PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrAVASTIN®

bevacizumab for injection

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

Antineoplastic

Hoffmann-La Roche Limited

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS	08/2023

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

AVASTIN (bevacizumab for injection) is indicated for:

- Metastatic Colorectal Cancer (mCRC)
  - Avastin 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 Avastin in combination with irinotecan.
  - Please refer to the Product Monographs for irinotecan, 5-fluorouracil and leucovorin for additional information on these products, and specifically DOSING AND ADMINISTRATION for guidance on dose adjustments.
- Locally Advanced, Metastatic or Recurrent Non-Small Cell Lung Cancer (NSCLC)
  - Avastin, 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-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer
  - Avastin, in combination with carboplatin and gemcitabine is indicated for the treatment of patients with first recurrence platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer. These patients should not have received prior VEGF-targeted therapy including Avastin.
  - The effectiveness of Avastin in platinum-sensitive recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer is based on an improvement of progression-free survival in patients who had first recurrence after 6 months of platinum-based chemotherapy. No overall survival benefit was demonstrated with Avastin.
- Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer
  - Avastin 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 Avastin.
  - The effectiveness of Avastin 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 Avastin.
- Malignant Glioma (WHO Grade IV) – Glioblastoma
  - Avastin, in combination with lomustine, is indicated for the treatment of patients with glioblastoma after relapse or disease progression, following prior therapy.
  - The efficacy of Avastin 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 14 CLINICAL TRIALS for information).

1.1 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics: Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness (see 7 WARNINGS AND PRECAUTIONS, Special Populations).

2 CONTRAINDICATIONS

AVASTIN is contraindicated in patients with known hypersensitivity to:

- This drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION and PACKAGING,
- Chinese hamster ovary cell products or other recombinant human or humanised antibodies.

Avastin is contraindicated in patients with untreated Central Nervous System (CNS) metastases (see 6 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Eye Disorders:** Avastin 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 7 WARNINGS AND PRECAUTIONS).

- **Gastrointestinal Perforations:** Avastin 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 Avastin (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 Avastin presenting with abdominal pain. The incidence of gastrointestinal perforation, some fatal, in Avastin 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, 0.6% in platinum-sensitive ovarian cancer, and 1.7% in platinum-resistant ovarian cancer studies. The incidence of gastrointestinal perforation in patients receiving irinotecan/bolus 5-fluorouracil/leucovorin with Avastin was 2%. Avastin therapy should be permanently discontinued in patients with gastrointestinal perforation (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).

- **Wound Healing Complications:** Avastin administration can result in wound dehiscence, in some instances resulting in fatality. Avastin therapy should be permanently discontinued in patients with wound dehiscence requiring medical intervention. Avastin should be discontinued at least 28 days prior to elective surgery. Avastin therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed (see 7 WARNINGS AND

PRECAUTIONS).

- **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 Avastin. Do not administer Avastin to patients with serious hemorrhage or recent hemoptysis (see 4 DOSAGE AND ADMINISTRATION, 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS).

4 DOSAGE AND ADMINISTRATION

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

4.1 Dosing Considerations

It is recommended that Avastin treatment be continued until progression of the underlying disease. There are no recommended dose reductions. Discontinue Avastin 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 Avastin 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

Metastatic Colorectal Cancer
The recommended dose of Avastin 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 Avastin, 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, Avastin was administered in addition to carboplatin/paclitaxel chemotherapy for up to 6 cycles of treatment followed by Avastin as a single agent until disease progression.

Platinum-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer
The recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

Avastin is administered in combination with carboplatin and gemcitabine for 6 cycles and up to 10 cycles followed by continued use of Avastin as single agent until disease progression.

Platinum-Resistant Recurrent Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer
The recommended dose of Avastin 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 section, Study MO22224 (AURELIA) for chemotherapy regimens).

Alternatively, the recommended dose of Avastin is 15 mg/kg every 3 weeks when administered in combination with topotecan given on days 1-5, every 3 weeks (see Clinical Trials section, Study MO22224 (AURELIA) for chemotherapy regimen).

Malignant Glioma (WHO Grade IV) - Glioblastoma
The recommended dose of Avastin 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 14 CLINICAL TRIALS).

4.3 Reconstitution

Parenteral Products:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the vial if visible particles are observed.

Avastin should be prepared by a healthcare professional using aseptic technique. Use sterile needle and syringe to prepare Avastin. Withdraw the necessary amount of Avastin 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 (see 11 STORAGE, STABILITY AND DISPOSAL).

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

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

Avastin is not formulated for intravitreal use (see 7 WARNINGS AND PRECAUTIONS).

4.4 Administration

Do not administer as an intravenous push or bolus.

The initial Avastin 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.

5 OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1 Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous	100 mg and 400 mg vials (25 mg/mL solution for injection)	α,α-trehalose dihydrate, polysorbate 20, sodium phosphate and Water for Injection.

Avastin 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. Avastin is available in packs of 1 vial.

7 WARNINGS AND PRECAUTIONS

General

All patients discontinuing treatment with Avastin 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 Avastin following variable and non-validated methods in compounding, storage, and handling of Avastin 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 Avastin to an authorized treatment in patients treated for wet age-related macular degeneration has reported an increased risk of intraocular inflammation for Avastin (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).

- **Unauthorized Intravitreal Use: Systemic Events**

An observational claims database[iii] study comparing unauthorized intravitreal Avastin to an authorized treatment in patients treated for wet age-related macular degeneration has reported an increased risk of hemorrhagic stroke for Avastin (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 Avastin to an authorized treatment for patients with wet age-related macular degeneration[v] has reported an increased risk of serious systemic adverse events for Avastin, 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.

Carcinogenesis and Mutagenesis

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

Cardiovascular

- **Hypertension**

An increased incidence of hypertension was observed in patients treated with Avastin. Clinical safety data from a single phase III study suggests that the risk of hypertension may be greater in platinum-sensitive recurrent ovarian cancer patients treated with Avastin (see 8 ADVERSE REACTIONS).

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

[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
[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

Avastin therapy. Frequently monitor of blood pressure (e.g. 2-3 weeks) during Avastin therapy in order to detect potentially serious complications of therapy, including hypertensive encephalopathy and Posterior Reversible Encephalopathy Syndrome (PRES) (see 7 WARNINGS AND PRECAUTIONS and 8 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. Avastin 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 8 ADVERSE REACTIONS).

- **Thromboembolism (see 8 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 Avastin in combination with chemotherapy compared to those who received chemotherapy alone.

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

Patients receiving Avastin 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 Avastin therapy. Caution should be used when treating such patients with Avastin (see 8 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 Avastin, 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 Avastin treatment.

In a clinical trial, patients with persistent, recurrent, or metastatic cervical cancer who were administered Avastin showed an increased risk of venous thromboembolic events (see 8 ADVERSE REACTIONS, Venous thromboembolism). Avastin is not authorized for use in cervical cancer.

Avastin 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 Avastin 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 Avastin.

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 8 ADVERSE REACTIONS). Avastin 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 Avastin, it should be treated with the standard medications for this purpose. Discontinuation of Avastin 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

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

Ear/Nose/Throat

- **Osteonecrosis of the Jaw (ONJ)**

Cases of ONJ have been reported in cancer patients treated with Avastin, 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 Avastin 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 Avastin. 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.

Gastrointestinal

- **Gastrointestinal Perforations and Fistula**

Patients may be at increased risk for the development of gastrointestinal perforation and fistulae when treated with Avastin and chemotherapy (see 8 ADVERSE REACTIONS). Avastin use has been associated with serious and sometimes fatal cases of gastrointestinal perforation and fistula in clinical trials (see 8 ADVERSE REACTIONS). In Avastin 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 Avastin.

In a clinical trial, patients with persistent, recurrent, or metastatic cervical cancer who were administered Avastin showed an increased risk of fistulae between the vagina and any part of the GI tract (gastrointestinal-vaginal fistulae) (see 8 ADVERSE REACTIONS, Gastrointestinal Perforations and Fistula). Prior radiation is an additional important risk factor for the development of GI-vaginal fistulae. Avastin is not authorized for use in cervical cancer.

Avastin 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 Avastin (see 8 ADVERSE REACTIONS).

- **Non-Gastrointestinal Fistula (see 8 ADVERSE REACTIONS)**

Patients may be at increased risk for the development of fistulae when treated with Avastin.

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

Permanently discontinue Avastin in patients with any Grade 4 fistula. Limited information is available on the continued use of Avastin in patients with other fistulae. In cases of internal fistula not arising in the GI tract, Avastin 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 Avastin-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 Avastin treatment, with most of the events occurring within the first 6 months of Avastin 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 Avastin in increasing this risk cannot be excluded.

- **Tracheoesophageal (TE) Fistula**

Cases of TE fistula have been reported in lung and esophageal cancer studies of Avastin 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 Avastin in indications other than lung or esophageal cancer cannot be excluded.

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

Genitourinary

- **Ovarian Failure**

Avastin may cause ovarian failure. Therefore, fertility preservation strategies and hormonal changes should be discussed with women of reproductive potential prior to starting treatment with Avastin (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women and 8 ADVERSE REACTIONS). Long term effects of the treatment with Avastin on fertility are unknown.

- **Proteinuria**

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

Temporarily suspend Avastin administration for ≥ 2 grams of proteinuria/24 hours and resume when proteinuria is <2 grams/24 hours. Avastin should be permanently discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome) (see 8 ADVERSE REACTIONS). Proteinuria may not completely resolve after discontinuation of Avastin.

Data from a post-marketing safety study showed poor correlation between UPCR (Urine Protein/Creatine 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 Avastin in combination with chemotherapy compared to those who received chemotherapy alone. Clinical safety data from a single phase III study suggests that the risk of proteinuria may be greater in platinum-sensitive recurrent ovarian cancer patients treated with Avastin (see 8 ADVERSE REACTIONS). Proteinuria (any Grade) was reported in 21.5% (53/247) of the patients in the Avastin arm versus 4.3% (10/233) of the patients in the chemotherapy arm. Grade ≥ 3 proteinuria was observed in 10.9% (27/247) of the patients treated with Avastin versus 0.9% (2/233) of the patients treated with chemotherapy alone. The incidence of Grade 3 proteinuria was common in patients treated with Avastin. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with Avastin, and in some instances resulted in fatal outcomes. In a published case series, kidney biopsy of six patients with proteinuria showed findings consistent with thrombotic microangiopathy.
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 8 ADVERSE REACTIONS)**

Patients treated with Avastin have an increased risk of hemorrhage, especially tumour-associated hemorrhage. Avastin can result in gastrointestinal bleeding, hematemesis, CNS hemorrhage, hemoptysis, epistaxis or vaginal bleeding. Patients should be monitored for bleeding events. Avastin should be permanently discontinued in patients who experienced Grade 3 or 4 bleeding (i.e. bleeding requiring medical intervention) during Avastin 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 Avastin in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting Avastin treatment, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating Avastin therapy in these patients. However, patients who developed venous thrombosis while receiving Avastin therapy did not appear to have increased rate of Grade 3 or above bleeding when treated with full dose of warfarin and Avastin concomitantly.

CNS hemorrhage
Cases of CNS hemorrhage, some with fatal outcome, have been observed with Avastin use. In one phase III study with platinum-sensitive recurrent ovarian cancer, one patient treated with Avastin experienced a Grade 4 hemorrhage stroke and one patient experienced a Grade 5 intracranial hemorrhage. Patients should be monitored for signs and symptoms of CNS bleeding, and Avastin treatment discontinued in case of intracranial bleeding.

The risk of CNS hemorrhage in patients with CNS metastases receiving Avastin could not be fully evaluated, as these patients were excluded from clinical trials (see 2 CONTRAINDICATIONS).

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

Non-CNS hemorrhage
In Study AVF4095g with platinum-sensitive recurrent ovarian cancer, 6/247 (2.4%) patients had serious non-CNS bleeding events.

Pulmonary Hemorrhage/ Hemoptysis
Patients with non–small cell lung cancer treated with Avastin 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 Avastin (see 8 ADVERSE REACTIONS).

