PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrMVASI®

bevacizumab for injection

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

In-house Standard

Anti-neoplastic

Amgen Canada Inc.
6775 Financial Drive, Suite 300
Mississauga, ON L5N 0A4

Date of Initial Approval:
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RECENT MAJOR LABEL CHANGES

N/A	

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MVASI® (bevacizumab for injection) is a biosimilar biologic drug (biosimilar) to AVASTIN®.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Indications have been granted on the basis of similarity between MVASI and the reference biologic drug AVASTIN®.

- **Metastatic Colorectal Cancer (mCRC)**

  MVASI (bevacizumab), 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 INTERACTIONS, Drug-Drug Interactions** for further information on the use of MVASI in combination with irinotecan.

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

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

  MVASI, 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**

  MVASI, 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 MVASI.

  The effectiveness of bevacizumab 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 bevacizumab.

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

  MVASI, 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 MVASI.

  The effectiveness of bevacizumab in platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer is based on a study in patients with disease progression within < 6 months from the most recent platinum-based chemotherapy, with a minimum of 4 platinum therapy cycles completed. A statistically significant improvement in progression-free survival was seen. No overall survival benefit was demonstrated with bevacizumab.

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

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

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

1.1 Pediatrics

The safety and efficacy of MVASI in patients under the age of 18 years have not been established (see **WARNINGS AND PRECAUTIONS**).

2 CONTRAINDICATIONS

MVASI is contraindicated in patients with known hypersensitivity to:

- Any components of the product (for a complete listing, see the **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING** section),
- Chinese hamster ovary cell products or other recombinant human or humanized antibodies.

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

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Eye Disorders**

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

- **Gastrointestinal Perforations**

  MVASI 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 bevacizumab (ie, 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 MVASI presenting with abdominal pain. The incidence of gastrointestinal perforation, some fatal, in bevacizumab treated patients ranges from 0.3 to 3.2%. Gastrointestinal perforations (including gastrointestinal fistula and abscess) have been reported in up to 2.7% in patients with metastatic colorectal cancer, 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 bevacizumab was 2%. MVASI therapy should be permanently discontinued in patients with gastrointestinal perforation (see **WARNINGS AND PRECAUTIONS, Gastrointestinal** and **ADVERSE REACTIONS, Gastrointestinal**)

- **Wound Healing Complications**

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

- **Hemorrhage**

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

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

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

There are no recommended dose reductions. Discontinue MVASI 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) venous thromboembolic events (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 MVASI for:

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

4.2 Recommended Dose and Dosage Adjustment

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

Metastatic Colorectal Cancer

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

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

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

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

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

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

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

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

Malignant Glioma (WHO Grade IV) - Glioblastoma

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

4.3 Administration

Do not administer as an intravenous push or bolus.

The initial MVASI 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.

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

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

MVASI should be prepared by a healthcare professional using aseptic technique. Withdraw the necessary amount of MVASI 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 the vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

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

5 OVERDOSAGE

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

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognize 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.

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.

MVASI 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. Nonmedicinal ingredients: α,α-trehalose dihydrate, polysorbate 20, sodium phosphate and Water for Injection. Packs of 1 vial.

7 DESCRIPTION

MVASI is a recombinant humanized monoclonal antibody that selectively binds to and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF).

8 WARNINGS AND PRECAUTIONS

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

General

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

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

Unauthorized Intravitreal Use: Eye Disorders

Individual cases and clusters of serious ocular adverse events affecting multiple patients have been reported from unauthorized intravitreal use of bevacizumab following variable and non-validated methods in compounding, storage, and handling of bevacizumab vials authorized for intravenous administration in cancer patients. These events included infectious endophthalmitis (some cases leading to permanent blindness, one case reported extraocular extension of infection resulting in meningoencephalitis), intraocular inflammation[1] (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[2] study comparing unauthorized intravitreal bevacizumab to an authorized treatment in patients treated for wet age-related macular degeneration has reported an increased risk of intraocular inflammation for bevacizumab (adjusted HR: 1.82; 99% CI: 1.20, 2.76) (Incidence 0.46 events per 100 patients per year; comparator 0.26 events per 100 patients per year) as well as an increased risk for cataract surgery (adjusted HR: 1.11; 99% CI: 1.01, 1.23) (Incidence 6.33 events per 100 patients per year; comparator 5.64 events per 100 patients per year).

Unauthorized Intravitreal Use: Systemic Events

An observational claims database[3] study comparing unauthorized intravitreal bevacizumab to an authorized treatment in patients treated for wet age-related macular degeneration has reported an increased risk of hemorrhagic stroke for bevacizumab (adjusted HR: 1.57; 99% CI: 1.04, 2.37) (Incidence 0.41 events per 100 patients per year; comparator 0.26 events per 100 patients per year) as well as an increased risk for overall mortality (adjusted HR: 1.11; 99% CI: 1.01, 1.23) (Incidence 6.03 events per 100 patients per year; comparator 5.51 events per 100 patients per year). A second observational study found similar results for all-cause mortality.[4] A randomized controlled clinical trial comparing unauthorized bevacizumab to an authorized treatment for patients with wet age-related macular degeneration[5] has reported an increased risk of serious systemic adverse events for bevacizumab, most of which resulted in hospitalization (adjusted risk ratio 1.29; 95% CI: 1.01, 1.66) (Incidence 24.1%; comparator 19.0%). The most frequent serious systemic adverse events reported directly to the sponsor include myocardial infarction, cerebrovascular accident, and hypertension.

