabolism and Nutrition Disorders** | | |
| Dehydration | 1 (1.6%) | 3 (4.8%) |
| **Musculoskeletal and Connective Tissue Disorders** | | |
| Musculoskeletal Pain | 0 (0.0%) | 2 (3.2%) |
| **Nervous System Disorders** | | |
| Peripheral Sensory Neuropathy | 0 (0.0%) | 5 (8.1%) |
| Headache | 0 (0.0%) | 2 (3.2%) |
| **Psychiatric Disorders** | | |
| Depression | 2 (3.2%) | 0 (0.0%) |
| **Renal and Urinary Disorders** | | |
| Proteinuria | 1 (1.6%) | 13 (21.0%) |
| Hydronephrosis | 3 (4.8%) | 0 (0.0%) |
| **Respiratory Thoracic and Mediastinal Disorders** | | |
| Epistaxis | 0 (0.0%) | 4 (6.5%) |
| **Skin and Subcutaneous Tissue Disorders** | | |

| System Organ Class / Preferred Term | Control Arm | Treatment Arm |
|---|---|---|
| | Paclitaxel + Placebo | Paclitaxel + Bevacizumab |
| | (n=55) | (n=60) |
| Palmar-Plantar Erythrodysaesthesia Syndrome | 8 (12.7%) | 17 (27.4%) |
| Erythema | 1 (1.6%) | 4 (6.5%) |
| Dermatitis | 2 (3.2%) | 0 (0.0%) |
| **Vascular Disorders** | | |
| Hypertension | 4 (6.3%) | 19 (30.6%) |
| Venous Thrombosis | 0 (0.0%) | 2 (3.2%) |
| **Blood and Lymphatic System Disorders** | | |
| Neutropenia | 25 (39.7%) | 21 (36.8%) |
| Anemia | 30 (47.6%) | 17 (29.8%) |
| Leukopenia | 13 (20.6%) | 9 (15.8%) |
| Thrombocytopenia | 12 (19.0%) | 8 (14.0%) |
| **Gastrointestinal Disorders** | | |
| Abdominal Pain | 6 (9.5%) | 7 (12.3%) |
| Nausea | 3 (4.8%) | 7 (12.3%) |
| Diarrhea | 1 (1.6%) | 6 (10.5%) |
| Constipation | 7 (11.1%) | 5 (8.8%) |
| Vomiting | 7 (11.1%) | 5 (8.8%) |
| Subileus | 3 (4.8%) | 4 (7.0%) |
| Abdominal Pain Upper | 2 (3.2%) | 3 (5.3%) |
| Ileus | 0 (0.0%) | 3 (5.3%) |
| Intestinal Obstruction | 0 (0.0%) | 2 (3.5%) |
| Toothache | 0 (0.0%) | 2 (3.5%) |
| Ascites | 4 (6.3%) | 1 (1.8%) |
| Abdominal Distension | 3 (4.8%) | 0 (0.0%) |
| **General Disorders And Administration Site Conditions** | | |
| Fatigue | 12 (19.0%) | 14 (24.6%) |
| General Physical Health Deterioration | 0 (0.0%) | 2 (3.5%) |
| Mucosal Inflammation | 3 (4.8%) | 1 (1.8%) |
| Pyrexia | 5 (7.9%) | 1 (1.8%) |
| General Symptom | 2 (3.2%) | 0 (0.0%) |
| **Infections And Infestations** | | |
| Infection | 4 (6.3%) | 8 (14.0%) |
| Urinary Tract Infection | 6 (9.5%) | 4 (7.0%) |
| Nasopharyngitis | 0 (0.0%) | 2 (3.5%) |

| System Organ Class / Preferred Term | Control Arm | Treatment Arm |
|---|---|---|
| | Paclitaxel + Placebo | Paclitaxel + Bevacizumab |
| | (n=55) | (n=60) |
| Tooth Infection | 0 (0.0%) | 2 (3.5%) |
| **Investigations** | | |
| Weight Decreased | 1 (1.6%) | 3 (5.3%) |
| Platelet Count Decreased | 4 (6.3%) | 2 (3.5%) |
| Weight Increased | 0 (0.0%) | 2 (3.5%) |
| **Nervous System Disorders** | | |
| Peripheral Sensory Neuropathy | 1 (1.6%) | 5 (8.8%) |
| **Renal And Urinary Disorders** | | |
| Proteinuria | 0 (0.0%) | 2 (3.5%) |
| **Respiratory, Thoracic And Mediastinal Disorders** | | |
| Dyspnoea | 4 (6.3%) | 6 (10.5%) |
| Cough | 0 (0.0%) | 2 (3.5%) |

**Malignant Glioma (WHO Grade IV) - Glioblastoma**

**Table 13 Summary of Related Adverse Events with a frequency of ≥ 1 % in either treatment arms in Study EORTC 26101**

| System Organ Class/Preferred Term | Control Arm | Treatment Arm |
|---|---|---|
| | Lomustine | Bevacizumab + Lomustine |
| | (n=147) | (n=278) |
| **Gastrointestinal Disorders** | | |
| Nausea | 21 (14.3%) | 57 (20.5%) |
| Vomiting | 7 (4.8%) | 19 (6.8%) |
| Stomatitis | 4 (2.7%) | 21 (7.6%) |
| Constipation | 8 (5.4%) | 15 (5.4%) |
| Diarrhoea | 5 (3.4%) | 18 (6.5%) |
| Abdominal Pain | 2 (1.4%) | 9 (3.2%) |
| Dry Mouth | 2 (1.4%) | 4 (1.4%) |
| Periodontal Disease | 0 (0%) | 6 (2.2%) |
| Mouth Haemorrhage | 0 (0%) | 5 (1.8%) |
| Gastrooesophageal Reflux Disease | 2 (1.4%) | 2 (0.7%) |
| Oesophageal Pain | 0 (0%) | 4 (1.4%) |
| Dyspepsia | 2 (1.4%) | 1 (0.4%) |
| Haemorrhoids | 0 (0%) | 3 (1.1%) |
| Rectal Haemorrhage | 0 (0%) | 3 (1.1%) |
| **General Disorders And Administration Site Conditions** | | |
| Fatigue | 51 (34.7%) | 143 (51.4%) |
| Malaise | 3 (2.0%) | 8 (2.9%) |
| Oedema Peripheral | 2 (1.4%) | 4 (1.4%) |
| Pyrexia | 0 (0%) | 5 (1.8%) |
| **Immune System Disorders** | | |
| Hypersensitivity | 1 (0.7%) | 5 (1.8%) |
| **Infections And Infestations** | | |
| Urinary Tract Infection | 1 (0.7%) | 5 (1.8%) |
| Herpes Zoster | 1 (0.7%) | 3 (1.1%) |
| Lung Infection | 2 (1.4%) | 2 (0.7%) |
| Wound Infection | 0 (0%) | 4 (1.4%) |
| Upper Respiratory Tract Infection | 0 (0%) | 3 (1.1%) |
| **Injury, Poisoning And Procedural Complications** | | |
| Wound Complication | 0 (0%) | 5 (1.8%) |

| System Organ Class/Preferred Term | Control Arm | Treatment Arm |
|---|---|---|
| | Lomustine | Bevacizumab + Lomustine |
| | (n=147) | (n=278) |
| Wound Dehiscence | 0 (0%) | 4 (1.4%) |
| **Investigations** | | |
| Weight Decreased | 2 (1.4%) | 9 (3.2%) |
| Gamma−Glutamyltransferase | 2 (1.4%) | 3 (1.1%) |
| **Metabolism And Nutrition Disorders** | | |
| Decreased Appetite | 4 (2.7%) | 26 (9.4%) |
| **Musculoskeletal And Connective Tissue Disorders** | | |
| Arthralgia | 1 (0.7%) | 12 (4.3%) |
| Myalgia | 1 (0.7%) | 7 (2.5%) |
| Muscular Weakness | 0 (0%) | 3 (1.1%) |
| **Nervous System Disorders** | | |
| Headache | 3 (2.0%) | 12 (4.3%) |
| Peripheral Sensory Neuropathy | 1 (0.7%) | 11 (4.0%) |
| Dysgeusia | 0 (0%) | 7 (2.5%) |
| Dizziness | 1 (0.7%) | 5 (1.8%) |
| Haemorrhage Intracranial | 0 (0%) | 5 (1.8%) |
| Peripheral Motor Neuropathy | 1 (0.7%) | 3 (1.1%) |
| **Respiratory, Thoracic And Mediastinal Disorders** | | |
| Epistaxis | 1 (0.7%) | 34 (12.2%) |
| Pulmonary Embolism | 0 (0%) | 13 (4.7%) |
| Dysphonia | 0 (0%) | 9 (3.2%) |
| Dyspnoea | 1 (0.7%) | 8 (2.9%) |
| Cough | 1 (0.7%) | 3 (1.1%) |
| Rhinitis Allergic | 1 (0.7%) | 3 (1.1%) |
| Pneumonitis | 3 (2.0%) | 0 (0%) |
| **Skin And Subcutaneous Tissue Disorders** | | |
| Pruritus | 1 (0.7%) | 8 (2.9%) |
| Rash Maculo−Papular | 3 (2.0%) | 6 (2.2%) |
| Alopecia | 1 (0.7%) | 6 (2.2%) |
| Dry Skin | 0 (0%) | 5 (1.8%) |
| Dermatitis Acneiform | 0 (0%) | 3 (1.1%) |
| Erythema | 2 (1.4%) | 0 (0%) |
| **Vascular Disorders** | | |
| Hypertension | 2 (1.4%) | 65 (23.4%) |

| System Organ Class/Preferred Term | Control Arm | Treatment Arm |
|---|---|---|
| | Lomustine | Bevacizumab + Lomustine |
| | (n=147) | (n=278) |
| Embolism | 0 (0%) | 10 (3.6%) |

All adverse events were collected in 425 patients enrolled in Study EORTC 26101 who received either Lomustine alone or bevacizumab plus Lomustine. All patients involved in the study had experienced first progression after radiation therapy concurrent/adjuvant chemotherapy for GBM. Of patients who discontinued any study treatment due to adverse events, there were 21.9% in the bevacizumab plus Lomustine arm, compared with 10.2% of patients in the Lomustine arm. In patients receiving bevacizumab plus Lomustine (N=278), the most frequently reported adverse events (regardless of drug relationship) of any grade (≥20%) were fatigue (61.9%), hypertension (33.1%), headache (31.7%), nausea (24.5%) and seizures (23.7%). The most frequently reported adverse events of grade ≥ 3 and with an incidence rate of at least 2 % were hypertension (15.1%), seizure (6.1%), fatigue (5.0%), pulmonary embolism (4.7%), dyspnea, (2.2%) and lung infection (2.2%).

## Further Information on Selected, Serious Adverse Drug Reactions

The following adverse drug reactions, reported using NCI-CTC (common toxicity criteria) for assessment of toxicity, have been observed in patients treated with bevacizumab.

## Cardiovascular

### Hypertension (see WARNINGS AND PRECAUTIONS)

An increased incidence of hypertension (all Grades) of up to 43.7% 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 NCI-CTC Grade 3 and 4 hypertension in patients receiving bevacizumab ranged from 3.0% 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 adequately controlled with oral anti-hypertensives such as angiotensin converting enzyme inhibitors, diuretics and calcium-channel blockers. It rarely resulted in discontinuation of treatment with bevacizumab or hospitalisation. Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal. ZIRABEV should be permanently discontinued in patients who develop hypertensive encephalopathy.

Hypertensive encephalopathy is a complication of malignant hypertension. Signs and symptoms may include severe hypertension associated with headache, nausea, vomiting, convulsions, or confusion. Hypertensive encephalopathy may be reversible if treated by progressively reducing blood pressure to near normal ranges within several hours.

**Posterior Reversible Encephalopathy Syndrome (PRES) (previously known as Reverse Posterior Leukoencephalopathy Syndrome (RPLS)) (see WARNINGS AND PRECAUTIONS)**

PRES has been reported with an incidence rate of up to 0.8% in clinical studies.

Symptoms usually resolve or improve within days, although some patients have experienced neurologic sequelae.

Two cases of PRES have been reported in one clinical study with platinum-resistant recurrent ovarian cancer. (1 patient in the treatment arm experienced Grade 3 PRES and 1 patient in the monotherapy crossover arm experienced Grade 4 PRES)

**Thromboembolism (see WARNINGS AND PRECAUTIONS)**

***Arterial Thromboembolism***

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

In clinical trials, the overall incidence ranged up to 5.9 % in the bevacizumab containing arms and 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 ischemic 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.

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

The incidence of all grade arterial thromboembolic events in study EORTC 26101 in patients with first recurrence of glioblastoma was comparable between the bevacizumab plus Lomustine arm and the Lomustine arm (11.5% vs. 10.9%;). The most commonly reported ATE events (in > 1% of patients in either treatment arm) were hemiparesis (19 patients [6.8%] in the bevacizumab plus Lomustine arm vs. 11 [7.5%] in the Lomustine arm) and embolism (11 [4.0%] vs. 3 [2.0%]).

***Venous Thromboembolism***

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

Grade 3-5 venous thromboembolic events have been reported in up to 7.8% of patients treated with chemotherapy plus bevacizumab compared with up to 4.9% in patients with chemotherapy alone.

Patients who have experienced a venous thromboembolic event may be at higher risk for a recurrence if they receive ZIRABEV in combination with chemotherapy versus chemotherapy alone.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer, Grade 3-5 venous thromboembolic events have been reported in up to 10.6% of patients treated with chemotherapy and bevacizumab compared with up to 5.4% in patients with chemotherapy alone. ZIRABEV is not authorized for use in cervical cancer.

In study EORTC 26101 in patients with first recurrence of glioblastoma, patients in the bevacizumab + Lomustine arm experienced a higher rate of all grade VTEs (13/278 [4.7%]) than in the Lomustine arm (3/147 [2.0%]). All patients were reported to have experienced events that were Grade ≥ 3.

**Congestive Heart Failure (CHF) (see WARNINGS AND PRECAUTIONS)**

In clinical trials with bevacizumab, congestive heart failure (CHF) was observed in all cancer indications studied to date, but occurred predominantly in patients with metastatic breast cancer. In study AVF2119g, the incidence of CHF Grade 3 or higher was 2.2% in patients treated with bevacizumab in combination with capecitabine compared with 0.5% in patients treated with capecitabine alone. In study E2100, the incidence of CHF Grade 3 or higher was 2.2% in patients treated with bevacizumab in combination with paclitaxel compared with 0.3% in patients treated with paclitaxel. In study BO17708, the incidence of CHF Grade 3 or higher ranged from 0 to 1.2% in patients treated with bevacizumab in combination with docetaxel compared to 0% in the docetaxel arm. In study AVF3694g, the incidence of CHF Grade 3 or higher was 2.0% in patients treated with bevacizumab in combination with taxanes, vs. 0% for taxanes alone, 2.9% for patients treated with bevacizumab plus anthracyclines vs. 0% for anthracyclines alone, and 1% for patients treated with bevacizumab plus capecitabine compared to 0.5% in patients treated with capecitabine alone.

Most patients 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.

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

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

**Non-Gastrointestinal Fistula (see WARNINGS AND PRECAUTIONS)**

Bevacizumab use has been associated with serious cases of fistulae (0.8%, 14/1804).

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer, 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. ZIRABEV is not authorized for use in cervical cancer.