- **Neutropenia and Infections (see 8 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 Avastin 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 Avastin in combination with chemotherapy (eg.cisplatin/gemcitabine) compared to those who received chemotherapy alone. Increased incidence of thrombocytopenia (any Grade) was reported in patients treated with Avastin (57.9%), 143/247) as compared to those who received chemotherapy alone (51.1%, 119/233) in the platinum-sensitive ovarian cancer indication clinical trial. Grade ≥ 3 thrombocytopenia was observed in 40.1% (99/247) of the patients treated with Avastin and in 33.9% (79/233) of the patients treated with chemotherapy alone. The incidence of Grade 3 thrombocytopenia was common in patients treated with Avastin. Patients > 65 years of age appeared to be at higher risk for Grade ≥3 thrombocytopenia compared with younger patients. In the platinum-sensitive ovarian cancer indication, a higher incidence of patients treated with Avastin developed thrombocytopenia that was accompanied or followed by a bleeding event compared with those treated with chemotherapy alone (see 8 ADVERSE REACTIONS).

Hepatic/Biliary/Pancreatic

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

Immune

- **Hypersensitivity Reactions, Anaphylactic Reactions (including Anaphylactic Shock), Infusion-Related Reactions**

Patients may be at risk of developing hypersensitivity reactions, anaphylactic reactions (including

anaphylactic shock), and infusion-related reactions. Close observation of the patient during and following the administration of bevacizumab is recommended. If an anaphylactic reaction occurs, the infusion should be permanently discontinued and appropriate medical therapies should be administered. A systematic premedication specifically for bevacizumab administration, in general, is not warranted; however, use of premedication should be based on clinical judgment. If an infusion-related reaction occurs, treatment should be temporarily interrupted until resolution of symptoms. Permanently discontinue Avastin for severe (Grade ≥3) infusion related-reaction.

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.

Neurologic

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

There have been rare reports of patients treated with Avastin 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. Three cases (2 confirmed and 1 unconfirmed of PRES were reported in the platinum-sensitive recurrent ovarian cancer study AVF4095g (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS). 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 Avastin. Discontinue Avastin 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 Avastin in patients previously experiencing PRES is not known (see 8 ADVERSE REACTIONS).

Peri-Operative Considerations

- **Wound Healing**

Avastin may adversely affect the wound healing process. Serious wound healing complications with a fatal outcome have been reported. In the platinum-sensitive recurrent ovarian cancer study AVF4095g, one (0.4%) non-fatal serious case of wound dehiscence was reported in a patient treated with Avastin and there was no case of serious wound complication reported in patients treated with chemotherapy alone.

Avastin 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 Avastin treatment, Avastin should be withheld until the wound is fully healed. Avastin therapy should be withheld for elective surgery (see 8 ADVERSE REACTIONS).

Necrotizing fasciitis including fatal cases, has rarely been reported in patients treated with Avastin; usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Avastin therapy should be discontinued in patients who develop necrotizing fasciitis, and appropriate treatment should be promptly initiated (see 8 ADVERSE REACTIONS, Post-Market Adverse Reactions and 14 CLINICAL TRIALS).

Renal

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

Reproductive Health: Female and Male Potential

- **Fertility**

Repeat dose safety studies in animals have shown that bevacizumab may have an adverse effect on female fertility (see 16 NON-CLINICAL TOXICOLOGY). 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 8 ADVERSE REACTIONS).

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate and well controlled studies in pregnant women. IgGs are known to cross the placental barrier, and Avastin 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 8 ADVERSE REACTIONS, Post-Market Adverse Reactions).

Therefore, Avastin 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 Avastin therapy and for at least 6 months following the last dose of Avastin.

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

Avastin 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.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

Avastin is not approved for use in patients under the age of 18 years. The safety and efficacy of Avastin in this population has not been established. The addition of Avastin 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).

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 Avastin (see 16 NON-CLINICAL TOXICOLOGY).

7.1.4 Geriatrics:

Patients receiving Avastin 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 Avastin (see 8 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 Avastin (see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS). The risk and benefit of Avastin administration in patients > 65 should be carefully evaluated prior to initiating therapy.

In study AVF4095g, the safety profile of the Avastin in platinum-sensitive recurrent ovarian cancer patients, ≥ 65 years of age is consistent with the known overall safety profile of Avastin across other tumor types. In addition to the higher risk of events in the elderly as noted above, events of hypertension, arthritis, increased blood pressure, dizziness, decreased appetite, and dysphonia occurred at a higher frequency in the elderly patients in study AVF4095g.

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

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Clinical trials have been conducted in patients with various malignancies treated with Avastin, predominantly in combination with chemotherapy. The safety profile from a clinical trial population of approximately 5000 patients is presented in this section.
The most serious adverse drug reactions were:

- Gastrointestinal Perforations (see 7 WARNINGS AND PRECAUTIONS)
- Hemorrhage including pulmonary hemorrhage/hemoptysis, which is more common in NSCLC

patients (see 7 WARNINGS AND PRECAUTIONS)
- Arterial Thromboembolism (see 7 WARNINGS AND PRECAUTIONS)
- Non-gastrointestinal Fistula
- Hypertensive Crises
- Posterior Reversible Encephalopathy Syndrome (PRES)
- Neutropenia and Infections
- Nephrotic Syndrome
- Congestive Heart Failure

Please refer to Further Information on Selected, Serious Adverse Drug Reactions for clinical trial frequency analysis of each serious adverse drug reaction listed above.

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

The most frequently observed adverse drug reactions across all clinical trials in patients receiving Avastin were fatigue or asthenia, diarrhea, hypertension, and abdominal pain, all with a frequency of very common (≥ 10%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, 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 may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 2 lists adverse drug reactions associated with the use of Avastin 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, Avastin 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 Abscess Cellulitis Infection	
Blood and the lymphatic systems disorders	Febrile neutropenia Leukopenia Neutropenia Thrombocytopenia	Anemia Lymphopenia	
Immune system disorders		Hypersensitivity, anaphylactic, infusion-related reactions	
Metabolism and nutrition disorders		Dehydration Hyponatremia	Anorexia Hypomagnesemia Hyponatremia
Nervous system disorders	Peripheral sensory neuropathy	Cerebrovascular accident Syncope Somnolence Headache	Dysgeusia Headache
Eye disorders			Eye disorder Lacrimation increased
Cardiac disorders		Cardiac failure congestive Supraventricular tachycardia	
Vascular disorders	Hypertension	Thromboembolism (arterial) Deep vein thrombosis Hemorrhage	Hypertension
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism Dyspnea Hypoxia Epistaxis	Dyspnea Epistaxis Rhinitis Cough
Gastrointestinal disorders	Diarrhea Nausea Vomiting Abdominal pain	Intestinal Perforation Ileus Intestinal obstruction Recto-vaginal fistulae* Gastrointestinal disorder Stomatits Proctalgia	Constipation Stomatitis Rectal hemorrhage

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%)
Endocrine disorders			Ovarian failure**
Skin and subcutaneous tissue disorders		Palmar-plantar erythrodysaesthesia syndrome	Exfoliative dermatitis Dry skin Skin discolouration
Musculoskeletal, connective tissue and bone disorders		Muscular weakness Myalgia Back pain	Arthralgia
Renal and urinary disorders		Proteinuria Urinary Tract Infection	Proteinuria
General disorders and administration site conditions	Asthenia Fatigue	Pain Lethargy Mucosal Inflammation	Pyrexia Asthenia Pain Mucosal inflammation
Reproductive System and Breast		Pelvic pain	
Investigations			Weight decreased

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

**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 Avastin 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 **System Organ Class (MedDRA)**	**Arm 1** **IFL* + Placebo** **(n = 396)**	**Arm 2** **IFL* + Avastin** **(n = 392)**
Patients with at least one adverse event	293 (74.0%)	333 (84.9%)
Cardiac Disorders Hypertension	9 (2.3%)	43 (11.0%)
Blood & Lymphatic System Disorders Leukopenia	123 (31.1%)	145 (37.0%)

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

Adverse Event **System Organ Class (MedDRA)**	**Arm 1** **IFL* + Placebo** **(n = 396)**	**Arm 2** **IFL* + Avastin** **(n = 392)**
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 5 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 + Avastin combination (Arm 3) and concurrently enrolled patients in IFL + placebo arm (Arm 1) and IFL + Avastin 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 + Avastin** **(n = 102)**	**Arm 3** **Bolus 5-FU/LV + Avastin** **(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%)	17 (16.7%)	9 (8.3%)
Stomatits	13 (13.3%)	24 (23.5%)	19 (17.4%)
Metabolism & Nutrition Disorders Anorexia	29 (29.6%)	44 (43.1%)	37 (33.9%)

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 + Avastin (n = 102)	Arm 3 Bolus 5-FU/LV + Avastin (n = 109)
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 + Avastin (Arm 2) was sufficiently safe, and subsequently enrollment in the 5-FU/LV + Avastin 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 + Avastin arm (see Table 6). Common adverse events of any Grade with a higher incidence of ≥10% in the 5 FU/LV + Avastin arm compared to the 5-FU/LV + placebo arm are displayed in Table 6.

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 + Avastin (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%)

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 + Avastin (n = 100)
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 + Avastin (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, Metastatic 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 Neutropenia	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%)

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)
Confusion	10 (2.3%)	11 (2.6%)
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 Avastin 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)

	Control Arm	**Treatment Arm**	**Treatment Arm**
	Carboplatin Paclitaxel	**Bevacizumab 7.5 mg/kg + Carboplatin Paclitaxel**	**Bevacizumab 15 mg/kg + Carboplatin Paclitaxel**
Body System/Preferred Term	**(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%)

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

	Control Arm	Treatment Arm	Treatment Arm
	Carboplatin Paclitaxel	Bevacizumab 7.5 mg/kg + Carboplatin Paclitaxel	Bevacizumab 15 mg/kg + Carboplatin Paclitaxel
Body System/Preferred Term	**(N=32)**	**(N=32)**	**(N=34)**
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%)
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%)

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

	Control Arm	Treatment Arm	Treatment Arm
	Carboplatin Paclitaxel	Bevacizumab 7.5 mg/kg + Carboplatin Paclitaxel	Bevacizumab 15 mg/kg + Carboplatin Paclitaxel
Body System/Preferred Term	**(N=32)**	**(N=32)**	**(N=34)**
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%)
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%)

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

	Control Arm	Treatment Arm	Treatment Arm
	Carboplatin Paclitaxel	Bevacizumab 7.5 mg/kg + Carboplatin Paclitaxel	Bevacizumab 15 mg/kg + Carboplatin Paclitaxel
Body System/Preferred Term	**(N=32)**	**(N=32)**	**(N=34)**
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			

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 Carboplatin Paclitaxel (N=32)	Treatment Arm Bevacizumab 7.5 mg/kg + Carboplatin Paclitaxel (N=32)	Treatment Arm Bevacizumab 15 mg/kg + Carboplatin Paclitaxel (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 patient 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 Carboplatin Paclitaxel (N=32)	Treatment Arm Bevacizumab 7.5 mg/kg + Carboplatin Paclitaxel (N=32)	Treatment Arm Bevacizumab 15 mg/kg + Carboplatin Paclitaxel (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%)
Thrombosis	0 (0.00%)	0 (0.00%)	2 (5.90%)

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

	Control Arm	Treatment Arm	Treatment Arm
	Carboplatin Paclitaxel	Bevacizumab 7.5 mg/kg + Carboplatin Paclitaxel	Bevacizumab 15 mg/kg + Carboplatin Paclitaxel
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 Increased	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%)

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

	Control Arm	Treatment Arm	Treatment Arm
	Carboplatin Paclitaxel	**Bevacizumab 7.5 mg/kg + Carboplatin Paclitaxel**	**Bevacizumab 15 mg/kg + Carboplatin Paclitaxel**
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 patient 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.