[1] 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
[2] Ibid
[3] Ibid
[4] 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
[5] Comparison of Age-Related Macular Degeneration Treatment Trials (CATT) Research Group, Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration. 10.1056/NEJMoa1102673

Cardiovascular

Hypertension

An increased incidence of hypertension was observed in patients treated with bevacizumab. 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 bevacizumab (see **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 MVASI treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Frequently monitor of blood pressure (eg, 2-3 weeks) during MVASI therapy in order to detect potentially serious complications of therapy, including hypertensive encephalopathy and Posterior Reversible Encephalopathy Syndrome (PRES) (see **Neurologic** and **ADVERSE REACTIONS**).

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

Thromboembolism **(**see **ADVERSE REACTIONS)**

Arterial Thromboembolism

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

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

Patients receiving MVASI 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 MVASI therapy. Caution should be used when treating such patients with MVASI (see **ADVERSE REACTIONS**). Regular clinical, and if necessary, special radiological investigations, should be performed to assess for signs of ATEs. Appropriate treatment, including permanent discontinuation of MVASI, 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 MVASI treatment.

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

MVASI 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 MVASI therapy if their condition deteriorates.

Congestive Heart Failure (CHF)/Cardiomyopathy

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

Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or CHF with MVASI.

CHF was observed in all cancer indications. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present (see **ADVERSE REACTIONS**). MVASI 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 MVASI, it should be treated with the standard medications for this purpose. Discontinuation of MVASI should be strongly considered in patients who develop clinically significant CHF, taking into account a careful benefit-risk assessment.

Gastrointestinal (see ADVERSE REACTIONS)

Gastrointestinal Perforations and Fistula

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

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

MVASI 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 MVASI (see **ADVERSE REACTIONS**).

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

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

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

Permanently discontinue MVASI in patients with any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, MVASI should be discontinued.

Serious and sometimes fatal non-gastrointestinal fistula formation involving tracheoesophageal, bronchopleural, biliary, vaginal, renal, and bladder sites occurs at a higher incidence in bevacizumab-treated patients compared to controls. Uncommon (≥ 0.1% to < 1%) reports of non- gastrointestinal perforation were observed in clinical studies across various indications at

any time points ranging from one week to greater than 1 year from initiation of bevacizumab treatment, with most of the events occurring within the first 6 months of bevacizumab therapy. Fistulae have also been reported in post-marketing experience. Although other risk factors (eg, diagnosis of cancer, cancer progression, cancer treatments) are known to be associated with an increased risk of development of fistulae, a role for MVASI in increasing this risk cannot be excluded.

Tracheoesophageal (TE) Fistula

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

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

Genitourinary

Ovarian Failure

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

Proteinuria

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

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

Data from a post-marketing safety study of bevacizumab 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 bevacizumab 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 bevacizumab (see **ADVERSE REACTIONS**). Proteinuria (any Grade) was reported in 21.5% (53/247) of the patients in the bevacizumab 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 bevacizumab versus 0.9% (2/233) of the patients treated with chemotherapy alone. The incidence of Grade 3 proteinuria was common in patients treated with bevacizumab. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with bevacizumab, 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 **ADVERSE REACTIONS**)

Patients treated with MVASI have an increased risk of hemorrhage, especially tumour-associated hemorrhage. MVASI can result in gastrointestinal bleeding, hematemesis, CNS hemorrhage, hemoptysis, epistaxis or vaginal bleeding. Patients should be monitored for bleeding events. MVASI should be permanently discontinued in patients who experienced Grade 3 or 4 bleeding (ie, bleeding requiring medical intervention) during MVASI therapy, and aggressive medical management should be initiated. Routine assessment of this event should include serial complete blood counts and physical examination.

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

CNS hemorrhage

Cases of CNS hemorrhage, some with fatal outcome, have been observed with bevacizumab use. In one phase III study with platinum-sensitive recurrent ovarian cancer, one patient treated with bevacizumab 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 MVASI treatment discontinued in case of intracranial bleeding.

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

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

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 MVASI 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 MVASI (see **ADVERSE REACTIONS,** Hemorrhage).

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

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

Thrombocytopenia

The incidence of thrombocytopenia was higher in patients receiving bevacizumab in combination with chemotherapy (eg, cisplatin/gemcitabine) compared to those who received chemotherapy alone. Increased incidence of thrombocytopenia (any Grade) was reported in patients treated with bevacizumab (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 bevacizumab 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 bevacizumab. 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 bevacizumab developed thrombocytopenia that was accompanied or followed by a bleeding event compared with those treated with chemotherapy alone (see **ADVERSE REACTIONS**).