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

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

**Gastrointestinal**

**Gastrointestinal Perforation and Fistula (see WARNINGS AND PRECAUTIONS)**

Bevacizumab has been associated with serious cases of gastrointestinal perforation or fistulae. Gastrointestinal perforations have been reported in clinical trials with an incidence of less than 1% in patients with metastatic breast cancer or non-squamous non-small cell lung cancer, up to 2% in patients with ovarian cancer, and up to 2.7% (including gastrointestinal fistula and abscess) in metastatic colorectal cancer patients. Fatal outcome was reported in approximately a third of serious cases of gastrointestinal perforations, which represents between 0.2% - 1% of all bevacizumab treated patients.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer, gastrointestinal perforations (all Grade) were reported in 3.2% of patients, all of whom had a history of prior pelvic radiation. ZIRABEV is not authorized for use in cervical cancer.

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

In a trial of patients with persistent, recurrent or metastatic cervical cancer, the incidence of gastrointestinal-vaginal fistulae was 8.3% in bevacizumab treated patients and 0.9% in control patients, all of whom had a history of prior pelvic radiation. Patients who develop gastrointestinal-vaginal fistulae may also have bowel obstructions and require surgical intervention as well as diverting ostomies. ZIRABEV is not authorized for use in cervical cancer.

In Study EORTC 26101 in patients with first recurrence of glioblastoma, 6 (2.2%) patients in the bevacizumab plus Lomustine and no patients in the Lomustine arm experienced gastrointestinal perforation events. The majority of patients experienced Grade ≥ 3 events (4 [1.4%] patients). There was 1 fatal event of large intestinal perforation among the four patients who experienced gastrointestinal perforation serious adverse events. Events were reported to have resolved in 4/6 (66.7%) patients.

A causal association of intra-abdominal inflammatory process and gastrointestinal perforation to

bevacizumab has not been established.

**Genitourinary**

**Ovarian Failure**

The incidence of new cases of ovarian failure, defined as amenorrhea lasting 3 or more months, FSH level ≥30 mIU/mL and a negative serum β -HCG pregnancy test, has been evaluated in a substudy (see WARNINGS AND PRECAUTIONS, Special Populations). New cases of ovarian failure were reported more frequently in patients receiving bevacizumab (39.0% vs. 2.6%). Age did not seem to have an influence on development of an ovarian failure for patients randomized to the mFOLFOX6 + bevacizumab arm compared with patients randomized to the mFOLFOX6 arm. Conclusions about age and risk of ovarian failure should be interpreted with caution, due to the small sample size of patients with ovarian failure in this substudy. After discontinuation of bevacizumab treatment, ovarian function recovered in a majority of women (86%). Long term effects of the treatment with bevacizumab on fertility are unknown.

**Proteinuria (see WARNINGS AND PRECAUTIONS)**

In clinical trials proteinuria was very common and has been reported in up to 38% of patients receiving bevacizumab. Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome. Grade 3 proteinuria was reported in up to 8.1% of treated patients, and Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4 % of treated patients.

Grades 3-4 proteinuria ranged from 0.7 to 7.4% in global studies. In an exploratory pooled analysis of 8,273 patients treated in 7 randomized clinical trials, 5.4% (271 of 5037) of patients receiving bevacizumab in combination with chemotherapy experienced Grade ≥2 proteinuria. The Grade ≥2 proteinuria resolved in 74.2% (201 of 271) of patients. Bevacizumab was re-initiated in 41.7% (113 of 271) of patients. Of the 113 patients who re-initiated bevacizumab, 47.8% (54 of 113) experienced a second episode of Grade ≥2 proteinuria.

**Hematologic**

**Hemorrhage (see WARNINGS AND PRECAUTIONS)**

***CNS Hemorrhage***

Cases of CNS hemorrhage, some with fatal outcome, have been observed in clinical trials of bevacizumab. Patients should be monitored for signs and symptoms of CNS bleeding, and bevacizumab treatment discontinued in case of intracranial bleeding.

Intracranial hemorrhage can occur in patients with relapsed glioblastoma. In study EORTC 26101, intracranial hemorrhage was seen in 2.5% of patients in the bevacizumab plus Lomustine arm versus 0.7% in the Lomustine arm.

Within 10 randomized controlled Phase III trials across the tumor indications advanced or metastatic colorectal cancer, renal cell cancer, NSCLC, breast cancer and pancreatic cancer, representing a total of 8036 patients, the incidence of intracranial hemorrhage (all Grades)[VI]

ranged between 0% and < 1% in both the control arms and in the bevacizumab arms. The incidence of Grade 5 events ranged between 0% and < 1% in both the control arms and in the bevacizumab arms.

[vi] Of note: In the three Eastern Co-operative Oncology Group (ECOG) trials out of the ten mentioned trials, only Grade 3 to 5 events were collected.

***Non-CNS hemorrhage***

Eighteen patients (in studies in patients with non-small cell lung cancer (NSCLC)) prematurely discontinued at least one component of study treatment due to a bleeding adverse event. In clinical trials across all indications the overall incidence of NCI-CTC Grade 3-5 bleeding events ranged from 0.4% to 6.9% in patients treated with bevacizumab, compared to 0 to 4.5% of patients in the chemotherapy control group. The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumour-associated hemorrhage (see below) and minor mucocutaneous hemorrhage (e.g. epistaxis).

***Tumour-associated hemorrhage***

Tumour associated hemorrhage was observed in bevacizumab studies. Major or massive pulmonary hemorrhage/hemoptysis has been observed primarily in studies in patients with non-small cell lung cancer. These events can occur suddenly and can present as major or massive pulmonary hemorrhage/hemoptysis. 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 pulmonary hemorrhage 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 pulmonary hemorrhage events have been observed in up to 2.3% of patients treated with bevacizumab plus chemotherapy as compared with <1% with chemotherapy alone. Grade 3-5 pulmonary hemorrhage/hemoptysis can occur suddenly and up to two thirds of these cases resulted in a fatal outcome.

There were four cases of cerebral hemorrhage; three cases were Grade 4 events and one case was a Grade 2 event. None of the patients with cerebral hemorrhage had brain metastasis at baseline.

Gastrointestinal hemorrhages, including rectal bleeding and melena have been reported in colorectal patients, and have been assessed as tumour-associated hemorrhages. Tumour-associated hemorrhages were also seen rarely in other tumour types and locations and

included cases of central nervous system (CNS) bleeding in patients with CNS metastases and in patients with glioblastoma.

Within 10 randomized controlled Phase III trials across the tumour indications advanced or metastatic colorectal cancer, renal cell cancer, NSCLC, breast cancer and pancreatic cancer, representing a total of 8036 patients, the incidence of gastrointestinal bleeding (all Grades)[vii] ranged between < 1% and 9% in the control arms and between 1% and 10% in the bevacizumab arms. The incidence of Grade 5 events ranged between 0% and < 1% in the control arms and between 0% and 1% in the bevacizumab arms.

[vii] Of note: In the three Eastern Co-operative Oncology Group (ECOG) trials out of the ten mentioned trials, only Grade 3 to 5 events were collected.

***Mucocutaneous Hemorrhage***

Across all bevacizumab clinical trials, mucocutaneous hemorrhages 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 change in the bevacizumab treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous hemorrhage (e.g. epistaxis) may be dose-dependant.

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

**Neutropenia and Infections (see WARNINGS AND PRECAUTIONS)**

An increased rate of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia, in some cases with a fatal outcome, was identified for patients treated with some myelotoxic/myelosuppressive chemotherapy regimens in combination with bevacizumab compared to chemotherapy alone. These increases were seen mainly in patients with non-small cell lung cancer, from ECOG4599 treated with carboplatin + paclitaxel in combination with bevacizumab (26.2% in the bevacizumab containing arm vs. 17.2% in the chemotherapy arm), and also in combination with myelosuppressive chemotherapy agents used to treat metastatic colorectal cancer (19.7% in the bevacizumab arm vs. 13.6% in the chemotherapy arm of AVF2107g).

Across the bevacizumab clinical trials, the frequencies of patients experiencing death due to neutropenia and infection occurring within 21 days after last study treatment dose of bevacizumab were generally low. In metastatic colorectal carcinoma trials, the frequency of fatal cases of neutropenia and infection was 0.9% and 1.3% in patients treated with bevacizumab plus chemotherapy and treated with chemotherapy alone, respectively. Events occurring in the bevacizumab treated patients included sepsis, necrotizing fasciitis, peritoneal abscess, and peritonitis. In study AVF3708, a non-comparative trial that led to approval of bevacizumab in recurrent glioblastoma multiforme, 1 of 163 patients (0.6%) treated with bevacizumab died of neutropenic infection. In non-small cell lung carcinoma trials, the frequencies of patients experiencing death due to neutropenia and infection were 1.0% and 0.3% in patients treated with chemotherapy plus bevacizumab and chemotherapy only, respectively. Events occurring in the bevacizumab treated patients included neutropenic infection, febrile neutropenia, infection, respiratory tract infection, pneumonia, bronchopneumonia, and empyema.

In Study EORTC 26101, the incidence of all infections was 31.3% in the bevacizumab arm, Grade 3-5 infection was 7.9%. Of the overall infection cases, one was fatal.

**Thrombocytopenia**

Across bevacizumab clinical trials, the reported incidence of thrombocytopenia (all Grade and Grade >=3) in patients treated with bevacizumab occurring within 21 days after the last study treatment dose of bevacizumab was 36.6% and 14.2% respectively.

The incidence of thrombocytopenia was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone. The incidence of Grade 3 thrombocytopenia was common in patients treated with bevacizumab. Patients > 65 years of age appeared to at higher risk for Grade ≥ 3 thrombocytopenia compared with younger patients.

**Hypersensitivity, Infusion Reactions (see WARNINGS AND PRECAUTIONS)**

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 bevacizumab clinical trials is common (up to 5% in bevacizumab-treated patients).

Infusion reactions reported in clinical trials and post-marketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis.

**Deaths**

In metastatic colorectal cancer trials, the incidence of fatal adverse events occurring within 21 days of the last study treatment dose of bevacizumab was 3.3% and 3.4% in patients treated with bevacizumab + chemotherapy and in patients treated with chemotherapy alone respectively.

In a single-arm trial of GBM patients, fatal adverse events occurred in 3.1% of patients treated with bevacizumab + chemotherapy.

In non small cell lung carcinoma trials, fatal adverse events occurred in 5.7% and 3.0% of patients treated with chemotherapy + bevacizumab and chemotherapy only, respectively.

For ovarian carcinoma, fatal adverse events occurred in 0.4% of patients treated with chemotherapy + bevacizumab, and 0.4% of patients treated with chemotherapy only.

In a platinum-resistant recurrent ovarian cancer trial, nine patients in the bevacizumab arm versus six patients in the chemotherapy arm died due to adverse events. In the bevacizumab + chemotherapy arm, the causes of death were aspiration pneumonia (2 patients), sepsis (2 patients), cardiac arrest, cardiopulmonary failure, gastrointestinal disorder, general physical health deterioration, and shock. In the chemotherapy arm, the causes of death were septic shock (2 patients), cardiac failure, multi-organ failure, peritonitis, and GI hemorrhage (latter occurred after the patient started crossover bevacizumab monotherapy).

## Pre-Operative Conditions

### Wound Healing (see **WARNINGS AND PRECAUTIONS**)

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

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).

Cases of serious wound healing complications have been reported during bevacizumab use, some of which had a fatal outcome (see **WARNINGS and PRECAUTIONS**, Peri-Operative Considerations -Wound Healing).

In Study EORTC 26101, the incidence of all grade wound healing complications including post-operative wound healing complications was higher in bevacizumab plus Lomustine arm than the Lomustine arm (4.7% vs. 0.7%) as was the incidence of Grade ≥ 3 events (1.8% vs. 0.7%).

## Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response to bevacizumab. In clinical trials of adjuvant colon carcinoma, 14 of 2233 evaluable patients (0.63%) tested positive for treatment-emergent anti-bevacizumab antibodies detected by an electrochemiluminescent (ECL) based assay. Among these 14 patients, three tested positive for neutralizing antibodies against bevacizumab using an enzyme-linked immunosorbent assay (ELISA). The clinical significance of these anti-product antibody responses to bevacizumab is unknown. Samples for assessment of human-anti-human antibody (HAHA) were not collected in the platinum-resistant ovarian cancer study MO22224.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the test method and may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to bevacizumab with the incidence of antibodies to other products may be misleading.

### Nasal Septum Perforations

Very rare cases of nasal septum perforations have been reported in patients treated with bevacizumab.

**Special Populations**

**Gender**

In clinical trials in mNSCLC, female patients treated with bevacizumab had an increased risk of Grade 3 adverse reactions of fatigue, abdominal pain and hypertension compared to both males and females treated with chemotherapy. Grades 1 and 2 AEs were not captured.

**Geriatrics (> 65 years of age)**

In randomised clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic events including cerebrovascular accidents, transient ischemic attacks, myocardial infarction, proteinuria, Grade 3-4 leukopenia, neutropenia, thrombocytopenia, diarrhea, and fatigue as compared to those aged ≤ 65 years when treated with bevacizumab (see **WARNINGS and PRECAUTIONS**). Other reactions with a higher frequency seen in patients over 65 were all Grade nausea, and headache.

No increase in the incidences of other reactions including gastrointestinal perforation, wound healing complications, and congestive heart failure was observed in elderly patients (> 65 years) receiving bevacizumab as compared to those aged ≤ 65 years treated with bevacizumab.

## 9.3 Less Common Clinical Trial Adverse Reactions

**Listing 1 Less Common NCI-CTC Grade 3-5 Non-Hematologic and Grade 4-5 Hematologic Clinical Trial Adverse Events (<1%) in Study E4599 including Control Arms**

**Blood/Bone Marrow:** Hemoglobin.
**Cardiovascular (Arrhythmia):** Vasovagal Episode, Sinus Bradycardia, Arrhythmia-Other, Conduction Abnormality, Dysrhythmia.
**Cardiovascular (General):** Cardiac-Left Ventricular Function, Edema, Cardiac Troponin I, Cardiac-Other, Pericardial Effusion/Pericarditis, Cardiac Troponin T.
**Coagulation:** Any Toxicity, PTT, PT.
**Constitutional Symptoms:** Weight Loss.
**Dermatology/Skin:** Wound – Infectious, Alopecia, Flushing, Pruritus, Radiation Dermatitis, Wound – Non-Infectious, Dermatitis, Skin-Other, Urticaria.
**Endocrine:** Any Toxicity, SIADH, Hypothyroidism.
**Gastrointestinal:** Dysphagia, GI−Other, Proctitis, Colitis, Ileus, Dyspepsia, Dysphagia−Esophageal Radiation, Fistula−Esophageal, Fistula−Rectal/Anal, Gastritis, Pancreatitis.
**Hemorrhage:** CNS Hemorrhage, Epistaxis, Hematemesis, Hemorrhage-Other, Vaginal Bleeding, Hemorrhage with Grade 3 or 4 Platelets.
**Hepatic:** SGOT, Alkaline Phosphatase, Bilirubin, GGT, Hypoalbuminemia, Hepatic-Other, Liver Dysfunction/Failure.
**Infection/Febrile Neutropenia:** Infection w/ Unknown ANC, Catheter-Related Infection.
**Metabolic/Laboratory:** Hyperkalemia, Amylase, Hypoglycemia, Hypercholesterolemia,

Hypocalcemia, Hypercalcemia, Hypermagnesemia, Hypernatremia, Hypertriglyceridemia, Hyperuricemia, Hypomagnesemia, Lipase, Metabolic-Other, Acidosis, Alkalosis.
**Muscoloskeletal:** Osteonecrosis.
**Neurology:** Depressed Level of Consciousness, Ataxia, Depression, Neurologic−Other, Speech Impairment, Hallucinations, Insomnia, Seizure, Memory Loss, Tremor, Cognitive Disturbance.
**Ocular/Visual:** Any Toxicity, Double Vision, Cataract, Blurred Vision.
**Pain:** Neuropathic Pain, Pleuritic Pain, Hepatic Pain, Pelvic Pain, Rigors/Chills, Weight Gain.
**Pulmonary:** ARDS, Pulmonary Fibrosis, Pneumothorax, Apnea, Voice Changes/Stridor.
**Renal/Genitourinary:** Creatinine, Incontinence, Renal Failure, Renal/GU-Other, Urinary Retention.
**Syndromes:** Any Toxicity, Syndromes-Other.