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Table 11 All Treatment−Related Adverse Events with a Frequency of ≥ 1% for both Treatment Arms in Study AVF4095g

Toxicity Category and Term	Control Arm	Treatment Arm
	Carboplatin+Gemcitabine + Placebo	Carboplatin+Gemcitabine + Bevacizumab
	(n=233)	(n=247)
Blood And Lymphatic System Disorders		
Anemia	44 (18.9%)	32 (13.0%)
Leukopenia	15 (6. 4.%)	13 (5.3%)
Neutropenia	50 (21.5%)	60 (24.3%)
Thrombocytopenia	31 (13.3%)	50 (20.2%)
Ear and Labyrinth Disorders		
Tinnitus	2 (0.9%)	3 (1.2%)
Eye Disorders		
Lacrimination Increased	2 (0.9%)	4 (1.6%)
Vision Blurred	2 (0.9%)	7 (2.8%)
Gastrointestinal Disorders		
Abdominal Discomfort	1 (0.4%)	4 (1.6%)
Abdominal Distension	3 (1.3%)	3 (1.2%)
Abdominal Pain	4 (1.7%)	8 (3.2%)
Constipation	25 (10.7%)	30 (12.1%)
Diarrhea	11 (4.7%)	24 (9.7%)
Dry Mouth	(0.00%)	4 (1.6%)
Dyspepsia	(0.00%)	5 (2.0%)
Gingival Bleeding	(0.00%)	12 (4.9%)
Gingival Pain	(0.0%)	4 (1.6%)
Glossodynia	(0.0%)	3 (1.2%)
Hematochezia	3 (1.3%)	1 (0.4%)
Nausea	36 (15.5%)	57 (23.1%)
Oral Pain	(0.00%)	6 (2.4%)
Rectal Hemorrhage	3 (1.3%)	6 (2.4%)
Stomatitis	6 (2.6%)	13 (5.3%)
Vomiting	11 (4.7%)	23 (9.3%)
General Disorders And Administration Site Conditions		
Asthenia	5 (2.1%)	5 (2.0%)
Chest Discomfort	(0.00%)	3 (1.2%)
Chest Pain	1 (0.4%)	3 (1.2%)

Table 11 All Treatment−Related Adverse Events with a Frequency of ≥ 1% for both Treatment Arms in Study AVF4095g

Toxicity Category and Term	Control Arm	Treatment Arm
	Carboplatin+Gemcitabine + Placebo	Carboplatin+Gemcitabine + Bevacizumab
	(n=233)	(n=247)
Chills	3 (1.3%)	6 (2.4%)
Fatigue	64 (27.5%)	73 (29.6%)
Influenza Like Illness	(0.00%)	3 (1.2%)
Mucosal Inflammation	5 (2.1%)	13 (5.3%)
Edema Peripheral	4 (1.7%)	9 (3.6%)
Pyrexia	5 (2.1%)	8 (3.2%)
Infections And Infestations		
Rhinitis	(0.00%)	3 (1.2%)
Sinusitis	5 (2.1%)	3 (1.2%)
Urinary Tract Infection	1 (0.4%)	3 (1.2%)
Injury, Poisoning And Procedural Complications		
Contusion	4 (1.7%)	14 (5.7%)
Investigations		
Alaninine Aminotransferase Increased	3 (1.3%)	1 (0.4%)
Blood Alkaline Phosphatase Increased	3 (1.3%)	2 (0.8%)
Blood Pressure Increased	(0.0%)	4 (1.6%)
Hemoglobin Decreased	9 (3.9%)	11 (4.5%)
Neutrophil Count Decreased	12 (5.2%)	8 (3.2%)
Platelet Count Decreased	8 (3.4%)	10 (4.0%)
Urine Protein/Creatinine Ratio Increased	2 (0.9%)	3 (1.2%)
White Blood Cell Count Decreased	11 (4.7%)	5 (2.0%)
Metabolism And Nutrition Disorders		
Decreased Appetite	14 (6.0%)	15 (6.1%)
Dehydration	4 (1.7%)	1 (0.4%)
Hypokalemia	5 (2.1%)	3 (1.2%)
Hypomagnesemia	(0.00%)	3 (1.2%)
Musculoskeletal And Connective Tissue Disorders		
Arthralgia	10 (4.3%)	15 (6.1%)
Muscle Spasms	1 (0.4%)	6 (2.4%)
Musculoskeletal Pain	3 (1.3%)	3 (1.2%)
Myalgia	5 (2.1%)	9 (3.6%)
Pain In Extremity	4 (1.7%)	10 (4.0%)
Nervous System Disorders		

Table 11 All Treatment−Related Adverse Events with a Frequency of ≥ 1% for both Treatment Arms in Study AVF4095g

Toxicity Category and Term	Control Arm	Treatment Arm
	Carboplatin+Gemcitabine + Placebo	Carboplatin+Gemcitabine + Bevacizumab
	(n=233)	(n=247)
Dizziness	3 (1.3%)	13 (5.3%)
Dysgeusia	9 (3.9%)	10 (4.0%)
Headache	22 (9.4%)	41 (16.6%)
Hypoaesthesia	3 (1.3%)	3 (1.2%)
Neuropathy Peripheral	7 (3.0%)	8 (3.2%)
Peripheral Sensory Neuropathy	3 (1.3%)	1 (0.4%)
Psychiatric Disorders		
Insomnia	1 (0.4%)	6 (2.4%)
Renal And Urinary Disorders		
Proteinuria	7 (3.0%)	49 (19.8%)
Respiratory, Thoracic And Mediastinal Disorders		
Cough	4 (1.7%)	4 (1.6%)
Dysphonia	4 (1.7%)	18 (7.3%)
Dyspnoea	7 (3.0%)	10 (4.0%)
Dyspnoea Exertional	4 (1.7%)	4 (1.6%)
Epistaxis	24 (10.3%)	106 (42.9%)
Nasal Congestion	2 (0.9%)	5 (2.0%)
Oropharyngeal Pain	3 (1.3%)	7 (2.8%)
Rhinorrhoea	4 (1.7%)	17 (6.9%)
Sinus Congestion	1 (0.4%)	4 (1.6%)
Skin And Subcutaneous Tissue Disorders		
Alopecia	7 (3.0%)	12 (4.9%)
Dry Skin	(0.00%)	5 (2.0%)
Ecchymosis	(0.00%)	3 (1.2%)
Erythema	3 (1.3%)	4 (1.6%)
Petechiae	2 (0.9%)	6 (2.4%)
Pruritus	4 (1.7%)	4 (1.6%)
Rash	14 (6.0%)	17 (6.9%)
Skin Discolouration	(0.0%)	5 (2.0%)
Skin Hyperpigmention	(0.0%)	3 (1.2%)
Vascular Disorders		
Deep Vein Thrombosis	1 (0.4%)	4 (1.6%)
Flushing	4 (1.7%)	4 (1.6%)

Table 11 All Treatment−Related Adverse Events with a Frequency of ≥ 1% for both Treatment Arms in Study AVF4095g

Toxicity Category and Term	Control Arm	Treatment Arm
	Carboplatin+Gemcitabine + Placebo	Carboplatin+Gemcitabine + Bevacizumab
	(n=233)	(n=247)
Hypertension	15 (6.4%)	80 (32.4%)
Thrombosis	(0.00%)	4 (1.6%)

The most frequent (≥20%) adverse events observed in the Avastin arm were anemia, neutropenia, thrombocytopenia, abdominal pain, constipation, diarrhea, nausea, vomiting, fatigue, arthralgia, back pain, dizziness, headache, insomnia, cough, dyspnea, epistaxis, alopecia, rash, and hypertension. The most frequent (≥20%) adverse events observed in the chemotherapy arm were anemia, neutropenia, thrombocytopenia, abdominal pain, constipation, diarrhea, nausea, vomiting, fatigue, decreased appetite, headache, peripheral neuropathy, dyspnea, alopecia, and rash.

22.3% of patients in the Avastin arm and 4.7% of patients in the chemotherapy alone arm experienced an adverse event of any Grade that led to discontinuation of study drug. The most common treatment-emergent adverse events leading to study drug discontinuation were neutropenia (1.6% in the Avastin arm vs 0.4% in the chemotherapy arm), thrombocytopenia (1.6% vs 0.9%), proteinuria (3.6% vs 0.0%), epistaxis (1.2% vs 0.0%), and hypertension (4.0% vs 0.0%).

Table 12 Treatment-Emergent Adverse Events Occurring in ≥2% of Platinum-Sensitive Recurrent Ovarian Cancer Patients Treated with Avastin+Chemotherapy Compared to Those Treated with Chemotherapy Alone in Study AVF4095g

Toxicity Category and Term	Control Arm	Treatment Arm
	Carboplatin+Gemcitabine + Placebo	Carboplatin+Gemcitabine + Bevacizumab
	(n=233)	(n=247)
Blood And Lymphatic System Disorders		
Thrombocytopenia	119 (51.1%)	143 (57.9%)
Gastrointestinal Disorders		
Diarrhoea	68 (29.2%)	95 (38.5%)
Gastritis	(0.0%)	5 (2.0%)
Gingival Bleeding	1 (0.4%)	17 (6.9%)
Gingival Pain	(0.0%)	8 (3.2%)
Glossodynia	(0.0%)	8 (3.2%)
Haemorrhoids	6 (2.6%)	19 (7.7%)
Nausea	153 (65.7%)	179 (72.5%)
Oral Pain	3 (1.3%)	13 (5.3%)

Table 12 Treatment-Emergent Adverse Events Occurring in ≥2% of Platinum-Sensitive Recurrent Ovarian Cancer Patients Treated with Avastin+Chemotherapy Compared to Those Treated with Chemotherapy Alone in Study AVF4095g

Toxicity Category and Term	Control Arm	Treatment Arm
	Carboplatin+Gemcitabine + Placebo	Carboplatin+Gemcitabine + Bevacizumab
	(n=233)	(n=247)
Rectal Haemorrhage	10 (4.3%)	21 (8.5%)
Stomatitis	16 (6.9%)	38 (15.4%)
Toothache	4 (1.7%)	12 (4.9%)
Vomiting	69 (29.6%)	82 (33.2%)
General Disorders And Administration Site Conditions		
Catheter Site Pain	5 (2.1%)	14 (5.7%)
Chest Pain	9 (3.9%)	18 (7.3%)
Fatigue	175 (75.1%)	202 (81.8%)
Mucosal Inflammation	23 (9.9%)	38 (15.4%)
Immune System Disorders		
Drug Hypersensitivity	18 (7.7%)	30 (12.1%)
Seasonal Allergy	3 (1.3%)	9 (3.6%)
Infections And Infestations		
Cellulitis	8 (3.4%)	14 (5.7%)
Influenza	1 (0.4%)	9 (3.6%)
Oral Herpes	2 (0.9%)	9 (3.6%)
Sinusitis	21 (9.0%)	36 (14.6%)
Upper Respiratory Tract Infection	28 (12.0%)	42 (17.0%)
Injury, Poisoning And Procedural Complications		
Contusion	21 (9.0%)	43 (17.4%)
Investigations		
Blood Pressure Increased	(0.0%)	7 (2.8%)
Haemoglobin Decreased	21 (9.0%)	30 (12.1%)
Metabolism And Nutrition Disorders		
Hyperglycaemia	17 (7.3%)	23 (9.3%)
Hyponatremia	5 (2.1%)	12 (4.9%)
Musculoskeletal And Connective Tissue Disorders		
Arthralgia	44 (18.9%)	69 (27.9%)
Back Pain	31 (13.3%)	51 (20.6%)
Muscle Spasms	14 (6.0%)	21 (8.5%)
Musculoskeletal Pain	15 (6.4%)	21 (8.5%)
Musculoskeletal Stiffness	1 (0.4%)	9 (3.6%)

Table 12 Treatment-Emergent Adverse Events Occurring in ≥2% of Platinum-Sensitive Recurrent Ovarian Cancer Patients Treated with Avastin+Chemotherapy Compared to Those Treated with Chemotherapy Alone in Study AVF4095g

Toxicity Category and Term	Control Arm	Treatment Arm
	Carboplatin+Gemcitabine + Placebo	Carboplatin+Gemcitabine + Bevacizumab
	(n=233)	(n=247)
Myalgia	32 (13.7%)	42 (17.0%)
Plantar Fasciitis	(0.0%)	6 (2.4%)
Nervous System Disorders		
Amnesia	2 (0.9%)	8 (3.2%)
Dizziness	39 (16.7%)	57 (23.1%)
Headache	70 (30.0%)	120 (48.6%)
Migraine	(0.0%)	6 (2.4%)
Psychiatric Disorders		
Anxiety	18 (7.7%)	29 (11.7%)
Depression	24 (10.3%)	34 (13.8%)
Insomnia	36 (15.5%)	51 (20.6%)
Renal And Urinary Disorders		
Proteinuria	8 (3.4%)	49 (19.8%)
Respiratory, Thoracic And Mediastinal Disorders		
Cough	43 (18.5%)	64 (25.9%)
Dysphonia	8 (3.4%)	33 (13.4%)
Dyspnoea	56 (24.0%)	74 (30.0%)
Epistaxis	33 (14.2%)	135 (54.7%)
Oropharyngeal Pain	23 (9.9%)	40 (16.2%)
Rhinorrhoea	9 (3.9%)	25 (10.1%)
Sinus Congestion	4 (1.7%)	19 (7.7%)
Skin And Subcutaneous Tissue Disorders		
Dry Skin	6 (2.6%)	13 (5.3%)
Nail Disorder	1 (0.4%)	7 (2.8%)
Petechiae	4 (1.7%)	13 (5.3%)
Pruritus	27 (11.6%)	35 (14.2%)
Skin Discolouration	(0.0%)	5 (2.0%)
Vascular Disorders		
Flushing	9 (3.9%)	15 (6.1%)
Hot Flush	13 (5.6%)	19 (7.7%)
Hypertension	20 (8.6%)	104 (42.1%)

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

Table 13 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%)
Infection	2 (1.1%)	3 (1.7%)

Table 13 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)
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%)

Table 13 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)
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 Avastin 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 Avastin 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 Avastin 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 Avastin 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 Avastin 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 Avastin 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 Avastin plus PLD arm were palmar-plantar erythrodysaesthesia syndrome (8.1%) and hypertension (3.2%). In the Avastin 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 Avastin plus topotecan arm was fatigue (3.5%).

Among patients initially randomized to chemotherapy alone, 72 (40%) crossed over to receive single-agent Avastin after progression of disease. Median duration of Avastin 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 14 Treatment-Emergent Adverse Events Occurring in ≥2% of Platinum-Resistant Recurrent Ovarian Cancer Patients Treated with Avastin+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%)
Bronchitis	0 (0.0%)	2 (3.3%)
Device Related Infection	0 (0.0%)	2 (3.3%)
Sinusitis	0 (0.0%)	2 (3.3%)

Table 14 Treatment-Emergent Adverse Events Occurring in ≥2% of Platinum-Resistant Recurrent Ovarian Cancer Patients Treated with Avastin+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)
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%)
Blood And Lymphatic System Disorders		

Table 14 Treatment-Emergent Adverse Events Occurring in ≥2% of Platinum-Resistant Recurrent Ovarian Cancer Patients Treated with Avastin+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)
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		
Palmar-Plantar Erythrodysaesthesia	8 (12.7%)	17 (27.4%)

Table 14 Treatment-Emergent Adverse Events Occurring in ≥2% of Platinum-Resistant Recurrent Ovarian Cancer Patients Treated with Avastin+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)
Syndrome		
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%)

Table 14 Treatment-Emergent Adverse Events Occurring in ≥2% of Platinum-Resistant Recurrent Ovarian Cancer Patients Treated with Avastin+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)
Nasopharyngitis	0 (0.0%)	2 (3.5%)
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 15 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%)

System Organ Class/ Preferred Term	Control Arm	Treatment Arm
	Lomustine	Bevacizumab + Lomustine
	(n = 147)	(n = 278)
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%)
Wound Dehiscence	0 (0%)	4 (1.4%)
Investigations		
Weight Decreased	2 (1.4%)	9 (3.2%)
Gamma−Glutamyltransferase Increased	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%)

System Organ Class/ Preferred Term	Control Arm	Treatment Arm
	Lomustine	Bevacizumab + Lomustine
	(n = 147)	(n = 278)
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%)
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 Avastin 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 Avastin plus Lomustine arm, compared with 10.2% of patients in the Lomustine arm. In patients receiving Avastin 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 Avastin.

Cardiovascular

Hypertension (see 7 WARNINGS AND PRECAUTIONS)
An increased incidence of hypertension (all Grades) of up to 43.7% has been observed in patients treated with Avastin compared with up to 14% in the comparator arm. In clinical trials across all indications the overall incidence of NCI-CTC Grade 3 and Grade 4 hypertension in patients receiving Avastin ranged from 3.0% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of patients treated with Avastin compared to up to 0.2% patients treated with the same chemotherapy alone. The incidence of hypertension in platinum-sensitive ovarian cancer patients was greater in the Avastin in combination with chemotherapy arm (43.7%) than the chemotherapy alone arm (8.6%). Grade ≥ 3 hypertension was also observed at a higher incidence in the Avastin arm (18.2%) compared with the chemotherapy arm (0.9%).

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 Avastin or hospitalisation. Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal. Avastin 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 7 WARNINGS AND PRECAUTIONS)
Three cases of PRES (2 confirmed and 1 unconfirmed) have been reported in one clinical study with platinum-sensitive recurrent ovarian cancer. 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 7 WARNINGS AND PRECAUTIONS)
Arterial Thromboembolism
An increased incidence of arterial thromboembolic events (ATEs) was observed in patients treated with Avastin 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 Avastin containing arms and up to 1.7% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving Avastin 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 Avastin treated patients versus 0.5% of patients in the control group: myocardial infarction was reported in 1.4% of Avastin 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 Avastin patients compared to 5.8% (6/104) in the chemotherapy control group.
In the study AVF4095g, 2.4% of the patients treated with Avastin and 0.4% of the patients who received chemotherapy alone had arterial thromboembolic events, and most of the events were of Grade 3 (1.6% in the Avastin arm versus 0.0% in the chemotherapy arm). One patient in the Avastin arm also had Grade 4 myocardial infarction which was assessed as not related to study medications by the investigator.

The incidence of all grade arterial thromboembolic events in study EORTC 26101 in patients with first recurrence of glioblastoma was comparable between the Avastin 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 Avastin 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 (VTEs) ranged from 2.8% to 17.3% in the Avastin 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 Avastin compared with up to 4.9% in patients with chemotherapy alone.

In the study AVF4095g, 8.1% of the patients treated with Avastin and 4.3% of the patients treated with chemotherapy alone experienced venous thromboembolic events. Grade ≥ 3 venous thromboembolic events were observed in 4.5% of the Avastin-treated patients and 2.6% of the chemotherapy-treated patients.

Patients who have experienced a venous thromboembolic event may be at higher risk for a recurrence if they receive Avastin 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 Avastin compared with up to 5.4% in patients with chemotherapy alone. Avastin is not authorized for use in cervical cancer.

In study EORTC 26101 in patients with first recurrence of glioblastoma, patients in the Avastin + 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 7 WARNINGS AND PRECAUTIONS)
In clinical trials with Avastin, congestive heart failure (CHF) was observed in all cancer indications studied to date, but occurred predominantly in patients with metastatic breast cancer. In the study AVF4095g, CHF Grade ≥ 3 was observed in two patients in each arm. However, CHF (any Grade) was greater in the Avastin arm (2.0%) compared with the control arm (0.9%), and 12.6% of patients in the Avastin arm compared with 9.0% in the control arm experienced cardiac-related adverse events (any Grade). In study AVF2119g, the incidence of CHF Grade 3 or higher was 2.2% in patients treated with Avastin 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 Avastin

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 Avastin 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 Avastin in combination with taxanes, vs. 0% for taxanes alone, 2.9% for patients treated with Avastin plus anthracyclines vs. 0% for anthracyclines alone, and 1% for patients treated with Avastin 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 Avastin, 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 7 WARNINGS AND PRECAUTIONS)
Avastin 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 Avastin treated patients and 1.4% of control patients were reported to have had non-gastrointestinal vaginal, vesical, or female genital tract fistulae. Avastin 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 Avastin, with most events occurring within the first 6 months of therapy.

Gastrointestinal
Gastrointestinal Perforation and Fistula (see 7 WARNINGS AND PRECAUTIONS)
Avastin 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 Avastin 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. Avastin is not authorized for use in cervical cancer.

In Avastin 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 Avastin 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. Avastin 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 Avastin 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 Avastin 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 7 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 7 WARNINGS AND PRECAUTIONS)

In clinical trials proteinuria was very common and has been reported in up to 38% of patients receiving Avastin. 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. In the study AVF4095g, a higher proportion of patients in the Avastin arm (21.5%) experienced proteinuria compared with the chemotherapy arm (4.3%). Grade ≥ 3 proteinuria was reported in 10.9% of the patients in the Avastin arm and 0.9% of the patients in the chemotherapy arm.

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 Avastin in

combination with chemotherapy experienced Grade ≥2 proteinuria. The Grade ≥2 proteinuria resolved in 74.2% (201 of 271) of patients. Avastin was re-initiated in 41.7% (113 of 271) of patients. Of the 113 patients who re-initiated Avastin, 47.8% (54 of 113) experienced a second episode of Grade ≥2 proteinuria.

The overall incidence of all Grade adverse events suggestive of renal impairment was higher in the Avastin in combination with cisplatin/gemcitabine arms compared with chemotherapy arm.

Hematologic

Hemorrhage (see 7 WARNINGS AND PRECAUTIONS)

CNS Hemorrhage

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

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 Avastin, compared to 0 to 4.5% of patients in the chemotherapy control group. The hemorrhagic events that have been observed in Avastin clinical studies were predominantly tumour-associated hemorrhage (see below) and minor mucocutaneous hemorrhage (e.g. epistaxis).

In patients with platinum-sensitive recurrent ovarian cancer, non-CNS hemorrhage events occurred in 68% of the patients treated with Avastin compared with 32.6% in the control arm. Grade 3 events were reported at a higher incidence in the Avastin arm (5.7%) compared with the control arm (0.9%). Epistaxis was the most frequently reported Grade 3 event in the Avastin arm.

Tumour-associated hemorrhage

Tumour associated hemorrhage was observed in Avastin 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, Avastin

[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.

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 Avastin 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 Avastin 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 Avastin 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.

Mucocutaneous Hemorrhage
Across all Avastin clinical trials, mucocutaneous hemorrhages were seen in up to 50% of patients treated with Avastin. 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 Avastin 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 7 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

[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.

myelosuppressive chemotherapy agents used to treat metastatic colorectal cancer (19.7% in the bevacizumab arm vs. 13.6% in the chemotherapy arm of AVF2107g). In study AVF4095g, incidences of infection were reported at 58.3% (144/247) in the Avastin arm versus 53.2% (124/233) in the chemotherapy only arm for all Grade events and 8.1% (20/247) versus 5.2% (12/233) for Grade ≥ 3 events.

Across the Avastin clinical trials, the frequencies of patients experiencing death due to neutropenia and infection occurring within 21 days after last study treatment dose of Avastin 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 Avastin plus chemotherapy and treated with chemotherapy alone, respectively. Events occurring in the Avastin treated patients included sepsis, necrotizing fasciitis, peritoneal abscess, and peritonitis. In study AVF3708, a non-comparative trial that led to approval of Avastin in recurrent glioblastoma multiforme, 1 of 163 patients (0.6%) treated with Avastin 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 Avastin and chemotherapy only, respectively. Events occurring in the Avastin treated patients included neutropenic infection, febrile neutropenia, infection, respiratory tract infection, pneumonia, bronchopneumonia, and empyema. No deaths due to neutropenia and infection were reported in the ovarian carcinoma study AVF4095g within 21 days after last study treatment dose.

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

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

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

In Study AVF4095g, thrombocytopenia of any Grade (57.9%, 143/247) and Grade ≥ 3 (40.1%, 99/247) was observed with Avastin. A total of 262 patients developed one or more events of thrombocytopenia and/or bleeding. Of these, 114 patients had bleeding episode(s) either accompanied by or following thrombocytopenia with a higher rate in the Avastin-chemotherapy arm (56.6%) compared to the placebo-chemotherapy arm (27.7%). The median time to onset of thrombocytopenia (any Grade) was 3.6 months in the Avastin arm versus 4.9 months in the chemotherapy arm, and time to resolution was longer in the Avastin arm (2.3 months) compared with that in the chemotherapy arm (0.8 months).