**Listing 2 Clinical Trial Adverse Events (<4 %*) in Study AVF0757g including Control Arms**

**Body as a Whole**: Face Edema, Infection Bacterial, Injection Site Edema, Injection Site Inflammation, Injection Site Reaction, Neoplasm, Sepsis, Abdomen Enlarged, Hernia, Infection Fungal, Injection Site Pain, Lab Test Abnormal, Neck Pain, Neck Rigidity, Flank Pain,Flu Syndrome.
**Cardiovascular:** Arrhythmia, Atrial Fibrillation, Bradycardia, Cerebral Ischemia, Migraine, Vascular Anomaly, Vascular Disorder, Endocarditis, Palpitation, Postural Hypotension, Angina Pectoris, Cardiovascular Disorder, Pericardial Effusion, Pulmonary Embolus.
**Digestive:** Gastrointestinal Disorder, Gastrointestinal Hemorrhage, Gingivitis, Glossitis, Hematemesis, Hepatic Failure, Increased Salivation, Jaundice, Melena, Mouth Ulceration, Abnormal Stools, Eructation, Gastroenteritis, Intestinal Obstruction, Salivary Gland Enlargement, Dry Mouth, Esophagitis.
**Endocrine:** Diabetes Mellitus, Hypothyroidism.
**Hemic and Lymphatic:** Prothrombin Decreased, Lymphadenopathy, Lymphangitis, Pancytopenia, Thrombocythemia, Leukocytosis, Thromboplastin Increased.
**Metabolic/Nutrition:** Alkalosis, Bilirubinemia, Creatinine Increased, Hypercalcemia, Hypoglycemia, Hypokalemia, Hypomagnesemia, Hypophosphatemia, Hypovolemia, Respiratory Alkalosis, Amylase Increased, Hyperkalemia, Calcium Disorder, Electrolyte Depletion, Weight Gain.
**Musculoskeletal:** Joint Disorder, Pathological Fracture, Tendon Disorder, Twitching.
**Nervous:** Abnormal Gait, Hallucinations, Hypertonia, Incoordination, Sleep Disorder, Speech Disorder, Thinking Abnormal, Tremor, Vertigo, Convulsion, Hyperesthesia, Myoclonus, Neuralgia, Nystagmus, Reflexes Increased, Stupor, Reflexes Decreased, Stupor, Reflexes Decreased.
**Respiratory:** Emphysema, Hypoxia, Laryngitis, Pleural Disorder, Pneumothorax, Respiratory Disorder.
**Skin and Appendages:** Fungal Dermatitis, Pustular Rash, Vesiculobullous Rash, Dry Skin, Herpes Simplex, Hirsutism, Maculopapular Rash, Skin Discoloration, Skin Ulcer.
**Special Senses:** Abnormal Vision, Dry Eyes, Otitis Media, Cataract NOS, Diplopia, Ear Disorder, Keratitis.
**Urogenital:** Albuminuria, Nephrosis, Nocturia, Urination Impaired, Vaginal Moniliasis, Breast Pain, Hematuria, Urinary Retention, Vaginal Hemorrhage, Dysuria.

*Due to the size of the trial and rates (1 patients per group equals <4%), the listing of adverse events is presented as the listing of adverse events occurring in <4 % of patients.

**Listing 3 Clinical Trial Related Adverse Events (< 1 %) in Study EORTC 26101 including Control Arm**

**Infections and Infestations**: Nail Infection, Rhinitis, Sinusitis, Skin Infection, Anorectal Infection, Appendicitis, Arthritis Infective, Bronchitis, Cystitis, Diverticulitis, Enterocolitis Infectious, Epididymitis, Escherichia Urinary Tract Infection, Gingivitis, Paronychia, Peritonitis, Pharyngitis, Sepsis, Soft Tissue Infection.
**Gastrointestinal Disorders**: Colitis, Dysphagia, Large Intestine Perforation, Abdominal Distension, Abdominal Pain Upper, Anal Fistula, Duodenal Ulcer, Gastritis, Gastrointestinal Perforation, Hemorrhoidal Hemorrhage, Oral Pain, Tooth Loss, Toothache.
**Nervous System Disorders**: Cerebral Ischemia, Lethargy, Paresthesia, Somnolence, Amnesia, Aphasia, Cerebrospinal Fluid Leakage, Disturbance In Attention, Dysarthria, Hemiparesis, Posterior Reversible Encephalopathy Syndrome.
**Skin and Subcutaneous Tissue Disorders:** Onychomadesis, Petechiae, Decubitus Ulcer, Dermatitis Bullous, Nail Disorder, Nail Ridging, Onychoclasis.
**Vascular Disorders**: Hematoma, Hot Flush, Deep Vein Thrombosis, Flushing, Hypotension, Phlebitis, Vasculitis.
**Eye Disorders:** Dry Eye, Lacrimation Increased, Blindness, Blindness Unilateral, Retinopathy, Vision Blurred. **Musculoskeletal and Connective Tissue Disorders**: Bone Pain, Neck Pain, Pain in Extremity, Muscle Spasms, Soft Tissue Disorder.
**General Disorders and Administration Site Conditions:** Chills, General Physical Health Deterioration, Injection Site Reaction, Localized Edema, Non-Cardiac Chest Pain, Edema.
**Renal and Urinary Disorders:** Acute Kidney Injury, Cystitis Non-infective, Proteinuria, Urinary Incontinence.
**Respiratory, Thoracic and Mediastinal Disorders**: Oropharyngeal Pain, Productive Cough.
**Investigations**: Weight Increased
**Blood and Lymphatic System Disorders:** Febrile Neutropenia, Thrombotic Thrombocytopenic Purpura.
**Cardiac Disorders:** Left Ventricular Dysfunction, Palpitations.
**Injury, Poisoning and Procedural Complications:** Infusion Related Reaction.
**Metabolism and Nutrition Disorders:** Dehydration, Hyperglycemia.
**Psychiatric Disorders:** Confusional State, Insomnia.
**Hepatobiliary Disorders:** Portal Hypertension.
**Immune System Disorders:** Anaphylactic Reaction.

## 9.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

**Abnormal Hematologic and Clinical Chemistry Findings**

**Laboratory Abnormalities**

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

Across clinical trials, the following Grade 3 and 4 laboratory abnormalities were seen with an increased (≥2%) incidence in patients treated with bevacizumab compared to those in the control groups: hyperglycemia, decreased hemoglobin, hypokalemia, hyponatremia, decreased white blood cell count, thrombocytopenia, increased PT 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.

## 9.5 Post-Market Adverse Reactions

| System Organ Class | Reactions (frequency)[1] |
|---|---|
| Body as a whole | Polyserositis |
| Gastrointestinal disorders | Gastrointestinal ulcer (frequency not known), intestinal necrosis, anastomotic ulceration |
| Cardiovascular | mesenteric venous occlusion |
| Congenital, familial and genetic disorders | Cases of fetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see **WARNINGS AND PRECAUTIONS**). |
| Hepatobiliary disorders | Gallbladder perforation (frequency not known) |
| Immune system disorders | Hypersensitivity reactions, including anaphylactic reaction, infusion reactions (frequency not known); possibly associated with the following co-manifestations: dyspnoea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting. (see **WARNINGS and PRECAUTIONS,** and **ADVERSE REACTIONS**) |

| System Organ Class | Reactions (frequency)[1] |
|---|---|
| Nervous system disorders | Hypertensive encephalopathy (very rare)<br>Posterior Reversible Encephalopathy Syndrome (PRES) (rare)<br>(see **WARNINGS and PRECAUTIONS**) |
| Respiratory, thoracic and mediastinal disorders | Nasal septum perforation (frequency not known)<br>Pulmonary hypertension* (frequency not known) Dysphonia (common) |
| Vascular disorders | Renal thrombotic microangiopathy, clinically manifested as proteinuria (frequency not known).<br>(see **WARNINGS AND PRECAUTIONS**, and **ADVERSE REACTIONS**) |
| Musculoskeletal and Connective Tissue disorders | Cases of Osteonecrosis of the Jaw (ONJ) have been observed in bevacizumab treated patients mainly in association with prior or concomitant use of bisphosphonates.<br>Cases of osteonecrosis at sites other than the jaw, have been observed in bevacizumab treated paediatric patients (See **WARNINGS and PRECAUTIONS**, Paediatric)**. |
| Infections and Infestations | Necrotizing fasciitis (rare), usually secondary to wound healing complications, gastrointestinal perforation or fistula formation (also see section **WARNINGS AND PRECAUTIONS**) |

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

* Symptoms of pulmonary hypertension include dyspnea on exertion, fatigue, syncope, anginal chest pain, hemoptysis, and Raynaud's phenomenon.

**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.

Renal failure, sepsis, febrile neutropenia, and non-gastrointestinal fistula were reported during post-marketing use of bevacizumab in combination with chemotherapy.

# 10 DRUG INTERACTIONS

## 10.1 Overview

No formal drug interaction studies with other antineoplastic agents have been conducted. However, the existing data suggest that bevacizumab does not affect the pharmacokinetics of 5-fluorouracil (5-FU), carboplatin, paclitaxel and doxorubicin.

## 10.2 Drug-Drug Interactions

In study AVF2107g, irinotecan concentrations were similar in patients receiving IFL (irinotecan/5-fluorouracil/leucovorin) alone and in combination with bevacizumab. Concentrations of SN38, the active metabolite of irinotecan, were analysed in a subset of patients, i.e. approximately 30 per treatment arms. Concentrations of SN38 were on average 33% higher in

patients receiving IFL in combination with bevacizumab compared with IFL alone. Due to high inter-patient variability and limited sampling, it is unclear if the observed increase in SN38 levels was due to bevacizumab. There was a small increase in diarrhea and leukopenia adverse events (known adverse drug reactions of irinotecan), and also more dose reductions of irinotecan were reported in the patients treated with IFL + bevacizumab. Patients who develop severe diarrhea, leukopenia or neutropenia with ZIRABEV and irinotecan combination therapy should have irinotecan dose modifications as specified in the irinotecan product information.

**Sunitinib Malate**

In two clinical studies of metastatic renal cell carcinoma, microangiopathic hemolytic anemia (MAHA) was reported in 7 of 19 patients (37%) treated with bevacizumab (10 mg/kg every two weeks) and sunitinib malate (50 mg daily) combination.

MAHA is a hemolytic disorder which can present with red cell fragmentation, anemia, 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 **WARNINGS AND PRECAUTIONS**).

The safety and efficacy of ZIRABEV in combination with sunitinib malate has not been established, therefore this combination is not recommended.

**Combination with platinum or taxene-based therapies**

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

**EGFR monoclonal antibodies in combination with bevacizumab chemotherapy regimens**

No interaction studies have been performed. EGFR monoclonal antibodies should not be administered for the treatment of mCRC in combination with bevacizumab-containing chemotherapy.

**Radiotherapy**

The safety and efficacy of concomitant administration of radiotherapy and ZIRABEV has not been established.

## 11 ACTION AND CLINICAL PHARMACOLOGY

### 11.1 Mechanism of Action

Bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab contains human framework regions with antigen binding regions of a humanised murine antibody that binds to VEGF.

Bevacizumab inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralising the biologic activity of VEGF reduces the vascularisation of tumours, thereby inhibiting tumour growth.

### 11.2 Pharmacodynamics

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

### 11.3 Pharmacokinetics

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

**Distribution:** Based on a population pharmacokinetic analysis of 491 subjects receiving Bevacizumab weekly, every 2 weeks, or every 3 weeks, in doses ranging from 1 to 20 mg/kg, the volume of the central compartment (Vc) was 2.66 L and 3.25 L for female and male subjects, respectively. Results also indicated that, after correcting for body weight, male subjects had a larger Vc (+22%) than females.

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

**Elimination:** Bevacizumab clearance was 0.207 L/day for females and 0.262 L/day for males. The Vc and clearance correspond to an initial half -life of 1.4 days and a terminal half- life of 20 days for females and 19 days for males. This half- life is consistent with the terminal elimination half- life for human endogenous IgG, which is 18 to 23 days. Results of the population pharmacokinetic analysis indicated that, after correcting for body weight, male subjects had a higher bevacizumab clearance (+26%) than females. However, no dose adjustment is required. There was no correlation between bevacizumab clearance and subject age. In patients with low albumin (≤ 29 g/dL) and high alkaline phosphatase (≥ 484 U/L) (both markers of disease

severity), bevacizumab clearance was approximately 20% faster than in patients with median laboratory values.

**Special Populations and Conditions**

The population pharmacokinetics of bevacizumab were analysed to evaluate the effects of demographic characteristics. The results showed no significant difference in the pharmacokinetics of bevacizumab in relation to age when body weight is taken into account.

***Hepatic Insufficiency***

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.

***Renal Insufficiency***

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.

## 12 STORAGE, STABILITY AND DISPOSAL

Store vials in a refrigerator at 2 - 8°C. Keep vial in the outer carton in order to protect from light. **Do not freeze. Do not shake**.