Hypersensitivity Reactions, Anaphylactic Reactions (Including Anaphylactic Shock), Infusion-Related Reactions (see 7 WARNINGS AND PRECAUTIONS)
In some clinical trials anaphylactic and anaphylactoid-type reactions were reported more frequently in patients receiving Avastin in combination with chemotherapies than with chemotherapy alone. The incidence of these reactions in Avastin 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.In study AVF4095g, anaphylactic and hypersensitivity reactions of any Grade were reported for a higher percentage of patients receiving Avastin in combination with chemotherapy (19%, 47/247) than patients who received chemotherapy with placebo (13.3%, 31/233) with a majority of events being Grade 1-2 in severity in both treatment arms. Similarly, a higher incidence of Grade 3-4 severity events of anaphylactic and hypersensitivity reactions was seen in the Avastin in combination with chemotherapy arm (6.5%, 16/247) compared to the chemotherapy alone arm (3.9%, 9/233).

Deaths

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

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

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

In a platinum-sensitive recurrent ovarian cancer trial, a total of five patients in the Avastin arm versus one patient in the chemotherapy arm died due to adverse events. One patient in each arm experienced a treatment-emergent Grade 5 AE (intracranial haemorrhage in the Avastin arm and acute myocardial infarction in the chemotherapy arm). In the Avastin arm, additional causes of death occurring later than 21 days after the last Avastin study treatment dose included sepsis, respiratory failure, and unspecified adverse events. Furthermore, another patient in the Avastin arm and two patients in the chemotherapy arm died of unknown causes.

In a platinum-resistant recurrent ovarian cancer trial, nine patients in the Avastin arm versus six patients in the chemotherapy arm died due to adverse events. In the Avastin + 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).

Peri-Operative Conditions

Wound Healing (see 7 WARNINGS AND PRECAUTIONS)

As Avastin may adversely impact wound healing, patients who had major surgery within the last 28 days prior to starting Avastin 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 Avastin 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 Avastin at the time of surgery. The incidence varied between 10% (4/40) and 20% (3/15). 4/247 (1.6%) patients treated with Avastin and 3/233 (1.3%) patients on chemotherapy alone developed wound healing complications in the platinum-sensitive recurrent ovarian cancer study AVF4095g.

Cases of serious wound healing complications have been reported during Avastin use, some of which had a fatal outcome (see 7 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 Avastin 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%).

Nasal Septum Perforations
Very rare cases of nasal septum perforations have been reported in patients treated with Avastin.

Special Populations
Gender
In clinical trials in mNSCLC, female patients treated with Avastin 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 Avastin (see 7 WARNINGS AND PRECAUTIONS). Other reactions with a higher frequency seen in patients over 65 were all Grade nausea, and headache.

In study AVF4095g, the safety profile of the Avastin in platinum-sensitive recurrent ovarian cancer patients, ≥ 65 years of age is consistent with the known overall safety profile of Avastin across other tumor types. In addition to the higher risk of events in the elderly as noted above, events of hypertension, arthritis, increased blood pressure, dizziness, decreased appetite, and dysphonia occurred at a higher frequency in the elderly patients in study AVF4095g.
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 Avastin as compared to those aged ≤ 65 years treated with Avastin.

8.3 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 patient 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.

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

Clinical Trial Findings

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

Across clinical trials, the following Grade 3 and 4 laboratory abnormalities were seen with an increased (≥2%) incidence in patients treated with Avastin 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 Avastin. The observed increase in serum creatinine was not associated with a higher incidence of clinical manifestations of renal impairment in patients treated with Avastin.

8.5 Post-Market Adverse Reactions

Table 16 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 7 WARNINGS AND PRECAUTIONS).
Hepatobiliary disorders	Gallbladder perforation (frequency not known)
Nervous system disorders	Hypertensive encephalopathy (very rare) Posterior Reversible Encephalopathy Syndrome (PRES) (rare) (see 7 WARNINGS AND PRECAUTIONS)
Respiratory, thoracic and mediastinal disorders	Nasal septum perforation (frequency not known) Pulmonary hypertension* (frequency not known) Dysphonia (common)
Vascular disorders	Renal thrombotic microangiopathy, clinically manifested as proteinuria (frequency not known) (see 7 WARNINGS AND PRECAUTIONS, and 8 ADVERSE REACTIONS)) aneurysms, dissections, and rupture
Musculoskeletal and Connective Tissue disorders	Cases of Osteonecrosis of the Jaw (ONJ) have been observed in Avastin treated patients mainly in association with prior or concomitant use of bisphosphonates. Cases of osteonecrosis at sites other than the jaw, have been observed in Avastin treated pediatric patients. (see 7 WARNINGS AND PRECAUTIONS, Pediatric)**.
Infections and Infestations	Necrotizing fasciitis (rare), usually secondary to wound healing complications, gastrointestinal perforation or fistula formation (see 7 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 Avastin in combination with chemotherapy.

9 DRUG INTERACTIONS

9.2 Drug Interactions 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.

9.4 Drug-Drug Interactions

Irinotecan

In study AVF2107g, irinotecan concentrations were similar in patients receiving IFL (irinotecan/5-fluorouracil/leucovorin) alone and in combination with Avastin. 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 Avastin 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 Avastin. 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 + Avastin. Patients who develop severe diarrhea, leukopenia or neutropenia with Avastin 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 7 WARNINGS AND PRECAUTIONS).

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

Combination with platinum- or taxane-based therapies

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

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 Avastin has not been established in approved indications.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Avastin 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.1 Bevacizumab is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps. Bevacizumab consists of 214 amino acids and has a molecular weight of approximately 149 000 daltons.

Avastin 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.

10.2 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.

The exposure-response relationships of bevacizumab have not been fully characterized in patients with multiple solid tumours.

Cardiac Electrophysiology:

In an open-label Phase III 3-arm study in adjuvant colon carcinoma (BO17920), serial ECG recordings were performed in 1,122 subjects, of which 756 were exposed to bevacizumab at a dose of either 5 mg/kg every 2 weeks, or 7.5 mg/kg every 3 weeks, in combination with chemotherapy for a total of 24 weeks. Bevacizumab was then administered as monotherapy at a dose of 7.5 mg/kg every 3 weeks.

Mean values of maximum changes from baseline for QTcF were similar across the treatment arms, with the majority of values (approximately 90%) ≤ 30 msec. A similar proportion of patients across the treatment arms had maximum changes from baseline of >30 to 60 msec, and there were a small

number of patients with values >60 msec. A similar profile was observed for maximum QTcB change from baseline. Mean values for maximum post-baseline QTcF intervals were similar for all treatment arms. With the exception of a single QTcF value of 555 msec, all individual maximum post baseline QTcF intervals were ≤ 500 ms. Maximum post baseline QTcB intervals showed similar findings. Change from baseline in ECG data for PQ, QRS, QT, and RR values showed no obvious imbalance between the treatment arms.

10.3 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.

The pharmacokinetics of bevacizumab are well described by a two-compartment model as per a population pharmacokinetic analysis of 491 subjects receiving Avastin weekly, every 2 weeks, or every 3 weeks, in doses ranging from 1 to 20 mg/kg.

The geometric mean (CV%) of bevacizumab AUC_{tau} after a single dose of 5 mg/kg Q2W, 10 mg/kg Q2W and 15 mg/kg Q3W were 734 (20.7%) mg/L*day, 1468 (20.7%) mg/L* day and 2801 (21.6%) mg/L*day, respectively. The geometric mean (CV%) of bevacizumab C_{max} after a single dose of 5 mg/kg Q2W, 10 mg/kg Q2W and 15 mg/kg Q3W were 128 (19.1%) mg/L, 256 (19.1%) mg/L and 384 (19.1%) mg/L, respectively. The geometric mean (CV%) of bevacizumab AUC_{tau} at steady state after 5 mg/kg Q2W, 10 mg/kg Q2W and 15 mg/kg Q3W were 1692 (31.2%) mg/L*day, 3383 (31.2%) mg/L*day and 5075 (31.2%) mg/L*day, respectively. The geometric mean (CV%) of bevacizumab C_{max} at steady state after 5 mg/kg Q2W, 10 mg/kg Q2W and 15 mg/kg Q3W were 215 (23.4%) mg/L, 430 (23.4%) mg/L and 445 (23.4%) mg/mL, respectively. After repeated doses of bevacizumab, the steady state was reached at Day 84. The geometric mean (CV%) of bevacizumab accumulation ratio was 1.53 (13.6%) for 5 mg/kg Q2W and 10 mg/kg Q2W and was 1.26 (10.1%) for 15 mg/kg Q3W, respectively.

Table 17 Summary of Bevacizumab Pharmacokinetic Parameters in Patients with Multiple Solid Tumours.

	Dose	C_{max} (mg/L)	C_{trough} (mg/L)	$AUC_{0-\infty}$ (mg/L*day)	AUC_{tau} [a] (mg/L*day)	$T_{½}$ (day)	CL (L/day)	Vc (L)	Vp (L)
Single dose	5 mg/kg	128 (19.1%)	32.1 (24.9%)	1692 (31.2%)	734 (20.7%)	20.3 (21.6%)	0.220 (33.0%)	2.87 (21.9%)	2.99 (21.9%)
	10 mg/kg	256 (19.1%)	64.2 (24.9%)	3383 (31.2%)	1468 (20.7%)				
	15 mg/kg	384 (19.1%)	75.2 (28.6%)[c]	5075 (31.2%)	2801 (21.6%)				

Steady State	5 mg/kg Q2W	215 (23.4%)	84.7 (38.4%)	NA	1692 (31.2%)				
	10 mg/kg Q2W	430 (23.4%)	169 (38.4%)	NA	3383 (31.2%)				
	15 mg/kg Q3W	445 (23.4%)	148 (41.4%)	NA	5075 (31.2%)				

Values are reported as geometric mean (geometric coefficient of variation - CV%) and are based on Population PK analysis of 491 subjects.

Abbreviations: C_{max}, maximum serum concentration; $AUC_{0-\infty}$-, area under the serum concentration-time curve after bevacizumab infusion from time 0 to infinity, AUC_{0-tau}, area under the serum concentration-time curve after bevacizumab infusion at steady state; $T_{1/2}$, terminal elimination half-life; CL, clearance; Vc, central volume of distribution; Vp, peripheral volume of distribution, NA, not applicable

[a] tau is 14 days for 5mg/kg Q2W and 10 mg/kg Q2W, tau is 21 days for 15 mg/kg Q3W

Absorption:
Bevacizumab is administered via the intravenous route and therefore is immediately and expected to be completely bioavailable.

Distribution:
Based on a population pharmacokinetic analysis of 491 subjects receiving Avastin weekly, every 2 weeks, or every 3 weeks, in doses ranging from 1 to 20 mg/kg, the geometric mean (CV%) of volume of the central compartment (Vc) and volume of distribution of peripheral compartment (Vp) were 2.87 L (21.9%) and 2.99 L (21.9%), respectively. The typical value 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:
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 geometric mean (CV%) of clearance (CL) was 0.220 (33.0%). Bevacizumab typical clearance was 0.207 L/day for females and 0.262 L/day for males. The typical Vc and typical clearance correspond to an initial typical 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 on exposure. The results showed no significant difference in the exposure of bevacizumab in relation to age, when body weight is taken into account.

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

11 STORAGE, STABILITY AND DISPOSAL

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

Avastin 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.

12 SPECIAL HANDLING INSTRUCTIONS

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: Avastin

Chemical name: bevacizumab

Molecular formula and molecular mass: bevacizumab is a highly purified, approximately 149, 000 dalton antibody that includes 1,320 amino acids.

Structural formula:

Figure 1 Primary Sequence of Bevacizumab Light Chain

```
        10        20        30        40        50        60
DIQMTQSPSSLSASVGDRVTITCSASQDISNYLNWYQQKPGKAPKVLIYFTSSLHSGVPS
        70        80        90       100       110       120
RFSGSGSGTDFTLTISSLQPEDFATYYCQQYSTVPWTFGQGTKVEIKRTVAAPSVFIFPP
       130       140       150       160       170       180
SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLT
       190       200       210
LSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
```

Figure 2 Primary Sequence of Bevacizumab Heavy Chain

```
        10        20        30        40        50        60
EVQLVESGGGLVQPGGSLRLSCAASGYTFTNYGMNWVRQAPGKGLEWVGWINTYTGEPTY
        70        80        90       100       110       120
AADFKRRFTFSLDTSKSTAYLQMNSLRAEDTAVYYCAKYPHYYGSSHWYFDVWGQGTLVT
       130       140       150       160       170       180
VSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVL
       190       200       210       220       230       240
QSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEL
       250       260       270       280       290       300
LGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE
       310       320       330       340       350       360
QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS
       370       380       390       400       410       420
REEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK
       430       440       450
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
```

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

Product Characteristics:

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

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Metastatic Colorectal Cancer

The safety and efficacy of the recommended dose of Avastin (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. Avastin 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 Avastin 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.

Study AVF2107g

Study Demographics and Trial Design

This was a phase III randomised, double blind, active controlled clinical trial evaluating Avastin 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 + Avastin (5 mg/kg every 2 weeks, Arm 2) (see Table 18). A third group of 110 patients received bolus 5 FU/LV + Avastin (Arm 3). Enrollment in Arm 3 was discontinued, as pre specified, once safety of Avastin with the IFL regimen was established and considered acceptable.

Table 18 Treatment Regimens in Study AVF2107g

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

Study Results

The primary efficacy parameter of the trial was duration of survival. The addition of Avastin to IFL resulted in a statistically significant increase in overall survival (see Table 19 and Figure 1). The clinical

benefit of Avastin, 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 **Figure *3***).

The efficacy results of Avastin in combination with IFL chemotherapy are displayed in Table 19 and Figure 1 and Figure 2 (Kaplan Meier plots for duration of survival and progression free survival).

Table 19 Efficacy Results for Study AVF2107g

	Arm 1 IFL + Placebo	**Arm 2 IFL + Avastin***
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 + Avastin), 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**

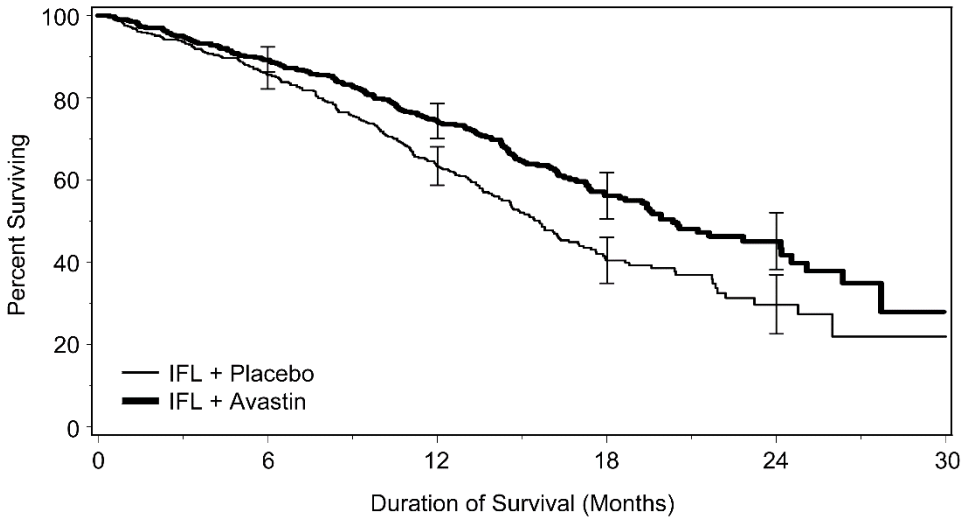


Figure 2 **Progression Free Survival during First-Line Therapy in Study AVF2107g**

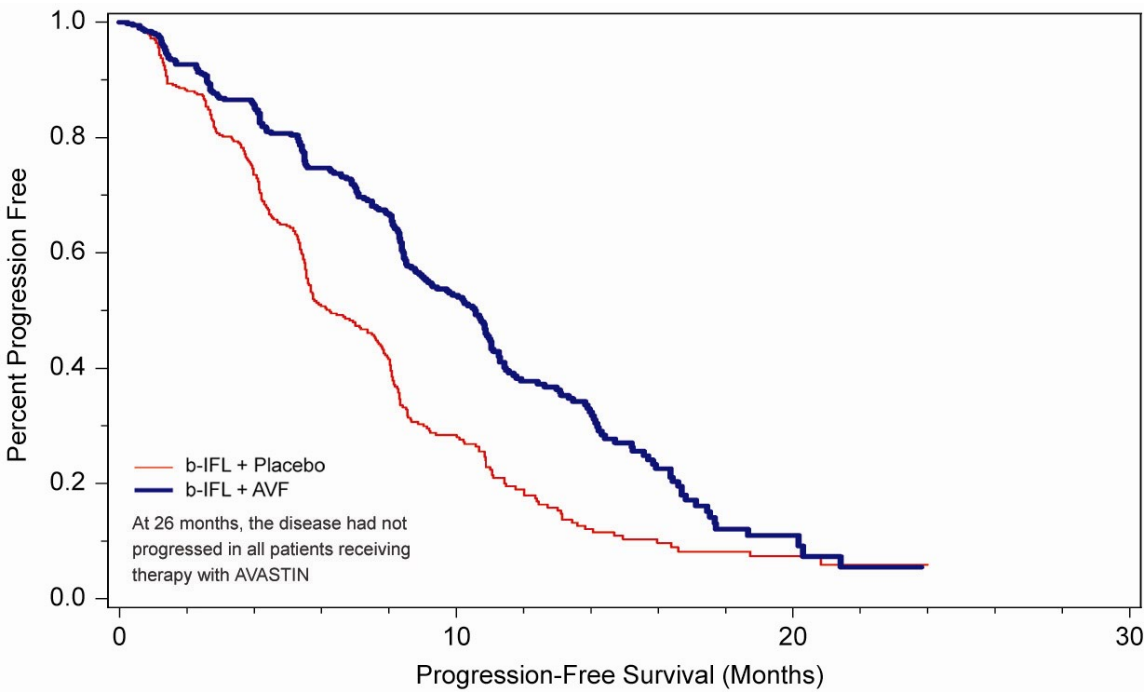
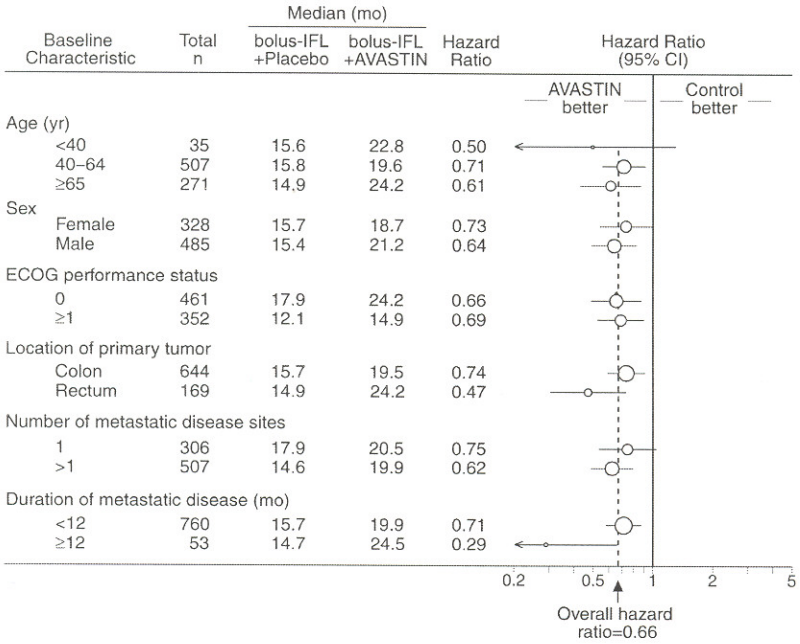


Figure 3 Duration of Survival by Baseline Risk Factor in Study AVF2107g



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.

Study AVF2192g

Study Demographics and Trial Design

This was a phase II randomized, active-controlled, open-labelled clinical trial investigating Avastin 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 + Avastin (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.

Study Results

The addition of Avastin 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 20). These efficacy data were consistent with the results observed in studies AVF2107g and AVF0780g.

Table 20 Treatment Regimens in Study AVF2192g

	Treatment	Starting Dose	Schedule
Arm 1	5-Fluorouracil Leucovorin	500 mg/m^2 IV 500 mg/m^2 IV	given once weekly for 6 weeks of 8-weeks cycle
	Placebo	IV	Every 2 weeks
Arm 2	5-Fluorouracil Leucovorin	500 mg/m^2 IV 500 mg/m^2 IV	given once weekly for 6 weeks of 8-weeks cycle
	Avastin	5 mg/kg IV	Every 2 weeks

5-Fluorouracil: IV bolus (slow push) 1 hour after initiation of the 2-hour leucovorin infusion.
Leucovorin: IV infusion over 2 hours

Study AVF0780

Study Demographics and Trial Design

This was a phase II randomised, active-controlled, open-labelled clinical trial investigating Avastin 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 + Avastin (5 mg/kg every 2 weeks). A third group of 33 patients received bolus 5-FU/LV + Avastin (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.

Study Results

The addition of 5 mg/kg every two weeks of Avastin 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 21). This efficacy data is consistent with the results from study AVF2107g.

Table 21 Efficacy Results for Study AVF0780g and AVF2192g

	AVF0780g			**AVF2192g**	
	5-FU/LV	**5-FU/LV + Avastin[a]**	**5-FU/LV + Avastin[b]**	**5-FU/LV + placebo**	**5-FU/LV + Avastin**
Number of Patients	36	35	33	105	104
Overall Survival					
Median (months)	13.6	17.7	15.2	12.9	16.6
95% Confidence Interval (CI)				10.35-16.95	13.63-19.32
Hazard ratio[C]	-	0.52	1.01		0.79
(95% CI)		(0.25; 1.08)	(0.53; 1.91)		(0.56; 1.10)
p-value		0.073	0.978		0.16
Progression-free Survival					
Median (months)	5.2	9	7.2	5.5	9.2
Hazard ratio		0.44	0.69 (0.38;		0.5 (0.34;
(95% CI)		(0.24; 0.8)	1.25)		0.73)
p-value	-	0.0049	0.217		0.0002
Overall Response Rate					
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

Table 21 Efficacy Results for Study AVF0780g and AVF2192g

	AVF0780g			AVF2192g	
	5-FU/LV	5-FU/LV + Avastin[a]	5-FU/LV + Avastin[b]	5-FU/LV + placebo	5-FU/LV + Avastin
Duration of Response					
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)

Study BO17920

Study Demographics and Trial Design

This was a phase III randomized open-label, 3-arm study evaluating the efficacy and safety of Avastin 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.

Study Results

More relapses and deaths due to disease progression were observed in both Avastin 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 Avastin to either chemotherapy regimen was not met. The hazard ratios for DFS were 1.17 (95% CI: 0.98-1.39) for the FOLFOX4 + Avastin arm and 1.07 (95% CI: 0.90-1.28) for the XELOX + Avastin 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 + Avastin arm and 1.15 (95% CI: 0.93-1.42) for the XELOX + Avastin arm compared to FOLFOX alone.

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

The safety and efficacy of Avastin 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

Study Demographics and Trial Design

E4599 was an open-label, randomised, active-controlled, multicentre clinical trial evaluating Avastin 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 Avastin 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 Avastin + carboplatin–paclitaxel arm continued to receive Avastin 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 Avastin and 21.1% (89/422) of patients received 13 or more administrations of Avastin.

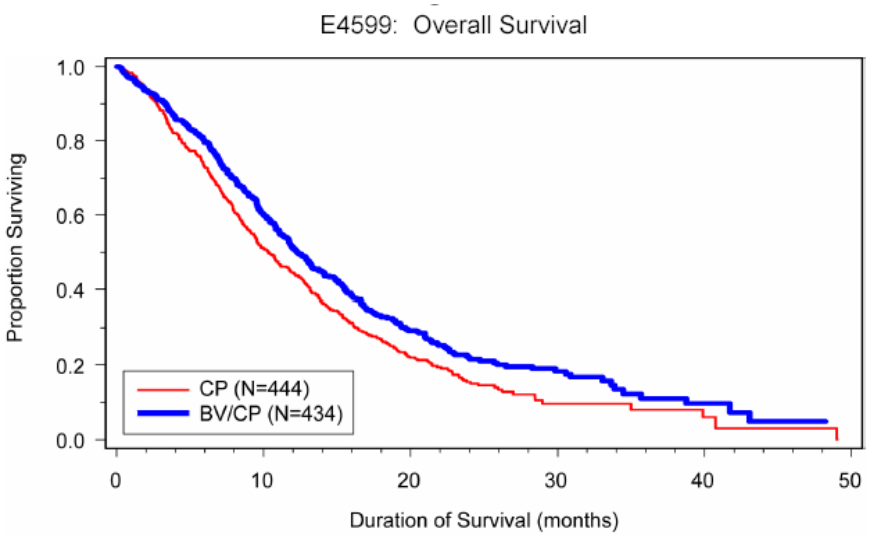
Study Results

The primary endpoint was duration of survival. Results are presented in Table 22.