ZIRABEV does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared solution. Chemical and physical in-use stability has been demonstrated for 48 hours at 2ºC to 30ºC in 0.9% sodium chloride solution. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

**Disposal of unused/expired medicines**
The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

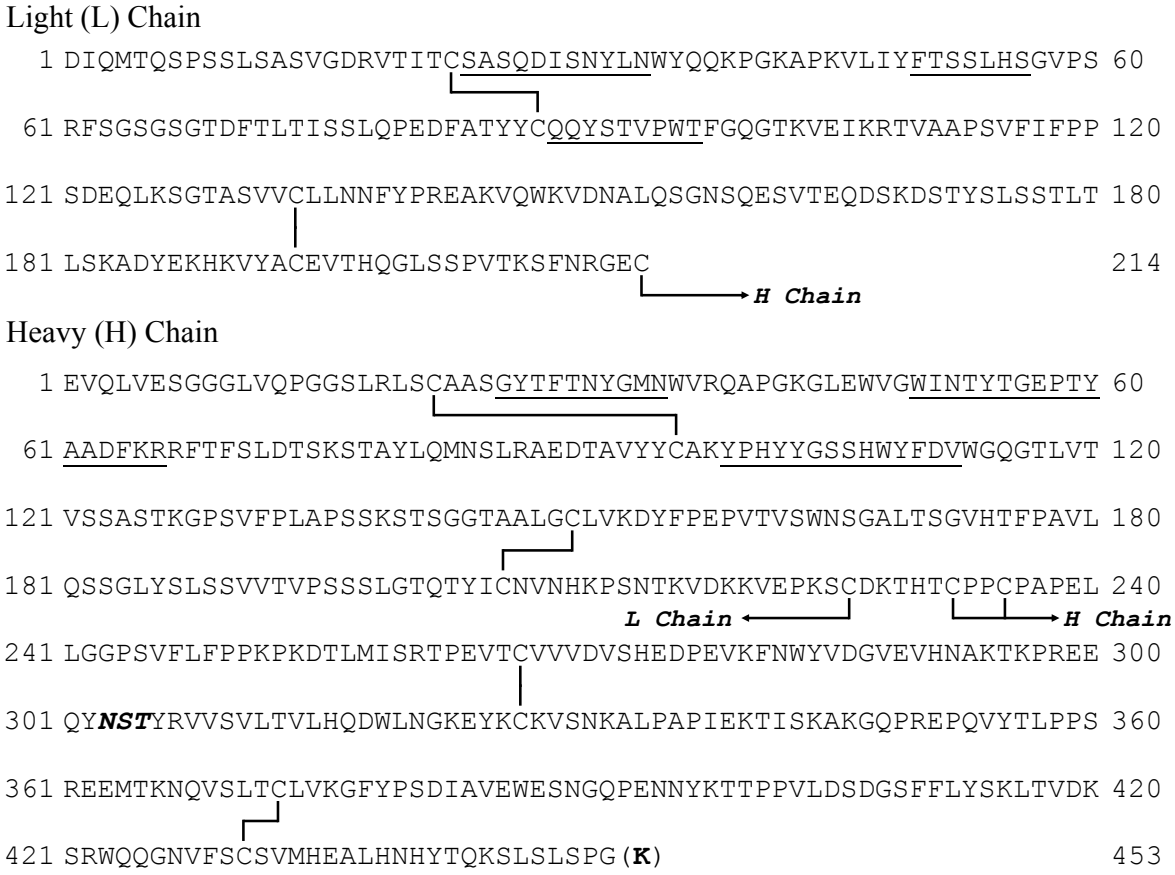
## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

**Drug Substance**

| | |
|---|---|
| Proper name: | bevacizumab for injection |
| Chemical name: | recombinant, humanized anti-VEGF monoclonal antibody |
| Molecular formula and molecular mass: | bevacizumab is a highly purified, approximately 149 000 dalton antibody |

Structural formula:




Physicochemical properties: Concentrate for solution for infusion: Clear to slightly opalescent, colourless to pale brown, sterile liquid for intravenous infusion.

## 14 COMPARATIVE CLINICAL TRIALS

### 14.1 Comparative Trial Design and Study Demographics

Clinical studies conducted to support similarity between ZIRABEV and the reference biologic drug included the following:

- Study B7391001 was a comparative PK study in healthy male volunteers.

- Study B7391003 was a comparative efficacy and safety clinical trial in patients with advanced (unresectable, locally advanced, recurrent or metastatic) non-squamous NSCLC.

An overview of the study design(s) and demographic characteristics of patients enrolled in each clinical study are presented in Table 14.

**Table 14 Summary of Trial Designs and Patient Demographics**

| Study # | Study Design | Dosage, route of administration, duration | No. of Subjects (by Treatment Group) | Sex and Mean age (Range) (years)(by Treatment Group) |
|---|---|---|---|---|
| B7391001 | Phase 1, randomized, double-blind (sponsor-unblinded), parallel-group, single-dose, 3-arm, comparative PK study of ZIRABEV with bevacizumab (EU) bevacizumab (US) administered to healthy male volunteers. | ZIRABEV: Single 5 mg/kg as a 90-minute IV infusion. | Randomized: 33 | Sex: Male Age 37.6 (22-53) |
| | | Bevacizumab-US: Single 5 mg/kg as a 90-minute IV infusion. | Randomized: 33 | Sex: Male Age 36.0 (21-50) |
| | | Bevacizumab-EU: Single 5 mg/kg as a 90-minute IV infusion. | Randomized: 36 | Sex: Male Age 39.1 (21-55) |

| Study # | Study Design | Dosage, route of administration, duration | No. of Subjects (by Treatment Group) | Sex and Mean age (Range) (years) (by Treatment Group) |
|---|---|---|---|---|
| B7391003 | Randomized, double-blind study of ZIRABEV plus paclitaxel-carboplatin and bevacizumab-EU plus paclitaxel-carboplatin for the first-line treatment of patients with advanced non-squamous NSCLC.<br><br>Patients were randomized (1:1) to receive at least 4 cycles and no more than 6 cycles of either ZIRABEV plus paclitaxel-carboplatin or bevacizumab-EU plus paclitaxel and carboplatin, followed by the previously assigned blinded bevacizumab monotherapy. | Bevacizumab: 15 mg/kg by IV infusion on Day 1 of each 21-day cycle.<br><br>Paclitaxel: 200 mg/m$^2$ by IV infusion on Day 1 of each 21-day cycle.<br><br>Carboplatin: AUC = 6 by IV infusion on Day 1 of each 21 day cycle | **ZIRABEV**<br>Randomized: 358<br><br>Treated: 356<br><br>**Bevacizumab-EU**<br>Randomized: 361<br><br>Treated: 358 | Sex: Male/Female 237/121<br>Age :61.7 (25-87)<br><br>Sex: Male/Female 230/131<br>Age : 60.9 (31-83) |

Abbreviations: AUC = area under curve; EU = European Union; IV = intravenous;

No. = Number; NSCLC = non-small cell lung cancer; PK = pharmacokinetics; US = United States.

## 14.2 Comparative Study Results

### 14.2.1 Comparative Bioavailability Studies

#### 14.2.1.1 Pharmacokinetics

**Study B7391001**

The PK study (B7391001) demonstrated that the 90% CIs for the test-to-reference ratios of $C_{MAX}$ and $AUC_T$, were within the pre-specified criteria for pharmacokinetic similarity of 80.0% to 125.0% for comparisons of ZIRABEV to bevacizumab-EU (Table 15).

**Table 15 - Bevacizumab**
**From measured data**

**[6]Geometric Mean**
**Arithmetic Mean (CV %)**

| Parameter | | Test (ZIRABEV) [7]N=32 | Reference (Bevacizumab-EU) N=33 | Percent (%) Ratio (Test/Reference) Of Geometric Means | 90% Confidence Interval for Ratio |
|---|---|---|---|---|---|
| [2]$AUC_T$ (mcg·hr/mL) | Geometric mean<br>Arithmetic mean (CV%) | 40330<br>40840 (16%) | 40490<br>41010 (16%) | 99.6 | 93.7 – 105.9 |
| [1]$AUC_I$ (mcg·hr/mL) | Geometric mean<br>Arithmetic mean (CV%) | 42490<br>43080 (16%) | 43100<br>43830 (19%) | 98.6 | 92.2 – 105.4 |
| [3]$C_{MAX}$ (mcg/mL) | Geometric mean<br>Arithmetic mean (CV%) | 141.5<br>142.9 (14%) | 135.5<br>137.0 (15%) | 104.4 | N/A |
| [4]$T_{1/2}$ (hr) | Arithmetic mean (CV%) | 396.8 (16%) | 417.2 (21%) | N/A | N/A |
| [5]$T_{max}$ (hr) | Median (Min-Max) | 1.67 (1.65-24.00) | 1.67 (1.67-4.00) | N/A | N/A |

[1]$AUC_I$ = area under the serum concentration-time profile from time 0 extrapolated to infinity, relevant when the dose is administered intravenously,
[2]$AUC_T$ = area under the serum concentration-time profile from time 0 to the time of the last quantifiable concentration,
[3]$C_{MAX}$ = maximum observed serum concentration,
[4]$T_{1/2}$ = Terminal half-life expressed as arithmetic mean (CV%),
[5]$T_{max}$= Time for $C_{MAX}$; Median and Range are presented,
[6]Geometric Means = exponentially transformed least squares means from the Analysis of Variance model fitted to log-transformed data, including treatment as the independent variable,
[7]N=Number of subjects in the treatment group,
All PK parameters were derived from non-compartmental analysis,
N/A: Not applicable.

### 14.2.2 Comparative Safety and Efficacy

#### 14.2.2.1 Efficacy

**Study B7391003 – Non Small Cell Lung Cancer**

The primary efficacy endpoint was the objective response rate (ORR) (assessed by the investigator) based onevaluating the best overall response (BOR) achieved by Week 19 and subsequently confirmed 6 weeks later, in accordance with Response Evaluation Criteria in Solid Tumors (RECIST version 1.1).

Comparability between ZIRABEV and bevacizumab-EU was demonstrated since the 95% confidence interval (CI) of the risk ratio in ORR was entirely contained within the pre-specified margin of (0.729, 1.371) (Table 16).

**Table 16. Summary of ORR – Primary Efficacy Endpoint - ITT Population**

| | ZIRABEV (N=358) | Bevacizumab-EU (N=361) |
|---|---|---|
| Best overall response, n (%) | | |
| Complete response (CR) | 9 (2.5) | 4 (1.1) |
| Partial response (PR) | 153 (42.7) | 157 (43.5) |
| Stable disease | 154 (43.0) | 166 (46.0) |
| Objective progression | 15 (4.2) | 14 (3.9) |
| Indeterminate[a] | 27 (7.5) | 20 (5.5) |
| [b]ORR, n (%) | 162 (45.3) | 161 (44.6) |
| 95% exact CI[c] | [40.01, 50.57] | [39.40, 49.89] |
| Risk ratio (ZIRABEV/Bevacizumab-EU)[d] | 1.0146 | |
| 95% CI of risk ratio[d] | [0.8628, 1.1933] | |

Abbreviations: CI=confidence interval, CR=complete response, EU=European Union, ITT=Intent-to-Treat, n/N=number of patients with observation/total number of patients, ORR=objective response rate, PR=partial response, RECIST=Response Evaluation Criteria in Solid Tumors

a. Indeterminate: Early death, unevaluable tumor assessment, and early study discontinuations.
b. ORR was defined as the percentage of patients within each treatment group who achieved complete response or partial response by Week 19 of the study in accordance with RECIST version 1.1 which was subsequently confirmed by 6 weeks thereafter.
c. Exact method based on the F-distribution was used.
d. Calculated based on 2-sided Miettinen and Nurminen method without strata for risk ratio for confirmed response.

#### 14.2.2.2 Safety

The types, frequency and severity of adverse events were comparable between the biosimilar and the reference biologic drug.

#### 14.2.2.3 Immunogenicity

Immunogenicity was evaluated in both clinical studies B7391001 and B7391003 using electrochemiluminescent (ECL) assays. Only samples confirmed positive for Anti-Drug Antibodies (ADAs) were subsequently analyzed for neutralizing antibodies (NAb).

For study B7391001, samples were evaluated for ADAs at baseline, Day 15, Day 29, Day 57, Day 71 and Day 100. For study B7391003, samples were evaluated for ADAs at baseline, cycles 1, 2, 3, 4, 6 and every other cycle through to Cycle 17 (up to Week 52) or End of Treatment.

The incidence of ADA and NAb from these 2 studies is presented in Table 17 below.

**Table 17 Summary of Percentage of Patients with Anti-Drug Antibodies and Neutralizing antibodies by Study and Treatment**

Number of Subjects/Patients (%)

| | B7391001[a] | | B7391003[a] | |
|---|---|---|---|---|
| | **ZIRABEV N=33** | **Bevacizumab-EU N=35** | **ZIRABEV N=356** | **Bevacizumab-EU N=358** |
| **Anti-Drug Antibody (ADA)** | | | | |
| | **n/N1 (%)** | **n/N1 (%)** | **n/N1 (%)** | **n/N1 (%)** |
| Baseline[b] | 0/33 (0.0) | 0/33 (0.0) | 1/352 (0.3) | 3/353 (0.8) |
| Post dose[c] | 2/33 (6.1) | 2/33 (6.1) | 5/339 (1.5) | 5/350 (1.4) |
| **Neutralizing Antibody (NAb)** | | | | |
| Baseline[d] | 0/33 (0.0) | 0/33 (0.0) | 1/352 (0.3) | 0/353 (0.0) |
| Post dose[e] | 0/33 (0.0) | 0/33 (0.0) | 0/339 (0.0) | 3/350 (0.9) |

Abbreviations: ADA = Anti-drug antibodies; EU = European Union; N = Number of evaluable subjects; NAb = Neutralizing antibody; All samples were taken prior to dosing at each visit. ADA positive sample was defined as ADA titer ≥2.29. NAb positive samples were defined as NAb titer ≥1.70.

a. ADA and NAb assay ZIRABEV as a labeling reagent. N= number of patients who received study drug.

Percentages of patients with ADA or NAb are calculated based on:

b. For calculation of the incidence of ADA at Baseline, n=number of patients with ADA positive at Baseline, N1= number of patients at Baseline.

c. For calculation of the overall incidence of ADA post dose, n= total number of patients with ADA positive sample(s) at any visit during the trial after the first dose, N1=total number of patients with at least one sample tested for ADA at any time during the trial after the first dose.

d. For calculation of the incidence of NAb at Baseline, n=number of patients with NAb positive at Baseline, N1= number of patients at Baseline.

e. For calculation of the overall incidence of NAb post dose, n= total number of patients with NAb positive sample(s) at any visit during the trial after the first dose, N1=total number patients with at least one sample tested for ADA at any time during the trial after the first dose.

Due to the low percentage of subjects with observed ADA in Study B7391001 and Study B7391003, the effects of immunogenicity on safety and efficacy could not be evaluated.

## 15 COMPARATIVE NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY

### 15.1 Comparative Non-Clinical Pharmacodynamics

Since ZIRABEV is a biosimilar, where the pharmacodynamics and pharmacokinetic properties of bevacizumab for injection have already been described by for the reference biologic drug AVASTIN, this section summarizes the extensive comparative studies that were conducted to compare the pharmacology of ZIRABEV to AVASTIN.

#### *In vitro* Studies

As part of the biosimilarity assessment, physiochemical and functional characterization of ZIRABEV, bevacizumab-US and bevacizumab-EU was undertaken. Within functional characterization, the biological activity and Fc-based functionality was characterized across the three materials in a number of *in vitro* functional and binding assays (Table18).

The extensive similarity assessment of ZIRABEV, bevacizumab-US, and bevacizumab-EU showed similar biological activity of both the Fab and Fc-based functionality.

An overview of these studies is provided in the table below:

**Table 18. List of Biological Assays for comparing ZIRABEV with Bevacizumab**

| Mechanism of Action | Method/Analytical Procedure | Results |
|---|---|---|
| **Known MoA** | | |
| Binding to VEGF Target Antigen | Inhibition of Cell Growth Assay | ZIRABEV relative potency (80 -109%) was observed to overlap that of the bevacizumab-US range (84 – 125%) and the bevacizumab-EU range (87 – 127%). |
| | Binding to $VEGF_{165}$ by ELISA | The binding activity of ZIRABEV (90 -115%) was observed to overlap that of the bevacizumab-US range (89 – 119%) and bevacizumab-EU range (89 – 114%). |
| | Binding to other VEGF isofoms ($VEGF_{121}$, $VEGF_{189}$, and $VEGF_{206}$) by ELISA | Similar binding to $VEGF_{121}$, $VEGF_{189}$, $VEGF_{206}$ for ZIRABEV, bevacizumab-US, and bevacizumab-EU. |
| **Not Relevant to MoA** | | |
| ADCC | ADCC Assay | No ADCC activity observed for ZIRABEV, bevacizumab-US, and bevacizumab-EU. |
| | Binding to FcγRIIIa 158V by SPR | Binding affinities and kinetics for ZIRABEV were similar to those for bevacizumab-US, and bevacizumab-EU. |
| CDC Activity | CDC Assay | No CDC activity observed for ZIRABEV, bevacizumab-US, and bevacizumab-EU. |
| | Binding to C1q by an immunoassay | Similar dose-dependent response curves for ZIRABEV bevacizumab-US, and bevacizumab-EU. |

| | | |
|---|---|---|
| Fcγ Receptor Binding | Binding to additional Fcγ receptors by SPR | Similar binding kinetics for ZIRABEV, bevacizumab-US, and bevacizumab-EU for FcγRI, FcγRIIa 131H and 131R, FcγRIIb, and FcγRIIIb. |
| FcRn Binding | Binding to the FcRn Receptor by SPR | FcRn binding affinities for ZIRABEV (82 - 118%) were observed to overlap the bevacizumab-US range (96 - 119%) and bevacizumab-EU range (97 - 117%). |

ADCC = antibody dependent cell-mediated cytotoxicity; CDC = complement-dependent cytotoxicity; ELISA = enzyme-linked immunosorbent assay; FcRn = neonatal Fc receptor; IgG1 = immunoglobulin G 1; MoA = mechanism of action; SPR = surface plasmon resonance; VEGF = vascular endothelial growth factor.