Table 22 Efficacy Results for Study E4599

	Arm 1 Carboplatin/Paclitaxel	**Arm 2 Carboplatin/ Paclitaxel + Avastin 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) 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 Avastin 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 203 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

Study Demographics and Trial Design

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 carboplatin/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.

Study Results

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 Avastin-treated patients with squamous cell histology and 4% (2 of 53) in Avastin-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-Sensitive Recurrent Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

Study AVF4095g

Study Demographics and Trial Design

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

Patients with histologically documented ovarian, primary peritoneal, or fallopian tube carcinoma that had recurred > 6 months after platinum-based chemotherapy, who had not received chemotherapy in the recurrent setting, and who had not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents were included in the study.

Avastin was administered in combination with carboplatin and gemcitabine for 6 to10 cycles followed by continued use of Avastin as single agent until disease progression.

Patient demographic characteristics were similar across the two treatment arms. All but one patient had an ECOG baseline performance status of 0 or 1. The median age of all randomized patients was 61 years (range, 28-87 years). The majority of patients were < 65 years (63%) of age and 37% were ≥ 65 years of age. Patients were predominantly White (90.9%), with an equal number of Asians and Black or African Americans enrolled (3.1% each); 2 patients (0.4%) were Native Hawaiian or Other Pacific Islander.

Stratification factors were time to recurrence since last platinum-based chemotherapy (6-12 months, > 12 months) and cytoreductive surgery for recurrent EOC, PPC, or FTC (yes, no).

A total of 484 patients with measurable disease were randomized in 1:1 to either:

- Carboplatin (AUC4, Day 1) and gemcitabine (1000 mg/m2 on Days 1 and 8) and concurrent placebo every 3 weeks for 6 and up to 10 cycles followed by placebo alone until disease progression or unacceptable toxicity
- Carboplatin (AUC4, Day 1) and gemcitabine (1000 mg/m2 on Days 1 and 8) and concurrent Avastin (15 mg/kg Day 1) every 3 weeks for 6 and up to 10 cycles followed by Avastin (15 mg/kg

every 3 weeks) alone until disease progression or unacceptable toxicity

Study Results

The primary endpoint was progression-free survival based on investigator assessment using RECIST criteria. Additional endpoints included objective response, duration of response, safety and overall survival. An independent review of the primary endpoint was also conducted and showed consistency with the investigator-assessed PFS as well as ORR results. OS benefit was not demonstrated in the study.

The results of this study are summarized in Table 24.

Table 24 Efficacy Results from Study AVF4095g

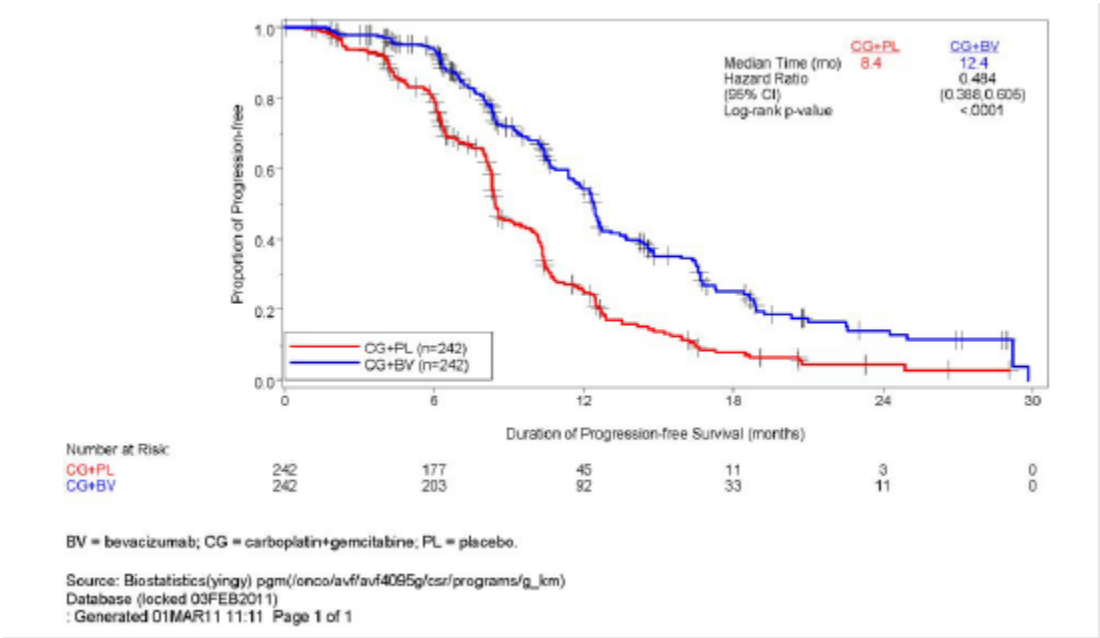
Progression-free survival		
	Investigator Assessment [1]	
	Placebo + C/G (n = 242)	Avastin + C/G (n = 242)
Median PFS (months)	8.4	12.4
Hazard ratio (95% CI)	0.484 [0.388, 0.605]	
p –value	<0.0001	
Objective response rate		
	Investigator Assessment	
	Placebo + C/G (n = 242)	Avastin + C/G (n = 242)
% pts with objective response	57.4 %	78.5%
p –value	<0.0001	
Overall survival (Interim)[2]		
	Placebo + C/G (n = 242)	Avastin + C/G (n = 242)
Median OS (months)	29.9	35.5
Hazard Ratio (95% CI)	0.751 [0.537, 1.052]	
p-value	0.094	
Overall survival (Final)[3]		
	Placebo + C/G (n = 242)	Avastin + C/G (n = 242)
Median OS (months)	32.9	33.6
Hazard Ratio (95% CI)	0.952 [0.771; 1.176]	

Table 24 Efficacy Results from Study AVF4095g

p-value	0.6479

C = carboplatin; G = gemcitabine
[1] Primary analysis
[2] Interim protocol-specified overall survival stratified analysis performed when approximately 29% of the patients had died and tested at the 0.001 level at the time of the OS interim analysis.
[3] Final overall survival stratified analysis performed when approximately 73% of the patients had died. α =0.001. OS benefit was not demonstrated in the study.
The overall Type I error rate for the two-sided test for the primary endpoint of PFS was controlled at α = 0.05. Only one futility interim analysis was planned for the primary endpoint PFS. As a result, the total α = 0.05 was reserved for the final PFS analysis. To protect the experiment-wise error rate among objective response and OS, a hierarchical procedure was used for testing the hypotheses associated with the two endpoints. Specifically, ORR was tested at the α = 0.05 level. If the active arm was declared superior to the control arm with respect to ORR, then OS was to be tested at the α = 0.05 level: the interim OS was tested at the α = 0.001 level, and the final OS at the α = 0.049 level.

Figure 5 Kaplan Meier Estimates of Progression-Free Survival Based on Investigator Assessment, Censoring for Non-Protocol Specified Therapy in Randomized Patients.



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

Study MO22224

Study Demographics and Trial Design

Study MO22224 (AURELIA) 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 %.

Study Results

The addition of Avastin 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 6. 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

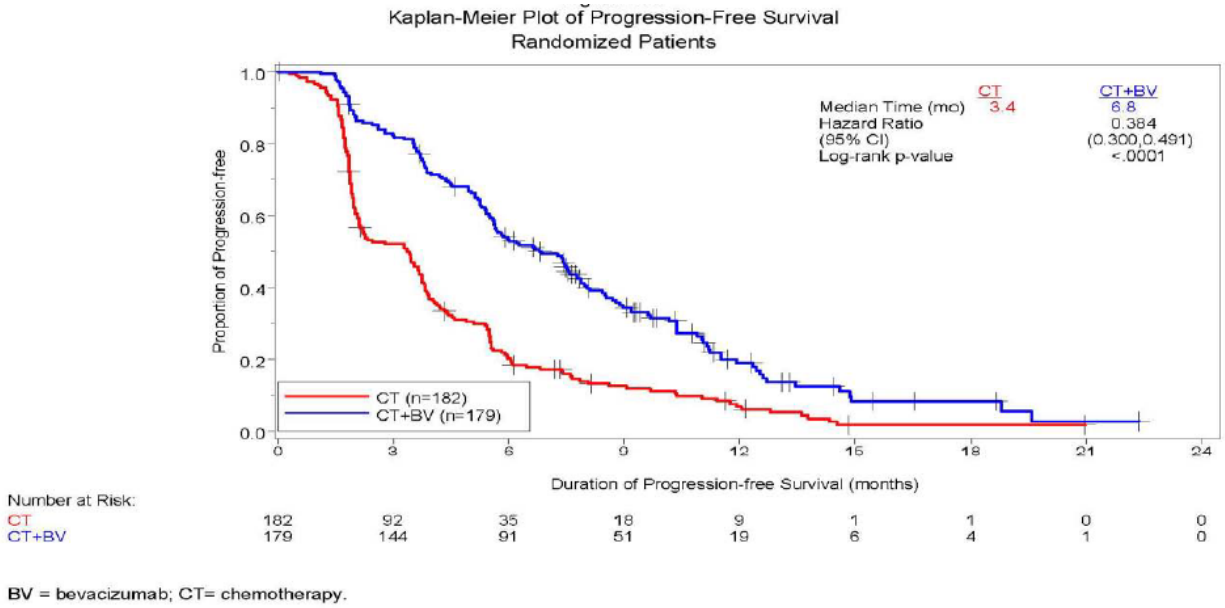
	CT (n=182)	CT+BV (n=179)
No. (%) patients with event	168 (92.3%)	140 (78.2%)
Median (months)	3.4	6.8
Hazard ratio* (95% CI)	0.384 [0.300, 0.491]	
p-value**	<0.0001	
Secondary Endpoints		
Objective Response Rate		
	Investigator Assessment	
	CT (n=182)	CT+BV (N=179)
No. patients with measurable disease at baseline	144	142
% pts with objective response	18 (12.5%)	40 (28.2%)
Median duration of response (months)	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 6 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]+Avastin (N=60)	CT[b] (N=63)	CT[b]+Avastin (N=57)	CT[b] (N=64)	CT[b]+Avastin (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)

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

Efficacy Parameter	Paclitaxel		Topotecan		PLD	
	CT[b] (N=55)	CT[b]+Avastin (N=60)	CT[b] (N=63)	CT[b]+Avastin (N=57)	CT[b] (N=64)	CT[b]+Avastin (N=62)
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

Study Demographics and Trial Design

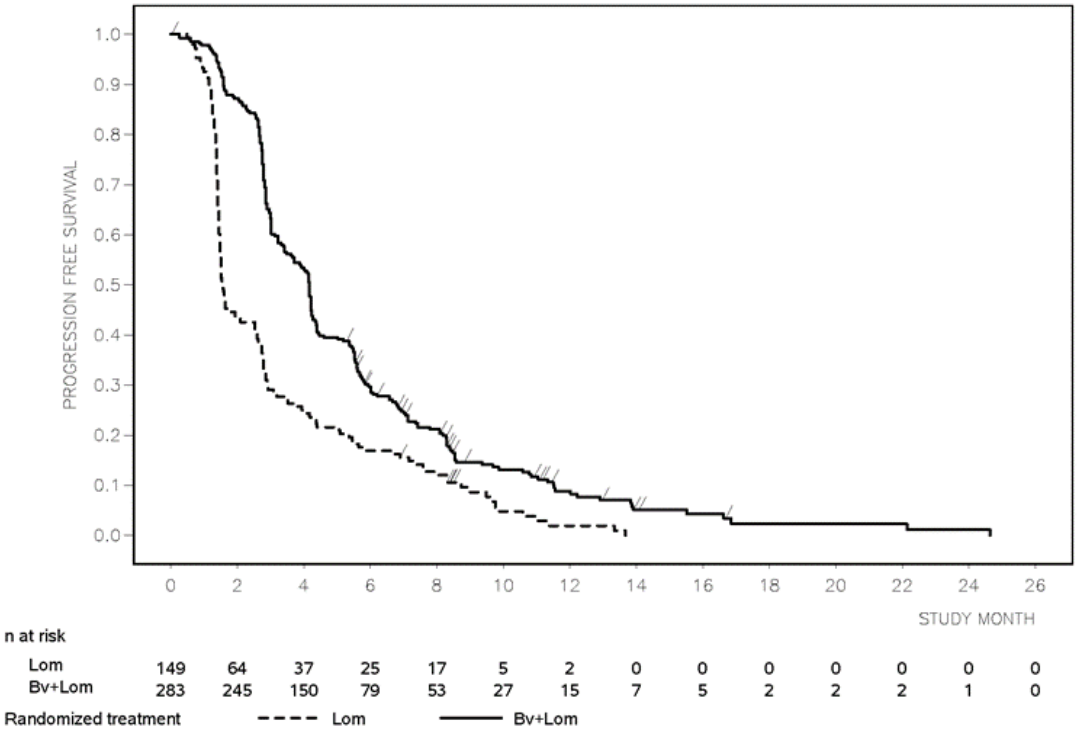
Patients with previously treated glioblastoma were evaluated in a multicenter, randomized, open-label Phase 3 study comparing Avastin plus Lomustine versus Lomustine. A total of 432 patients with first progression following the treatment with radiotherapy and temozolomide were randomized (2:1) to receive either Avastin (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 Avastin 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 Avastin plus Lomustine arm and 61.1% in the Lomustine arm) were male.