### 15.2 Comparative Toxicology

The nonclinical regulatory toxicology program consisted of Good Laboratory Practises (GLP)-compliant, comparative, 1-month repeat-dose toxicity study of ZIRABEV and bevacizumab-EU in young male cynomolgus monkeys. Responses following IV injection of 10 mg/kg/dose twice weekly for 1 month (9 total doses) to 4 animals/group were similar for ZIRABEV and bevacizumab-EU. There were no ZIRABEV or bevacizumab-EU -related clinical signs, or effects on body weight, food consumption, ophthalmic examinations, respiration rate, electrocardiograms (ECGs), hematology, coagulation, clinical chemistry, or urinalysis parameters. Mean systemic exposures (as assessed by maximum serum concentration [$C_{max}$]; area under the plasma concentration-time curve from 72 hours [$AUC_{72}$]) for ZIRABEV and bevacizumab-EU appeared similar. No ADAs were detected in animals administered either ZIRABEV or bevacizumab-EU. All animals survived to their scheduled euthanasia, and there were no ZIRABEV or bevacizumab-EU-related changes in organ weights or macroscopic findings. The only ZIRABEV and bevacizumab-EU-related effect was the microscopic observation of physeal dysplasia in the distal femur, which was considered adverse in these growing animals. Physeal dysplasia is related to the inhibition of blood vessel formation and is consistent with the expected pharmacologically-mediated effects of bevacizumab on growing bone. There was no biologically-, or toxicologically-relevant difference in the incidence and severity of the physeal dysplasia between ZIRABEV and bevacizumab-EU dosed groups.

## 16 CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG

**Clinical Efficacy**

### Metastatic Colorectal Cancer

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

- AVF2107g: A weekly schedule of irinotecan/bolus 5-fluorouracil/leucovorin (IFL regimen) for a total of 4 weeks of each 6 week cycle;
- AVF0780g: In combination with bolus 5-fluorouracil/leucovorin (5 FU/LV) for a total of 6 weeks of each 8 week cycle (Roswell Park regimen),

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

All three trials evaluated bevacizumab at a dose of 5 mg/kg of body weight every 2 weeks and both enrolled patients with previously untreated metastatic carcinoma of the colon or rectum.

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

This was a phase III randomised, double blind, active controlled clinical trial evaluating bevacizumab in combination with IFL as first line treatment for metastatic carcinoma of the colon or rectum. Eight hundred thirteen patients were randomised to receive IFL + placebo (Arm 1) or IFL + bevacizumab (5 mg/kg every 2 weeks, Arm 2) (see Table 19). A third group of 110 patients received bolus 5 FU/LV + bevacizumab (Arm 3). Enrollment in Arm 3 was discontinued, as pre specified, once safety of bevacizumab with the IFL regimen was established and considered acceptable.

**Table 19 Treatment Regimens in Study AVF2107g**

| | Treatment | Starting Dose | Schedule |
|---|---|---|---|
| Arm 1 | Irinotecan<br>5-Fluorouracil<br>Leucovorin | 125 mg/m$^2$ IV<br>500 mg/m$^2$ IV<br>20 mg/m$^2$ IV | Given once weekly for 4 weeks every 6 weeks |
| | Placebo | IV | Every 2 weeks |
| Arm 2 | Irinotecan<br>5-Fluorouracil<br>Leucovorin | 125 mg/ m$^2$ IV<br>500 mg/ m$^2$ IV<br>20 mg/ m$^2$ IV | Given once weekly for 4 weeks every 6 weeks |
| | Bevacizumab | 5 mg/kg IV | Every 2 weeks |
| Arm 3 | 5-Fluorouracil<br>Leucovorin | 500 mg/ m$^2$ IV<br>500 mg/ m$^2$ IV | Given once weekly for 6 weeks every 8 weeks |
| | Bevacizumab | 5 mg/kg IV | Every 2 weeks |

5-Fluorouracil: IV bolus injection immediately after leucovorin
Leucovorin: IV bolus injection (over 1-2 minutes) immediately after each irinotecan dose

The primary efficacy parameter of the trial was duration of survival. The addition of bevacizumab to IFL resulted in a statistically significant increase in overall survival (see Table 20 and Figure 1). The clinical benefit of bevacizumab, as measured by survival, was seen in all pre specified patient subgroups, including those defined by age, sex, performance status, location of primary tumour, number of organs involved, and duration of metastatic disease (see Figure3).

The efficacy results of bevacizumab in combination with IFL chemotherapy are displayed in Table 20 and Figures 1 and 2 (Kaplan Meier plots for duration of survival and progression free survival).

**Table 20 Efficacy Results for Study AVF2107g**

| | Arm 1 IFL + Placebo | Arm 2 IFL + bevacizumab* |
|---|---|---|
| Number of Patients | 411 | 402 |
| Overall Survival | | |
| Median (months) | 15.6 | 20.3 |
| 95% confidence interval (CI) | 14.29-16.99 | 18.46-24.18 |
| Hazard ratio** (95% CI) | | 0.66 (0.54; 0.81) |
| p-value | | 0.00004 |
| Progression-free Survival | | |
| Median (months) | 6.2 | 10.6 |
| 95% confidence interval | 5.59-7.66 | 9.03-11.04 |
| Hazard ratio ( 95% CI) | | 0.54 (0.45; 0.66) |
| p-value | | < 0.00001 |
| Overall Response Rate | | |
| Rate (per cent) | 34.8 | 44.8 |
| 95% confidence interval | 30.2-39.6 | 39.9-49.8 |
| p-value | | 0.0036 |
| Duration of Response | | |
| Median (months) | 7.1 | 10.4 |
| 25-75 percentile (months) | 4.7-11.8 | 6.7-15.0 |

*5 mg/kg every 2 weeks **Relative to control arm

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

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

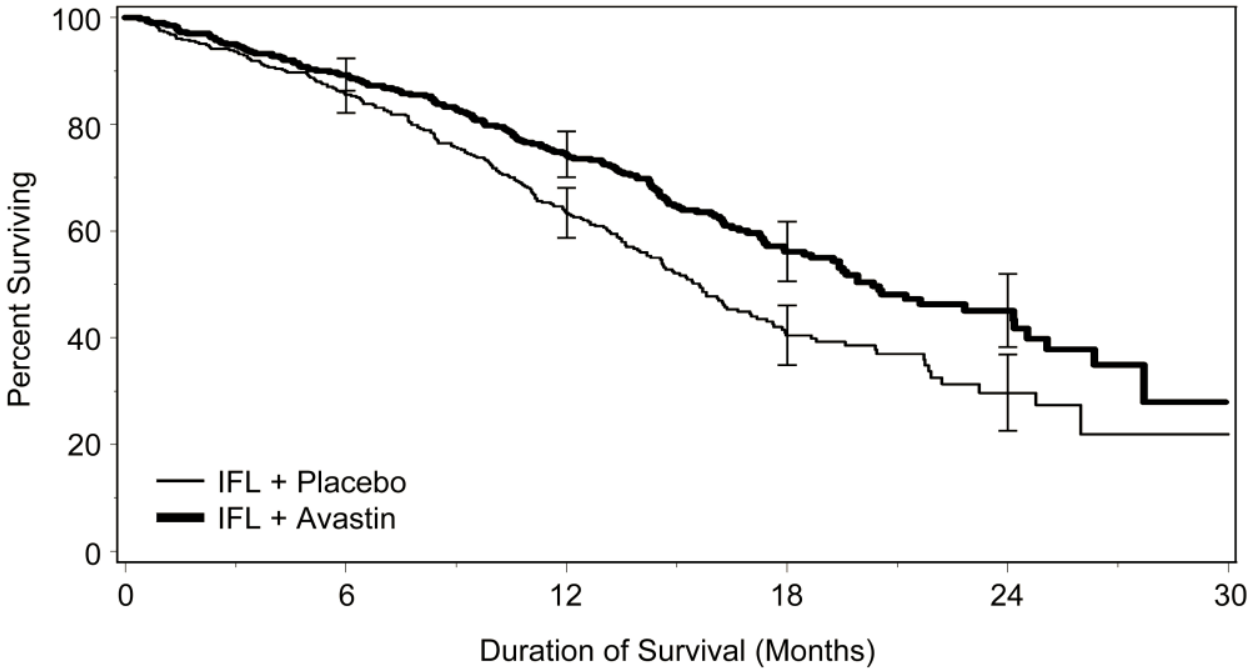



**Figure 2 Progression Free Survival during First-Line Therapy in Study AVF2107g**

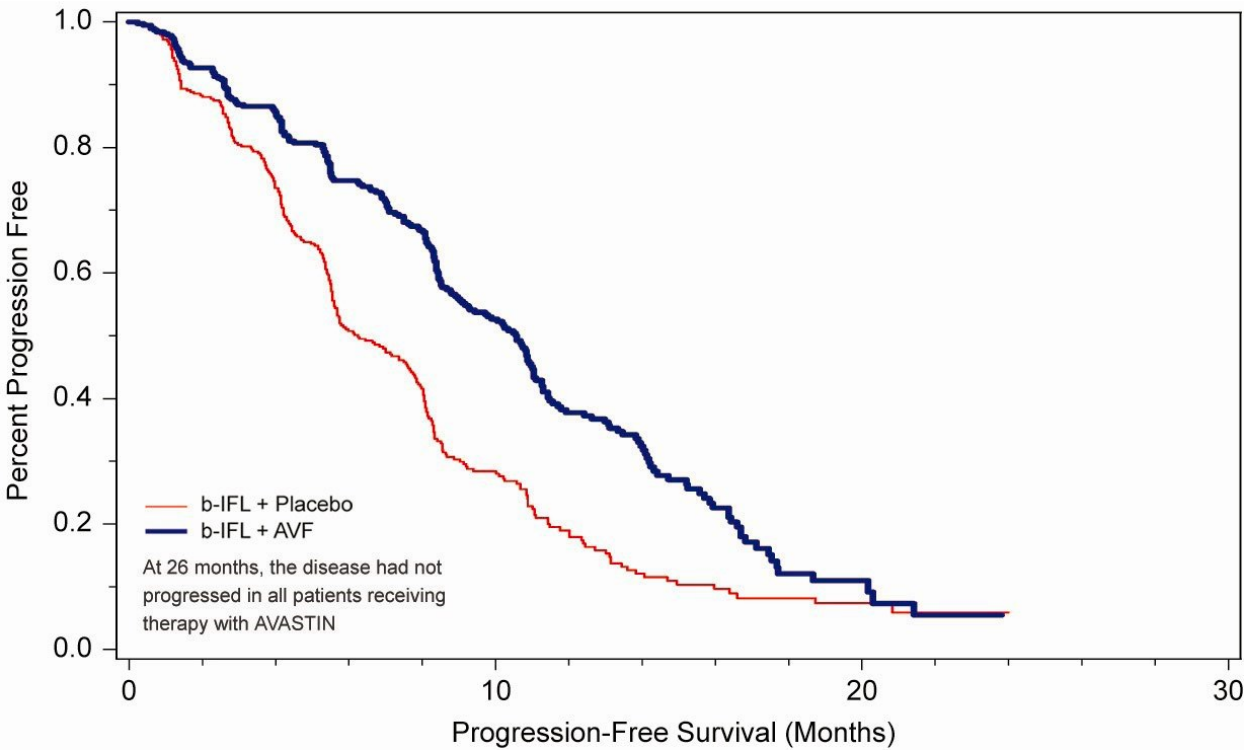
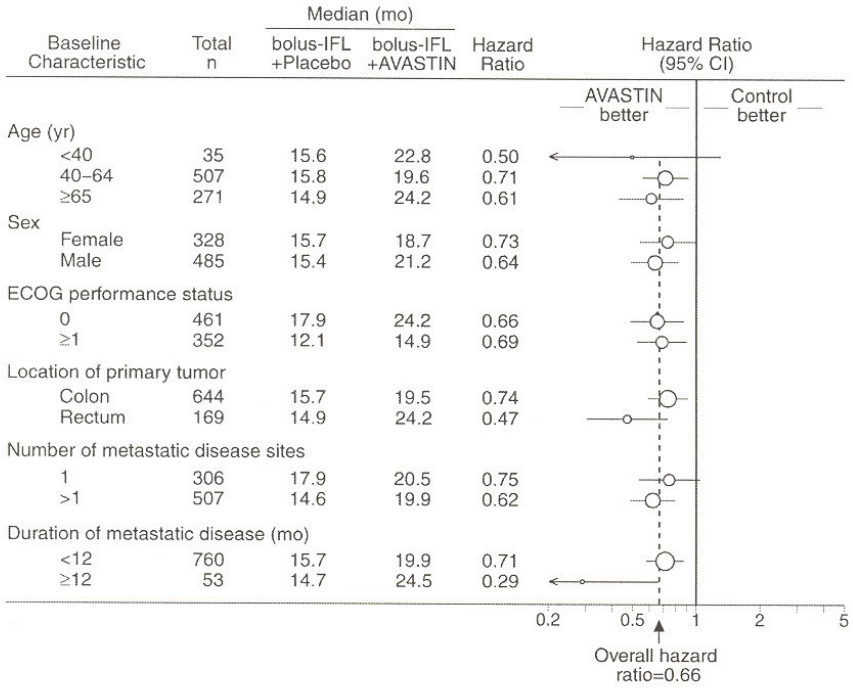


**Figure 3 Duration of Survival by Baseline Risk Factor in Study AVF2107g**




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

***Bevacizumab in Combination with 5 FU/LV Chemotherapy for the First Line Treatment of Metastatic Carcinoma of the Colon or Rectum in patients who were not optimal candidates for first-line irinotecan treatment (AVF2192g)***

This was a phase II randomized, active-controlled, open-labelled clinical trial investigating bevacizumab in combination with 5 FU/Leucovorin as first-line treatment for metastatic colorectal cancer in patients who were not optimal candidates for first-line irinotecan treatment. Patients had to be either more susceptible to irinotecan toxicity (≥ 65 years, prior radiotherapy to pelvis or abdomen) or less likely to benefit from irinotecan treatment (PS ≥ 1, baseline albumin < 3.5 g/dl) in order to be eligible for enrolment. One hundred and five patients were randomized to 5 FU/LV + placebo arm and 104 patients randomized to 5 FU/LV + bevacizumab (5 mg/kg every 2 weeks). All treatments were continued until disease progression. The overall age was 71 years; 28.2% of patients had an ECOG performance status of 0, 65.1% had a value of 1 and 6.7% had a value of 2. The addition of bevacizumab 5 mg/kg every two weeks to 5 FU/LV resulted in higher objective response rates, significantly longer progression free survival, and a trend in longer survival, compared with 5 FU/LV chemotherapy alone (see Table 21). These efficacy data were consistent with the results observed in studies AVF2107g and AVF0780g.

**Table 21 Treatment Regimens in Study AVF2192g**

| | Treatment | Starting Dose | Schedule |
|---|---|---|---|
| Arm 1 | 5-Fluorouracil<br>Leucovorin | 500 mg/ $m^2$ IV<br>500 mg/ $m^2$ IV | given once weekly for 6 weeks of 8-weeks cycle |
| | Placebo | IV | Every 2 weeks |
| Arm 2 | 5-Fluorouracil<br>Leucovorin | 500 mg/ $m^2$ IV<br>500 mg/ $m^2$ IV | given once weekly for 6 weeks of 8-weeks cycle |
| | bevacizumab | 5 mg/kg IV | Every 2 weeks |
| 5-Fluorouracil: IV bolus (slow push) 1 hour after initiation of the 2-hour leucovorin infusion.<br>Leucovorin: IV infusion over 2 hours | | | |

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

This was a phase II randomised, active-controlled, open-labelled clinical trial investigating bevacizumab in combination with 5-FU/LV as first-line treatment of metastatic colorectal cancer. Seventy one patients were randomised to receive bolus 5-FU/LV or 5-FU/LV + bevacizumab (5 mg/kg every 2 weeks). A third group of 33 patients received bolus 5-FU/LV + bevacizumab (10 mg/kg every 2 weeks). Patients were treated until disease progression. The primary endpoints of the trial were objective response rate and progression free survival. The addition of 5 mg/kg every two weeks of bevacizumab to 5-FU/LV resulted in higher objective response rates, longer progression free survival, and a trend in longer survival, compared with 5-FU/LV chemotherapy alone (see Table 22). This efficacy data is consistent with the results from study AVF2107g.

**Table 22 Efficacy results for Study AVF0780g and AVF2192g**

| | AVF0780g | | | AVF2192g | |
|---|---|---|---|---|---|
| | **5-FU/LV** | **5-FU/LV + bevacizumab[a]** | **5-FU/LV + bevacizumab[b]** | **5-FU/LV + placebo** | **5-FU/LV + bevacizumab** |
| Number of Patients | 36 | 35 | 33 | 105 | 104 |
| Overall Survival<br>Median (months) | 13.6 | 17.7 | 15.2 | 12.9 | 16.6 |
| 95% Confidence Interval (CI) | | | | 10.35-16.95 | 13.63-19.32 |
| Hazard ratio[c]<br>(95% CI) | - | 0.52<br>(0.25; 1.08) | 1.01<br>(0.53; 1.91) | | 0.79<br>(0.56; 1.10) |
| p-value | | 0.073 | 0.978 | | 0.16 |
| Progression-free Survival<br>Median (months) | 5.2 | 9 | 7.2 | 5.5 | 9.2 |
| Hazard ratio<br>(95% CI) | | 0.44<br>(0.24; 0.8) | 0.69<br>(0.38; 1.25) | | 0.5<br>(0.34; 0.73) |
| p-value | - | 0.0049 | 0.217 | | 0.0002 |
| Overall Response Rate<br>Rate (per cent) | 16.7 | 40 | 24.2 | 15.2 | 26 |
| 95% confidence interval | 7.0-33.5 | 24.4-57.8 | 11.7-42.6 | 9.2-23.9 | 18.1-35.6 |
| p-value | | 0.029 | 0.43 | | 0.055 |
| Duration of Response<br>Median (months) | NR | 9.3 | 5 | 6.8 | 9.2 |
| 25-75 percentile (months) | 5.5-NR | 6.1-NR | 3.8-7.8 | 5.59-9.17 | 5.88-13.01 |

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

**Adjuvant Colon Cancer (aCC)**

***BO17920***

This was a phase III randomized 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. At the time of the clinical cut-off for end-of-study follow-up (which occurred 2 years after the primary analysis for DFS and was at least 5 years after the last patient was randomized), the unstratified hazard ratio for overall survival was 1.27 (95% CI: 1.03-1.57) for the FOLFOX4 + bevacizumab arm and 1.15 (95% CI: 0.93-1.42) for the XELOX + bevacizumab arm compared to FOLFOX alone.

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

The safety and efficacy of bevacizumab in the treatment of patients with non-small cell lung cancer (NSCLC) was assessed in addition to a carboplatin/paclitaxel chemotherapy regimen in studies E4599 and AVF0757g.

***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 randomized to platinum-based chemotherapy (paclitaxel 200 mg/m2 and carboplatin AUC = 6.0, both by IV infusion) (PC) on day 1 of every 3-week cycle for up to 6 cycles or PC in combination with bevacizumab at a dose of 15 mg/kg IV infusion day 1 of every 3-week cycle. After completion of six cycles of carboplatin-paclitaxel chemotherapy or upon premature discontinuation of chemotherapy, patients on the bevacizumab + carboplatin–paclitaxel arm continued to receive bevacizumab as a single agent every 3 weeks until disease progression. 878 patients were randomized to the two arms.

The combination of carboplatin and paclitaxel is used as a current Canadian standard of care in major treatment centers for the treatment of NSCLC.

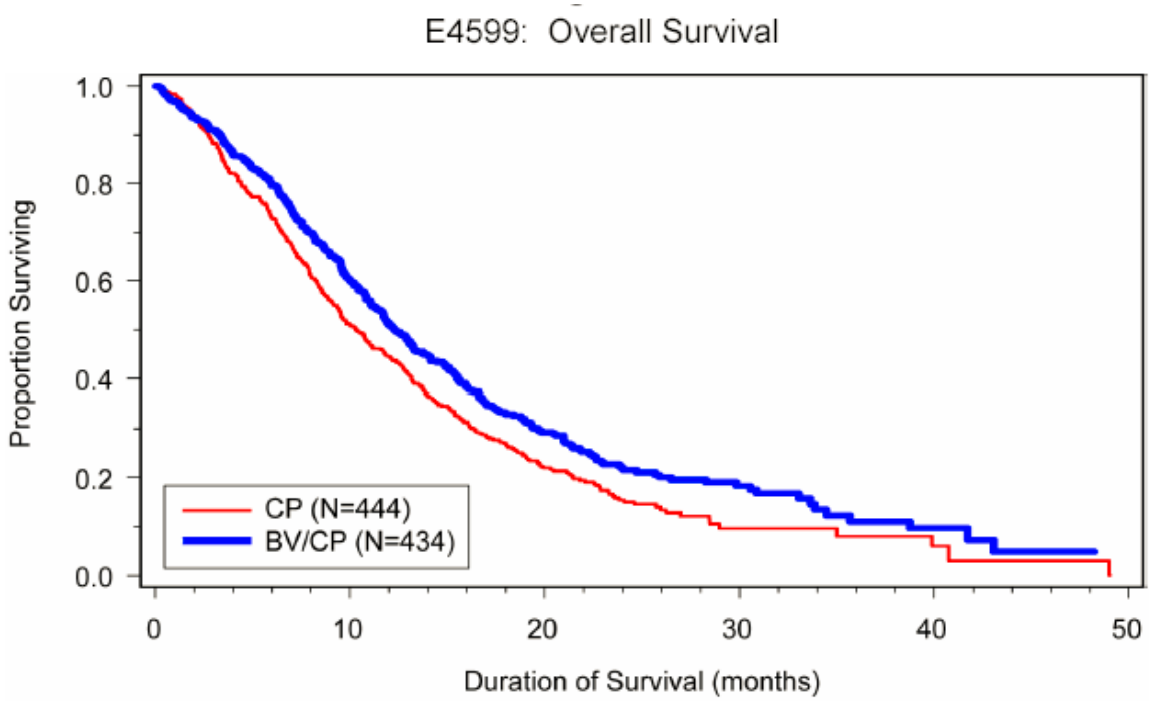
During the study, of the patients who received trial treatment, 32.2% (136/422) of patients received 7-12 administrations of bevacizumab and 21.1% (89/422) of patients received 13 or more administrations of bevacizumab.

The primary endpoint was duration of survival. Results are presented in Table 23.

**Table 23 Efficacy Results for Study E4599**

| | Arm 1<br><br>Carboplatin/ Paclitaxel | Arm 2<br><br>Carboplatin/ Paclitaxel + bevacizumab 15 mg/kg q 3 weeks |
|---|---|---|
| Number of Patients | 444 | 434 |
| Overall Survival | | |
| Median (months) | 10.3 | 12.3 |
| Hazard ratio | | 0.80 (p=0.003)<br>95% CI (0.69, 0.93) |
| Overall Response Rate | | |
| Rate (percent) | 12.9 | 29.0 (p<0.0001) |

**Figure 4 Study E4599: Kaplan Meier Plot of Overall Survival (All Randomized Patients)**




BV/CP = bevacizumab + carboplatin/paclitaxel; CP = carboplatin/paclitaxel.

In an exploratory analysis across patients' subgroups, improvement in duration of survival was not observed with bevacizumab treatment in females. The hazard ratio (HR) of survival for females was HR 0.99 (95% CI: 0.79, 1.25; p = 0.95), patients aged 65 years or older HR 0.91 (95% CI: 0.72, 1.14) or weight loss of 5% or greater in the 6 months prior to treatment initiation HR 0.96 (95% CI: 0.73, 1.26).

In a pre-specified exploratory analysis, improvement in the duration of survival was not consistent in all histology subtypes. The majority of the patients in this trial (69.3%) had adenocarcinoma, which was the only subgroup considered large enough from which to draw a conclusion regarding overall survival. In an exploratory analysis, the extent of bevacizumab benefit on overall survival was less pronounced in the subgroup of patients who did not have adenocarcinoma histology. The hazard ratio (HR) of survival for different histological subtypes was as follows: adenocarcinoma HR 0.69 (95% CI: 0.58, 0.83), squamous HR 0.00 (95% CI: 0.00, -), large cell undifferentiated HR 1.15 (95% CI: 0.60, 2.24), bronchoalveolar (BAC) HR 1.48 (95% CI: 0.57, 3.89), NSCLC, NOS HR 1.16 (95% CI: 0.84, 1.61) and other HR 0.92 (95% CI: 0.43, 1.98).

**Table 24 Histological Subtypes in study E4599**

| | CP N=442 N (%) | Bv15+CP N=433 N (%) | Total N=875 N (%) |
|---|---|---|---|
| **Adenocarcinoma** | 302 (68.3%) | 300 (69.3%) | 602 (68.8%) |
| **Squamous carcinoma** | 2 (0.5%) | 1 (0.2%) | 3 (0.3%) |
| **Large cell undifferentiated** | 30 (6.8%) | 18 (4.2%) | 48 (5.5%) |
| **Bronchioalveolar (BAC)** | 11 (2.5%) | 12 (2.8%) | 23 (2.6%) |
| **NSCLC, NOS** | 86 (19.5%) | 79 (18.2%) | 165 (18.9%) |
| **Other** | 11 (2.5%) | 23 (5.3%) | 34 (3.9%) |

***Study AVF0757g***

The design for the pivotal phase III trial (study E4599) was based on the findings from an earlier supporting phase II study AVF0757g. In this randomized, multicenter, open label, Phase II trial, 99 patients were randomized to treatment; 32 patients were assigned to the control arboplatin/paclitaxel arm (CP), 32 patients to the 7.5 mg/kg/q3w bevacizumab plus carboplatin/paclitaxel arm (Bv7.5+CP) and 35 patients to the 15 mg/kg/q3w bevacizumab plus carboplatin/paclitaxel arm (Bv15+CP). Study AVF0757g was designed to test the efficacy, safety, pharmacokinetics, and pharmacodynamics of bevacizumab in combination with carboplatin/paclitaxel chemotherapy in subjects with locally advanced, metastatic, or recurrent NSCLC.

With respect to the demographic and baseline characteristics imbalances between treatment arms were noted in the proportion of men to women, patients with an ECOG performance status of 0, disease duration of <1year, squamous cell histology, cancer stage (IIIB and IV) and prior cancer treatment. Primary efficacy endpoints were time to disease progression (TTP) and best confirmed

response rate as assessed both by the investigator and by a blinded independent review facility (IRF). Though not statistically significant based on the IRF assessment, there was a trend for improvement in TTP (7.0 vs 6.0 months) and the response rate (40% vs 31%) for patients in the 15 mg/kg arm compared with the control arm. There was not a statistically significant difference in survival between patients in the 15 mg/kg arm and the control arm (14.4 vs 13.3 months), however, 19 out of 32 patients randomized to the control arm crossed over to receive bevacizumab following disease progression.

In this trial, the incidence of serious or fatal pulmonary hemorrhage was 31% (4 of 13) in bevacizumab -treated patients with squamous cell histology and 4% (2 of 53) in bevacizumab - related patients with histology other than squamous cell. The subgroup of subjects with squamous cell histology appeared to be at higher risk for this toxicity and was excluded from Study E4599. Rates of most serious adverse events (SAEs), hypertension and proteinuria were similar to the pivotal trial E4599. Other safety signals (headache, respiratory tract infections, epistaxis, fever, and rash) were considered manageable.

**Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer**

**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, randomized, two-arm Phase III evaluation of bevacizumab plus chemotherapy (CT+BV) versus chemotherapy alone (CT).

A total of 361 patients were enrolled into this study and administered either chemotherapy (based on the decision of the investigator, patients were assigned to receive one of three chemotherapy agents (paclitaxel, topotecan, or PLD)) alone or in combination with bevacizumab:

- CT Arm (chemotherapy alone):
  - Paclitaxel 80 mg/m2 as a 1-hour IV infusion on Days 1, 8, 15, and 22 every 4 weeks.
  - Topotecan 4 mg/m2 as a 30 minute IV infusion on Days 1, 8, and 15 every 4 weeks. Alternatively, a 1.25 mg/m2 dose could be administered over 30 minutes on Days 1–5 every 3 weeks.
  - PLD 40 mg/m2 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 IV every 2 weeks (or bevacizumab 15 mg/kg every 3 weeks if used in combination with topotecan 1.25 mg/m2 on Days 1–5 on a every 3 weeks schedule).

Patients enrolled in the trial remained on treatment until disease progression, unacceptable toxicities, or patient request for withdrawal.

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. Patients with refractory disease (i.e., progression while on preceding platinum therapy) were excluded.

Randomization was stratified by the following factors: chemotherapy selected (paclitaxel; topotecan; PLD), prior anti-angiogenic therapy (yes or no), and platinum-free interval (<3; 3−6 months).

The primary endpoint was progression-free-survival based on investigator assessment. The secondary endpoints were objective response rate based on investigator assessment and overall survival.

The baseline patient demographic characteristics were well balanced between the CT and CT+BV arms. Nearly all patients were white. The median age was 61.0 (range: 25−84) years, and 36.8% of all patients were 65 years or older. The majority of patients in both arms had an ECOG PS of 0 (CT: 56.4% vs. CT+BV: 61.2%). In the CT arm, the percentage of patients with an ECOG PS of 1 or ≥2 was 38.7% and 5.0%, and in the CT+BV arm, the percentage of patients with an ECOG PS of 1 or ≥2 was 29.8% and 9.0 %.

The addition of bevacizumab to chemotherapy demonstrated a statistically significant improvement in investigator assessed PFS, which was supported by a retrospective independent review analysis. Study results for the intent to treat (ITT) population are presented in Table 25 and Figure 5. Results for the separate chemotherapy cohorts are presented in Table 26.