Study Results

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 Avastin 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 7. Among the 399 patients with measurable disease, ORR was 26% in those receiving Avastin 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 Avastin+ 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 7 Investigator-Assessed Progression-Free Survival in Study EORTC 26101



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

Pediatric Studies

Study BO20924 (Bernie)

Study Demographics and Trial Design

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.

Study Results

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)

Study Demographics and Trial Design

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.

Study Results

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).

14.3 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity.

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-sensitive recurrent ovarian cancer study AVF4095g or 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 Avastin with the incidence of antibodies to other products may be misleading.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Physeal Development
In studies of up to 26 weeks duration in cynomolgus monkeys, Avastin 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.

Immunogenicity
Non-clinical toxicology studies of up to 26 weeks duration in cynomolgus monkeys did not reveal evidence of immunogenicity based on absence of detectable serum anti-drug antibodies.

Carcinogenicity: Studies have not been performed to evaluate the carcinogenic and mutagenic potential of Avastin.

Genotoxicity: No studies have been performed to establish the mutagenic potential of Avastin.

Reproductive and Developmental Toxicology: No specific studies in animals have been performed to evaluate the effect of Avastin 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 Avastin for 13 or 26 weeks. The doses associated with

this effect were ≥ 4 times the human therapeutic dose or ≥ 2-fold above the expected human exposure based on average serum concentrations in female monkeys. In rabbits, administration of 50 mg/kg of bevacizumab resulted in a significant decrease in ovarian weight and number of corpora lutea. The results in both monkeys and rabbits were reversible upon cessation of treatment. The inhibition of angiogenesis following administration of bevacizumab is likely to result in an adverse effect on female fertility.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]AVASTIN®

bevacizumab for injection

Read this carefully before you start taking **Avastin** 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 **Avastin**.

Serious Warnings and Precautions

- **Eye disorders:** Avastin should not be injected in the eye. Side effects were seen in the eye and body as a whole in some patients who had Avastin injected in the eye.
- **Hole in the stomach or bowel:** At any time during treatment, Avastin may cause a hole in the stomach or bowel which can be deadly. Treatment should be stopped if this happens. Side effects include stomach pain, constipation, and vomiting.
- **Wound healing complications:** Avastin may cause wounds to open and not heal, which can be deadly. Avastin treatment should be stopped if this happens and for one month after having surgery or until the wound is fully healed. Avastin should be stopped at least 28 days before elective surgery.
- **Bleeding:** Avastin 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 Avastin 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 Avastin. Treatment with Avastin should be permanently stopped if serious bleeding occurs (i.e. requiring medical attention).

What is Avastin used for?

- **Colon Cancer:** Avastin 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.
- **Lung Cancer:** Avastin 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.
- **Platinum-Sensitive Ovarian Cancer:** Avastin is used in combination with a specific type of chemotherapy (carboplatin and gemcitabine) for the treatment of people diagnosed with recurrent, platinum-sensitive, epithelial ovarian, fallopian tube, or primary peritoneal cancer that comes back at least 6 months after the last time the patient responded to a chemotherapy regimen containing a platinum agent. Epithelial ovarian cancer is cancer that develops on the surface of the ovary. Fallopian tube cancer is cancer that forms in a woman's fallopian tubes,

the small ducts that link a woman's ovaries to her uterus. Primary peritoneal cancer is cancer of the tissue that lines the abdominal wall and covers organs in the abdomen.

- **Platinum-Resistant Ovarian Cancer:** Avastin 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.
- **Glioblastoma:** Avastin 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 Avastin work?

Avastin is not chemotherapy but is given in combination with a specific type of chemotherapy. Avastin is a monoclonal antibody. While chemotherapy attacks the tumour directly, Avastin 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). Avastin works by blocking angiogenesis. By preventing the growth of new blood vessels, Avastin helps starve the tumour of oxygen and other nutrients. This makes it hard for the tumour to grow.

What are the ingredients in Avastin?

Medicinal ingredients: bevacizumab

Non-medicinal ingredients: α,α-trehalose dihydrate, polysorbate 20, sodium phosphate and Water for Injection.

Avastin comes in the following dosage forms:

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

Do not use Avastin if:

- you are allergic to bevacizumab or any of its ingredients in Avastin;
- your cancer has spread to your brain or spine. Avastin 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 Avastin. Talk about any health conditions or problems you may have, including if you:

- have high blood pressure or heart problems;
- are pregnant or plan to become pregnant;
- are breast-feeding;
- have any allergies to this drug or its ingredients;
- plan to have surgery or have had surgery in the last 28 days;
- 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:

- **Children and adolescents:** Avastin should not be given to children or adolescents. This is because the effects of Avastin in people younger than 18 years of age are not known.
- **Females of childbearing potential:** Avastin may cause fertility problems. Avastin 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 Avastin. Avastin 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 Avastin and for at least 6 months after your last dose of Avastin. If you become pregnant during treatment with Avastin, tell your doctor immediately.**Driving and using machines:** It is not known whether Avastin affects your ability to drive or use tools or machines.
- 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 Avastin:

- **irinotecan:** Your doctor may adjust the dose of irinotecan if you have side effects known to be related to it.
- **sunitinib malate**: the safety and efficacy of Avastin in combination with sunitinib malate has not been established, therefore this combination is not recommended.
- **platinum- or taxane-based therapies for lung:** These therapies in combination with Avastin may increase the risk of severe side effects.
- **EGFR monoclonal antibodies:** The interaction of Avastin in combination with EGFR monoclonal antibodies has not been studied, therefore this combination is not recommended.

How to take Avastin:

Avastin will be given to you by a healthcare professional in a healthcare setting. Do not use this medication if it looks cloudy or is leaking.

Usual dose:

Colon Cancer: The usual dose of Avastin 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.

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

Platinum-Sensitive Ovarian Cancer: The usual dose of Avastin is based on your weight in kg (15 mg/kg). Avastin is given once every 3 weeks for as long as your physician recommends therapy.

Platinum-Resistant Ovarian Cancer: The usual dose of Avastin is based on your weight in kg (10 mg/kg or 15 mg/kg). Avastin 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 Avastin that is right for you, based on if and what type of chemotherapy you are also receiving.

Glioblastoma: The usual dose of Avastin is based on your weight in kg (10 mg/kg). Avastin is given once every 2 weeks in combination with lomustine very 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/m2), up to a maximum dose of 160 mg. It can be increased to 110 mg/m2, up to a maximum 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 Avastin is given, it will take about 90 minutes. Once your doctor has made sure that you have no problems with the Avastin 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, or a person you are caring for, have taken too much Avastin, contact a 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 Avastin, your doctor will decide when you should receive your next dose.

What are possible side effects from using Avastin?

These are not all the possible side effects you may have when taking Avastin. If you experience any side effects not listed here, tell your healthcare professional.

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

Very Common (may affect more than 1 in 10 patients):

- Lack of energy or strength
- Loss of appetite
- Sores in the mouth
- Runny nose
- Dry, scaling skin or changes in skin colour
- Changes in the sense of taste
- Difficulty in sleeping
- Chills or excessive sweating
- Abnormal urine test (protein in the urine)
- Tingling sensation or numbness in toes and fingers
- Bruising
- Change in moods
- Weight loss
- Tiredness

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

- Heart pain (angina))
- Altered voice such as hoarseness

- Swelling and numbness of the hand and feet

Frequency unknown:
- Ulcers in the stomach and bowel

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

Changes in your blood and urine tests done by your doctor may occur while you are receiving Avastin. 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 Avastin for cancer treatment, the following side effects may occur when Avastin 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			
High blood pressure: 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 more than 10-15 minutes and cannot be stopped.		✓	✓
Diarrhea		✓	
Vomiting		✓	
Constipation		✓	
Bleeding from the rectum or stomach: symptoms include fresh blood in stools and/or dark stools		✓	

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**	
Decreased number of white blood cells: symptoms could include fever, sore throat, infection		✓	
Decreased number of red blood cells in the blood that carry oxygen: 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: You may not experience any symptoms, but possible symptoms associated with low blood pressure are: lightheadedness, dizziness, fainting		✓	
Dilation (widening) of the blood vessels: symptoms may include low blood pressure, dizziness, flushing		✓	
Weakened heart muscle/loss of the heart's pumping ability: shortness of breath, fatigue, persistent coughing or wheezing, increased heart rate, swelling in the feet or ankles		✓	✓
Eye problems: for example: excessive tearing, blurred vision, an experience of discomfort or pain to the eyes due to light exposure		✓	
Bronchitis: an inflammation of the main air passages to the lungs)		✓	
Infections: mouth, throat, sinus, lungs or urine infections		✓	
Excess of sugar in the blood: symptoms may include frequent hunger, frequent thirst, frequent urination		✓	

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	
Low levels of sodium and magnesium in the blood		✓	
Coughing		✓	
COMMON			
Perforation of the gut (leakage of the bowel): sudden onset of abdominal pain, abdominal tenderness with vomiting, high fever, constipation, vomiting		✓	✓
Allergic reactions: difficulty breathing, chest pain, redness or flushing of the skin, rash, shivering, nausea, vomiting		✓	✓
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 recurrent ovarian cancer, and between the vagina and the gut in patients with cervical cancer (unauthorized use)		✓	✓
Blood clots: In the deep veins of the leg, symptoms include pain, swelling, warm to the touch, and tenderness of the leg. In the lung, symptoms include: shortness of breath, chest pain, light headedness		✓	✓
Stroke or heart attack: Symptoms of stroke include sudden loss of speech or numbness of part or all of the body, loss of vision or blurred vision, unexplained		✓	✓

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**	
dizziness and/or sudden falls. Symptoms of a heart attack include: chest pain with spreading to the left arm, jaw and/or back, shortness of breath.			
Hemorrhage: gastrointestinal bleeding, significant blood in vomit, bleeding from rectum or stomach (fresh blood in stools or dark stool), bleeding from the nose that lasts more than 10-15 minutes and cannot be stopped, spitting of blood		✓	✓
Wounds opening and not healing: the skin near a surgical area can appear fully or partially open		✓	✓
Nephrotic syndrome: swelling in the face, arms, legs, belly area, foamy appearance of urine and poor appetite		✓	✓
Pain: in the pelvis and anal regions		✓	
UNCOMMON			
Non-gastrointestinal perforations and fistulae: Depending on the organs involved the symptoms could 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): headache, confusion, seizures and visual loss.		✓	✓
RARE			
Tracheoesophageal fistula: abnormal tube like connection between internal parts of the body		✓	✓

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	
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			
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 you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell 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 (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) 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 vials in a refrigerator at 2ºC to 8ºC. Keep vial in the outer carton in order to protect from light. **Do not freeze. Do not shake.**

Keep out of reach and sight of children.

If you want more information about Avastin:

- 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: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website (www.rochecanada.com), or by calling 1-888-762-4388.

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