**Table 25 Efficacy Results from Study MO22224 (AURELIA)**

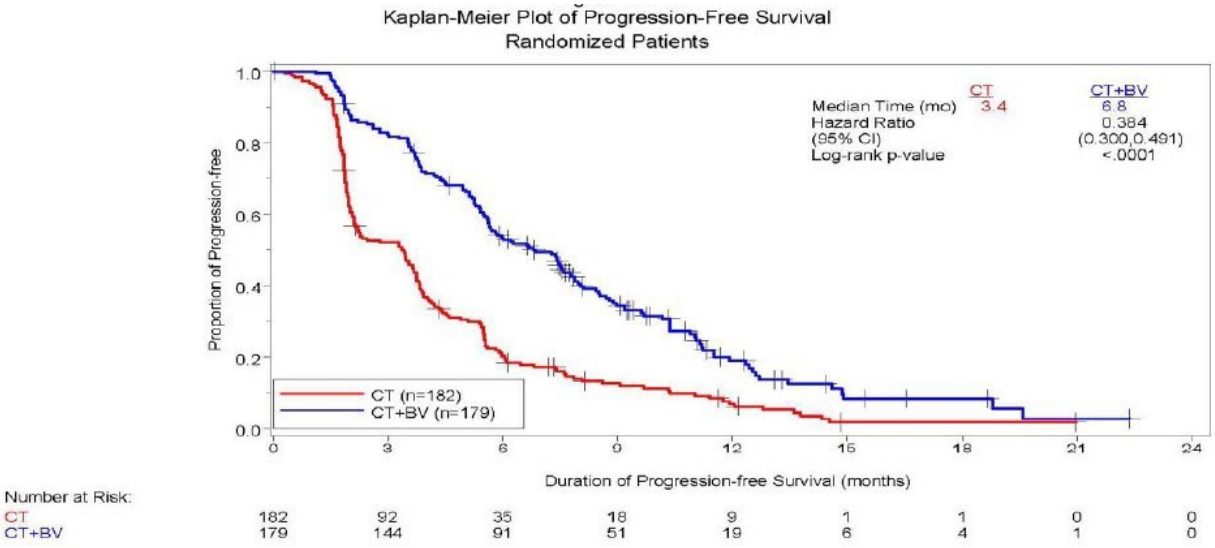
| **Primary Endpoint** | | |
|---|---|---|
| **Progression-Free Survival** | | |
| | Investigator Assessment | |
| | CT (n=182) | CT+BV (n=179) |
| No. (%) patients with event | 168 (92.3%) | 140 (78.2%) |
| Median (months) | 3.4 | 6.8 |
| Hazard ratio* (95% CI) | 0.384 [0.300, 0.491] | |
| p-value** | <0.0001 | |
| **Secondary Endpoints** | | |
| **Objective Response Rate** | | |
| | Investigator Assessment | |
| | CT (n=182) | CT+BV (N=179) |
| No. patients with measurable disease at baseline | 144 | 142 |
| % pts with objective response | 18 (12.5%) | 40 (28.2%) |
| Median duration of response | 5.4 | 9.4 |

| Overall Survival (final analysis) | | |
|---|---|---|
| | CT (n=182) | CT+BV (n=179) |
| No. (%) patients who died | 136 (74.7%) | 128 (71.5%) |
| Median OS (months) | 13.3 | 16.6 |
| Hazard Ratio* (95% CI) | 0.887 (0.691, 1.140) | |

CT = Chemotherapy alone; CT+BV= Chemotherapy plus bevacizumab

*Based on a stratified Cox proportional hazards model adjusting for the three stratification factors used for randomization (chemotherapy selected (paclitaxel; topotecan; PLD), prior anti-angiogenic therapy (yes or no), and platinum-free interval (<3; 3−6 months)).
** P-value based on a two-sided stratified log-rank test adjusting for the following stratification factors: chemotherapy selected (paclitaxel; topotecan; PLD), prior anti-angiogenic therapy (yes or no), and platinum-free interval (<3; 3−6 months).

**Figure 5 Kaplan Meier Plot of Progression-Free Survival Based on Investigator Assessment in Randomized Patients**




BV = bevacizumab; CT= chemotherapy.

**Table 26 Efficacy Results in Chemotherapy Cohorts from Study MO22224 (AURELIA)**

| Efficacy Parameter | Paclitaxel | | Topotecan | | PLD | |
|---|---|---|---|---|---|---|
| | CT[b] (N=55) | CT[b]+ bevacizumab (N=60) | CT[b] (N=63) | CT[b]+ bevacizumab (N=57) | CT[b] (N=64) | CT[b]+ bevacizumab (N=62) |
| **PFS per Investigator** | | | | | | |
| No. (%) of subjects with an event | 50 (90.9%) | 39 (65.0%) | 57 (90.5%) | 45 (78.9%) | 61 (95.3%) | 56 (90.3%) |
| Median (months) (95% CI) | 3.9 (3.5, 5.5) | 9.6 (7.8, 11.5) | 2.1 (1.9, 2.3) | 6.2 (5.3, 7.6) | 3.5 (1.9, 3.9) | 5.1 (3.9, 6.3) |
| HR (95% CI)[a] | 0.47 (0.31, 0.72) | | 0.24 (0.15, 0.38) | | 0.47 (0.32, 0.71) | |
| **Overall Survival** | | | | | | |
| No. (%) of subjects who died | 41 (74.5%) | 36 (60.0%) | 43 (68.3%) | 44 (77.2%) | 52 (81.3%) | 48 (77.4%) |
| Median (months) (95% CI) | 13.2 (8.2, 19.7) | 22.4 (16.7, 26.7) | 13.3 (10.4, 18.3) | 13.8 (11.0, 18.3) | 14.1 (9.9, 17.8) | 13.7 (11.0, 18.3) |
| HR (95% CI)[a] | 0.64 (0.41, 1.01) | | 1.12 (0.73, 1.73) | | 0.94 (0.63, 1.42) | |
| **Objective Response Rate** | | | | | | |
| Number of Patients with Measurable Disease at Baseline | 43 | 45 | 50 | 46 | 51 | 51 |
| Rate, % (95% CI) | 30 (17, 44) | 53 (39, 68) | 2 (0, 6) | 17 (6, 28) | 8 (0, 15) | 16 (6, 26) |
| Median of Response Duration (months) | 6.8 | 11.6 | NE | 5.2 | 4.6 | 8.0 |

[a]per stratified Cox proportional hazards model adjusting for the three stratification factors used for randomization (chemotherapy selected (paclitaxel; topotecan; PLD), prior anti-angiogenic therapy (yes or no), and platinum-free interval (<3; 3−6 months)).
[b]Chemotherapy
NE = Not Estimable

**Malignant Glioma (WHO Grade IV) – Glioblastoma**

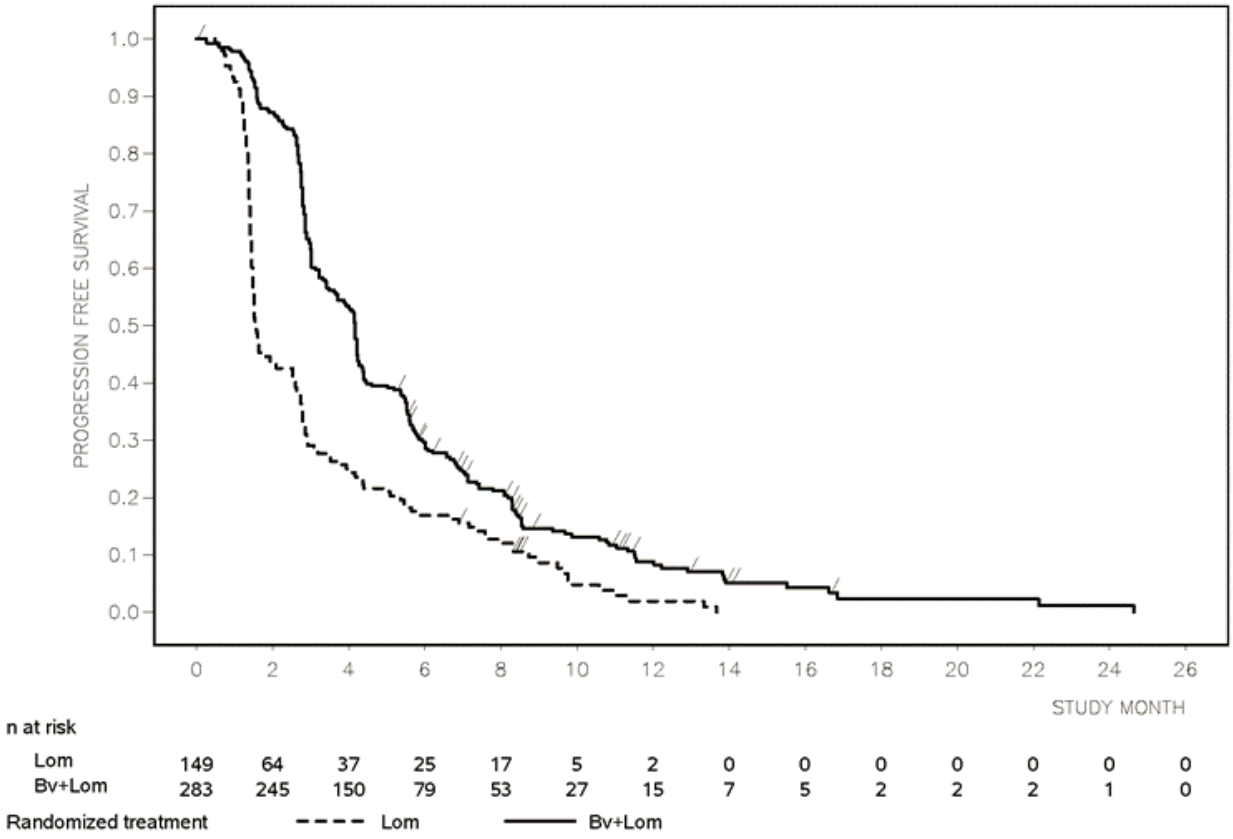
***Study EORTC 26101***

Patients with previously treated glioblastoma were evaluated in a multicenter, randomized, open-label Phase 3 study comparing bevacizumab plus Lomustine versus Lomustine. A total of 432 patients with first progression following the treatment with radiotherapy and temozolomide were randomized (2:1) to receive either bevacizumab (10 mg/kg IV infusion every 2 weeks; n = 283) plus Lomustine (every 6 weeks; 90 mg/m2 [maximum dose 160 mg] in the first cycle and the dose could be escalated to 110 mg/m2 (maximum dose 200 mg) from the second cycle onwards in the absence of Grade > 1 hematological toxicity during the first cycle) or Lomustine (110 mg/m2 [maximum dose 200 mg] every 6 weeks; n=149) until disease progression or unacceptable toxicity. Randomization was stratified by World Health Organization performance status (0 vs. > 0), steroid use (yes vs. no), largest tumour diameter (≤ 40 vs. > 40 mm) and institution. The primary outcome measure of the study was OS. Key secondary outcome measures included investigator-assessed PFS and ORR. Tumour response was assessed per the modified Response Assessment in Neuro-oncology (RANO) criteria.

The median patient age was 57.0 years on bevacizumab plus Lomustine and 59.0 years on Lomustine. Overall, 24.8% of patients were 65 years old or older. The majority of patients (60.4% in the bevacizumab plus Lomustine arm and 61.1% in the Lomustine arm) were male.

There was no difference in OS (HR=0.91, p = 0.4578); therefore, all secondary outcome measures can be interpreted as descriptive only. PFS was shown to be longer among patients receiving bevacizumab plus Lomustine compared to those receiving Lomustine alone; the unblinded investigator-assessed results were a median PFS of 4.2 months vs. 1.5 months [HR 0.52 (95% CI 0.41, 0.64)]. The results are presented in Figure 6. Among the 399 patients with measurable disease, ORR was 26% in those receiving bevacizumab plus Lomustine and 6% in those receiving only Lomustine. A retrospective PFS analysis was conducted on subjects with available diagnostic information (91.2% and 95.3% of subjects receiving bevacizumab + Lomustine and Lomustine alone, respectively) by a blinded central review and results were a median PFS of 2.8 months vs. 1.5 months [HR 0.53 (95% CI 0.42, 0.66)].

**Figure 6** **Investigator-Assessed Progression-Free Survival in Study EORTC 26101**




Among the patients taking corticosteroids at baseline (50.5% in the bevacizumab plus Lomustine arm and 49.7% in the Lomustine arm), more patients in the bevacizumab plus Lomustine arm than in the Lomustine arm discontinued corticosteroids (23.1% vs. 12.2%).

## Pediatric Studies

### Study BO20924 (Bernie)

In a randomized phase II study (BO20924) a total of 154 patients aged ≥ 6 months to <18 years with newly diagnosed metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma were treated with standard of care (induction IVADO/IVA+/- local therapy followed by maintenance vinorelbine and cyclophosphamide) with or without bevacizumab (2.5 mg/kg/week) for a total duration of treatment of approximately 18 months.

At the time of the final primary analysis, the primary endpoint of Event Free Survival (EFS) by an independent central review did not show a statistically significant difference between the two treatment arms, with HR of 0.93 (95% CI: 0.61, 1.41).

### Study BO25041 (Herby)

In a randomized phase II study (BO25041) a total of 121 patients aged ≥ 3 years to <18 years with newly diagnosed supratentorial or infratentorial cerebellar or peduncular high-grade glioma (HGG) were treated with post-operative radiation therapy (RT) and adjuvant temozolomide (T) with and without bevacizumab: 10 mg/kg every 2 weeks IV.

The study did not meet its primary endpoint of demonstrating a significant improvement of EFS (Central Radiology Review Committee (CRRC)-assessed) when bevacizumab was added to the RT/T arm compared with RT/T alone (HR = 1.44; 95% CI: 0.90, 2.30).

## 17 NON-CLINICAL TOXICOLOGY – REFERENCE BIOLOGIC DRUG

### Physeal Development

In studies of up to 26 weeks duration in cynomolgus monkeys, bevacizumab was associated with physeal dysplasia. Physeal dysplasia was characterised primarily by thickened growth plate cartilage, subchondral bony plate formation and inhibition of vascular invasion of the growth plate. This effect occurred at doses ≥ 0.8 times the human therapeutic dose and exposure levels slightly below the expected human clinical exposure, based on average serum concentrations. It should be noted, however, that physeal dysplasia occurred only in actively growing animals with open growth plates.

### Wound Healing

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

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

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

### Renal Function

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

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

**Albumin**

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

**Hypertension**

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

**Hemostasis**

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

**Mutagenicity/Carcinogenicity**

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

**Reproductive toxicity**

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

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

## 18 SUPPORTING PRODUCT MONOGRAPHS

1. PrAVASTIN® (100 mg and 400 mg vials – 25 mg/mL solution for infusion), Control No. 207259, Product Monograph, Hoffman-La Roche Limited, June 06, 2018.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PATIENT MEDICATION INFORMATION**

# PrZIRABEV™

(pronounced) ZIE' rah-bev

**bevacizumab for injection**

Read this carefully before you start taking ZIRABEV and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about ZIRABEV.

ZIRABEV is a biosimilar biologic drug (biosimilar) to the reference biologic drug PrAVASTIN®. A biosimilar is authorized based on its similarity to a reference biologic drug that was already authorized for sale.

**Serious Warnings and Precautions**

**Eye disorders**

ZIRABEV was not developed to be injected in the eye and should be used as authorized. Side effects affecting the eye and the body as a whole were seen in some patients who had ZIRABEV injected in their eye(s).

**Gastrointestinal Perforations**

ZIRABEV treatment can cause gastrointestinal perforation (hole in the stomach or bowel) which can be fatal. ZIRABEV treatment should be stopped if this happens. Gastrointestinal perforation can happen at any time during treatment: symptoms include abdominal pain, constipation and vomiting.

**Wound Healing Complications**

ZIRABEV treatment can cause wound dehiscience (wounds opening and not healing), which can be fatal. ZIRABEV treatment should be stopped if this happens and for one month after having surgery or until the wound is fully healed. ZIRABEV should be stopped at least 28 days before elective surgery.

**Hemorrhage**

Treatment with ZIRABEV can result in serious or fatal bleeding, including coughing up blood, bleeding in the stomach, vomiting of blood, bleeding in the brain, nosebleeds, and vaginal bleeding. These events occurred up to 5 times more often in people who received ZIRABEV compared to patients who received only chemotherapy. People who have recently coughed up blood (greater than or equal to a half teaspoon of red blood) or have serious bleeding should not receive ZIRABEV. Treatment with ZIRABEV should be permanently stopped if serious bleeding occurs (i.e. requiring medical attention).

**What is ZIRABEV used for?**

- Metastatic Colorectal Cancer: ZIRABEV is used in combination with a specific type of chemotherapy (intravenous 5-fluorouracil [5-FU]-based chemotherapy) for treatment of people diagnosed with metastatic colorectal cancer for the first time. Metastatic colorectal cancer is cancer of the colon or rectum that has spread to other organs in the body.

- Metastatic Lung Cancer: ZIRABEV is used in combination with a specific type of chemotherapy (carboplatin and paclitaxel) for the treatment of people diagnosed with metastatic non small cell lung cancer. Metastatic non small cell lung cancer is cancer of the lungs that has spread to other organs in the body.

- Recurrent Platinum-Resistant Ovarian Cancer: ZIRABEV is used in combination with a specific type of chemotherapy (paclitaxel, topotecan, or pegylated liposomal doxorubicin) for the treatment of people diagnosed with recurrent, platinum-resistant, epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens. Recurrent platinum-resistant ovarian cancer is the type of cancer

that progresses within 6 months after the last time the patient responded to a chemotherapy regimen containing a platinum agent.

- Recurrent Glioblastoma: ZIRABEV is used in combination with lomustine (a specific type of chemotherapy) for the treatment of patients with a particular type of brain cancer called glioblastoma in which the cancer reoccurred after a previous treatment.

**How does ZIRABEV work?**

ZIRABEV is not chemotherapy but is given in combination with a specific type of chemotherapy. ZIRABEV is a monoclonal antibody. While chemotherapy attacks the tumour directly, ZIRABEV attacks the blood vessels that surround the tumour.

In order to grow and spread, tumours need a constant supply of oxygen and other nutrients. Tumours get this supply by creating their own network of blood vessels. This process is called angiogenesis (an´-gee-o-jen´-i-sis). ZIRABEV works by blocking angiogenesis. By preventing the growth of new blood vessels, ZIRABEV helps starve the tumour of oxygen and other nutrients. This makes it hard for the tumour to grow.

**What are the ingredients in ZIRABEV?**

The medicinal ingredient is called bevacizumab

The non-medicinal ingredients are (in alphabetical order): Edetate disodium dihydrate (EDTA), Polysorbate 80, Sodium hydroxide, Succinic Acid, Sucrose, Water for Injection

**ZIRABEV comes in the following dosage forms:**

ZIRABEV is available as single use vials in the presentations listed below:

- 100 mg/4 mL (25 mg/mL)

- 400 mg/16 mL (25 mg/mL)

The vial stopper is not manufactured with natural rubber latex.

**Do not use ZIRABEV if:**

ZIRABEV should not be used by people who are allergic to it or any of its ingredients or by people whose cancer has spread to their central nervous system (to their brain or spine). ZIRABEV should not be taken for at least 28 days following surgery.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ZIRABEV. Talk about any health conditions or problems you may have, including if you:**

- have high blood pressure
- plan to have surgery or have had surgery in the last 28 days
- have ever had a heart attack or stroke

- are pregnant or planning to become pregnant
- are breast feeding
- have any allergies to this drug or its ingredients
- have any illnesses or diseases affecting your kidneys;
- have heart failure or weakened heart muscles
- have ever coughed up blood or observed abnormal vaginal bleeding
- are diabetic.

**Other warnings you should know about:**

ZIRABEV should not be used during pregnancy as it may cause harm to your unborn baby. Therefore, you should use effective methods of contraception while taking ZIRABEV and for at least 6 months after your last dose of Bevacizumab. If you become pregnant during treatment with ZIRABEV tell your doctor immediately.

ZIRABEV may affect the hormonal balance of women and their ability to get pregnant as a result of ovarian failure. If you are a woman of reproductive potential, talk to your doctor before starting treatment with ZIRABEV.

If you develop headache, vision problems, dizziness, or change in mental status (for example, confusion) contact your doctor immediately.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with ZIRABEV:**

Drugs that may interact with ZIRABEV include: irinotecan and sunitinib malate. Your doctor may adjust the dose of irinotecan if you have side effects known to be related to it. The safety and effectiveness of ZIRABEV in combination with sunitinib malate has not been established, therefore this combination is not recommended.

Tell your doctor if you are using platinum- or taxane-based therapies for lung. These therapies in combination with ZIRABEV may increase the risk of severe side effects.

The interaction of ZIRABEV in combination with EGFR monoclonal antibodies has not been studied, therefore this combination is not recommended.

**How to take ZIRABEV:**

ZIRABEV is given intravenously (through a needle placed in a vein in the arm, hand, or through a central line).

**Usual dose:**

<u>Metastatic Colorectal Cancer</u>

The usual dose of ZIRABEV is based on your weight in kg (5 mg/kg) and it is given once every 14 days for as long as your physician recommends therapy.

Metastatic Lung Cancer

The usual dose of ZIRABEV is based on your weight in kg (15 mg/kg) and on the specific type of chemotherapy given along with the ZIRABEV. ZIRABEV is given once every 3 weeks for as long as your physician recommends therapy.

Ovarian Cancer (Platinum-resistant recurrent disease)

The usual dose of ZIRABEV is based on your weight in kg (10 mg/kg or 15 mg/kg). ZIRABEV is given once every 2 weeks or 3 weeks for as long as your physician recommends therapy. Your doctor will prescribe a dose and schedule of ZIRABEV that is right for you, based on if and what type of chemotherapy you are also receiving.

Recurrent Glioblastoma

The usual dose of ZIRABEV is based on your weight in kg (10 mg/kg). ZIRABEV is given once every 2 weeks in combination with lomustine every 6 weeks for as long as your physician recommends therapy. The dose of lomustine in the first treatment is 90 mg per square metre of your body surface area (mg/m$^2$), up to a maximum dose of 160 mg. It can be increased to 110 mg/m$^2$, up to a maximum of 200 mg, from the second treatment onwards. The increase dose of lomustine after the first treatment will be determined by your doctor based on your blood work.

The first time ZIRABEV is given, it will take about 90 minutes. Once your doctor has made sure that you have no problems with the ZIRABEV infusions, (i.e. after the first or second infusion), subsequent infusions may require less time, usually about 30 or 60 minutes.

**Overdose:**

If you think you have taken too much ZIRABEV, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

In addition to the possible side-effects listed below, an overdose may cause a severe headache.

**Missed Dose:**

If you miss a dose of ZIRABEV, your doctor will decide when you should receive your next dose.

**What are possible side effects from using ZIRABEV?**

These are not all the possible side effects you may feel when taking ZIRABEV. If you experience any side effects not listed here, contact your healthcare professional.

Like all medications, ZIRABEV can cause some unwanted side effects. The following side effects were seen in clinical trials when ZIRABEV in combination with chemotherapy or ZIRABEV alone was given to patients:

Very Common (more than 1 in 10 patients):

- High blood pressure
- Diarrhea, vomiting
- Abdominal pain
- Constipation
- Nausea
- Lack of energy or strength
- Loss of appetite
- Pain (including joint pain)
- Bleeding (from the nose or rectum)
- Sores in the mouth
- Shortness of breath
- Runny nose
- Dry, scaling skin or changes in skin colour
- Changes in the sense of taste
- Eye problems (for example: excessive tearing, blurred vision, an experience of discomfort or pain to the eyes due to light exposure)
- A decrease in certain white blood cells in the blood that help fight off infection
- Decrease in the number of red blood cells [anemia]
- Difficulty in sleeping
- Fever, chills or excessive sweating
- Headache
- Abnormal urine test (protein in the urine)
- Tingling sensation or numbness in toes and fingers
- Bronchitis (an inflammation of the main air passages to the lungs)
- Bruising
- Change in moods
- Infections (mouth, throat, sinus, lungs or urine infections)
- Excess of sugar in the blood
- Weight loss
- Widening of the blood vessels
- Low levels of sodium and magnesium in the blood
- Coughing
- Tiredness

Common (less than 1 in 10 patients but more than 1 in 100 patients):

- Pain (including muscle pain, chest pain, heart pain (angina), back pain, and pain in the pelvis and anal regions)
- Stroke/heart attack
- Blood clots
- Perforation of the gut (hole in the stomach or bowel)
- Altered voice such as hoarseness
- Swelling and numbness of the hand and feet

- Urinary (bladder or kidney) infection
- Infections of the skin or deeper layers under the skin
- Fistula (abnormal tube like connection between internal parts of the body that are not normally connected) such as between the stomach and intestines (gastrointestinal fistula), in patients with metastatic colorectal cancer and platinum resistant ovarian cancer, and between the vagina and the gut in patients with cervical cancer (unauthorized use)
- Allergic reactions
- Nephrotic syndrome (a type of kidney disorder)

Uncommon (less than 1 in 100 patients but more than 1 in 1000 patients):

- Non-gastrointestinal perforations and fistulae (abnormal holes or tubes in areas of the body other than the gastrointestinal tract)
- Posterior Reversible Encephalopathy Syndrome (PRES) a syndrome characterized by headache, confusion, seizures and visual loss

Rare (less than 1 in 1000 patients but more than 1 in 10,000 patients):

- Tracheoesophageal fistula (abnormal tube like connection between internal parts of the body that are not normally connected) such as between the trachea (or windpipe) and esophagus (tube connecting the mouth to the stomach)
- Severe bacterial infection of the skin and soft tissue (necrotizing fasciitis)
- Bleeding (in the brain)

Frequency unknown:

- Ulcers in the stomach and bowel
- Jaw bone damage resulting from poor blood supply to the jaw bone
- Perforation in the gallbladder (hole in the digestive organ that stores bile)

If your blood pressure increases while you are taking ZIRABEV, it is important to contact your doctor.

Changes in your blood and urine tests done by your doctor may occur while you are receiving ZIRABEV. These changes may include a lower white cell count, and protein in the urine. Your doctor will discuss these results with you.

Elderly patients (65 years or older) have a greater risk of developing the following side effects: blood clots (that may lead to stroke or heart attack), a decrease in certain white blood cells and platelets, protein in the urine, diarrhea and fatigue.

Outside of the authorized use of ZIRABEV for cancer treatment, the following side effects may occur when ZIRABEV is injected directly into the eye (unauthorized use):

- Infection or inflammation of the eye globe, which may lead to permanent blindness
- Redness of the eye, small particles or spots in your vision (floaters), eye pain, which may lead to permanent blindness

- Seeing flashes of light with floaters, progressing to a loss of some of your vision
- Increased eye pressure
- Bleeding in the eye
- Surgery of the eye lens due to cataract
- Other serious side effects affecting other organs, which may be severe and lead to hospitalisation, e.g. heart attack, stroke, and high blood pressure

| **Serious side effects and what to do about them** | | | |
|---|---|---|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| **VERY COMMON (more than 1 in 10 patients)**<br>**High blood pressure**<br>You may not experience any symptoms, but possible symptoms associated with high blood pressure are: headache, blurred vision, fatigue, irregular fast, hard heartbeats | | √ | |
| Bleeding from the nose that lasts for more than 10-15 minutes and cannot be stopped | | | √ |
| Diarrhea | | √ | |
| Vomiting | | √ | |
| Constipation | | √ | |
| Bleeding from the rectum or stomach<br>Symptoms include fresh blood in stools and/or dark stools | | √ | |
| Decreased number of white blood cells<br>Symptoms could include fever, sore throat, infection | | √ | |
| Decreased number of red blood cells in the blood that carry oxygen<br>Symptoms could include feeling of weakness or fatigue in general or during exercise, poor concentration | | √ | |
| Pain (chest pain, back pain, abdominal pain, muscle pain, joint pain) | | √ | |
| Low blood pressure<br>You may not experience any symptoms, but possible | | √ | |

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| symptoms associated with low blood pressure are: lightheadedness, dizziness, fainting | | | |
| Dilation (widening) of the blood vessels<br>Symptoms may include low blood pressure, dizziness, flushing | | √ | |
| Bronchitis (an inflammation of the main air passages to the lungs) | | √ | |
| Excess of sugar in the blood<br>Symptoms may include frequent hunger, frequent thirst, frequent urination | | √ | |
| Infections (mouth, throat, sinus, lungs or urine infections) | | √ | |
| Weakened heart muscle/loss of the heart's pumping ability (symptoms may include shortness of breath, fatigue, persistent coughing or wheezing, increased heart rate, swelling in the feet or ankles) | | √ | |
| Low levels of sodium and magnesium in the blood | | √ | |
| Coughing | | √ | |
| **COMMON (**less than 1 in 10 patients but more than 1 in 100 patients)<br>Perforation of the gut (leakage of the bowel)<br>Symptoms include: sudden onset of abdominal pain, abdominal tenderness with vomiting, high fever | | | √ |
| Allergic reactions<br>Symptoms include difficulty in breathing, chest pain, redness or flushing of the skin, rash, shivering, nausea, vomiting | | √ | |
| Blood clots<br>In the deep veins of the leg, symptoms include: pain, swelling, warm to the touch, and | | √ | |

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| tenderness of the leg.<br>In the lung, symptoms include: shortness of breath, chest pain, light headedness | | | |
| Stroke or heart attack<br>Symptoms of stroke include: sudden loss of speech or numbness of part or all of the body, loss of vision or blurred vision, unexplained dizziness and/or sudden falls.<br>Symptoms of a heart attack include: chest pain with spreading to the left arm, jaw and/or back, shortness of breath | | | √ |
| Pain in the pelvis and anal regions | | √ | |
| Fistula<br>Abnormal tube-like connection between internal organs and skin or other tissues that are not normally connected, including connections between the vagina and the gut in patients with cervical cancer (unauthorized use) | | | √ |

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| Nephrotic syndrome (a type of kidney disorder)<br>Symptoms include swelling in the face, arms, legs, belly area, foamy appearance of urine and poor appetite | | √ | |
| **UNCOMMON** (less than 1 in 100 patients but more than 1 in 1000 patients)<br>Non-gastrointestinal perforations and fistulae<br>Depending on the organs involved the symptoms could be as follows: leakage of urine, abnormal and bad odor in the genital area, abdominal pain, vomiting, fever, gradually increasing/worsening of shortness of breath (dyspnoea), cough, chest pain, yellowish discoloration of the skin etc. | | √ | √ |
| Posterior Reversible Encephalopathy Syndrome (PRES)<br>Symptoms include headache, confusion, seizures and visual loss | | | √ |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

Store in a refrigerator at the recommended temperature of 2 – 8 °C. Do not freeze. Do not shake. Keep vial in the outer carton in order to protect from light.

Keep out of reach and sight of children.

**If you want more information about ZIRABEV:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.pfizer.ca, or by calling 1-800-463-6001

This leaflet was prepared by Pfizer Canada ULC

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