Hepatic/Biliary/Pancreatic

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

Hypersensitivity Reactions, Infusion Reactions

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

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

Neurologic

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

There have been rare reports of patients treated with bevacizumab developing signs and symptoms that are consistent with PRES, a rare neurological disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Three cases (2 confirmed and 1 unconfirmed of PRES were reported in the platinum-sensitive recurrent ovarian cancer study AVF4095g (see **Neurologic** and **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 non-small cell lung cancer, 0.2% in ovarian cancer, and 0.3% in renal cancer. No cases of PRES were reported in metastatic colorectal carcinoma and breast cancer trials.

The symptoms of PRES may be difficult to differentiate from those of uncontrolled hypertension, therefore neurological examination should be carried out in a patient presenting with the above signs and symptoms. Brain imaging, particularly Magnetic Resonance Imaging (MRI), confirms the diagnosis of PRES. The onset of symptoms has been reported to occur from 16 hours to 1 year after initiation of bevacizumab. Discontinue MVASI 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 MVASI in patients previously experiencing PRES is not known (see **ADVERSE REACTIONS**).

Osteonecrosis of the Jaw (ONJ)

Cases of ONJ have been reported in cancer patients treated with bevacizumab, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates, for which ONJ is an identified risk. Caution should be exercised when MVASI 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 MVASI. In patients who have previously received or are receiving i.v. bisphosphonates invasive dental procedures should be avoided, if possible. Other known risk factors for ONJ include other treatments such as radiotherapy and glucocorticoids.

Peri-Operative Considerations

Wound Healing

MVASI 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 bevacizumab and there was no case of serious wound complication reported in patients treated with chemotherapy alone.

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

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

Renal

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

8.1 Special Populations

8.1.1 Pregnant Women

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

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

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

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

Women of Reproductive Potential:

Repeat dose safety studies in animals have shown that bevacizumab may have an adverse effect on female fertility (see **COMPARATIVE NON-CLINICAL PHARMACOLOGY AND 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 **ADVERSE REACTIONS**).

8.1.2 Breast-feeding

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

8.1.3 Pediatrics

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

In published reports, cases of osteonecrosis at sites other than the jaw have been observed in patients under the age of 18 years exposed to bevacizumab (see **COMPARATIVE NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY, Comparative Toxicology**).

8.1.4 Geriatrics

Patients receiving MVASI 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 MVASI (see **ADVERSE REACTIONS**). In randomized clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic events (including cerebrovascular accidents, transient ischemic attacks, myocardial infarction), Grade 3-4 leukopenia, neutropenia, thrombocytopenia, proteinuria, diarrhea and fatigue as compared to those aged ≤ 65 years when treated with bevacizumab (see **WARNINGS AND PRECAUTIONS, Cardiovascular** and **ADVERSE REACTIONS**). The risk and benefit of MVASI administration in patients > 65 should be carefully evaluated prior to initiating therapy.

In study AVF4095g, the safety profile of the bevacizumab in platinum-sensitive recurrent ovarian cancer patients, ≥ 65 years of age is consistent with the known overall safety profile of bevacizumab 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 bevacizumab had a greater relative risk for proteinuria as compared to younger patients.

9 ADVERSE REACTIONS

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

9.1 Adverse Reaction Overview

Clinical trials have been conducted in patients with various malignancies treated with bevacizumab, predominantly in combination with chemotherapy. The safety profile from a clinical trial population of approximately 5000 patients is presented in this section.

The most serious adverse drug reactions were:

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

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

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

9.2 Clinical Trial Adverse Reactions

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

Table 1 lists adverse drug reactions associated with the use of bevacizumab in combination with different chemotherapy regimens in multiple indications. These reactions had occurred either with at least a 2% difference compared to the control arm (NCI-CTC Grade 3-5 reactions) or with at least a 10% difference compared to the control arm (NCI-CTC Grade 1-5 reactions), in at least one of the major clinical trials. The adverse drug reactions listed in the table 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, MVASI may exacerbate these reactions when combined with chemotherapeutic agents. Examples include palmar-plantar erythrodysesthesia syndrome with capecitabine or pegylated liposomal doxorubicin and peripheral sensory neuropathy with paclitaxel or oxaliplatin and nail disorders or alopecia with paclitaxel.

Table 1. Very Common and Common Adverse Drug Reactions

System Organ Class (SOC)	NCI-CTC Grade 3-5 Reactions (≥ 2 % difference between the study arms in at least one clinical trial)		All Grade Reactions (≥ 10 % difference between the study arms in at least one clinical trial)
	Very Common (≥ 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	
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 Stomatitis Proctalgia	Constipation Stomatitis Rectal hemorrhage
Endocrine disorders			Ovarian failure**
Skin and subcutaneous tissue disorders		Palmar-plantar erythrodysesthesia 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

Table 1. Very Common and Common Adverse Drug Reactions

System Organ Class (SOC)	NCI-CTC Grade 3-5 Reactions (≥ 2 % difference between the study arms in at least one clinical trial)		All Grade Reactions (≥ 10 % difference between the study arms in at least one clinical trial)
	Very Common (≥ 10%)	**Common** (≥ 1% - < 10%)	**Very Common** (≥ 10%)
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
NCI-CTC = National Cancer Institute - Common Toxicity Criteria

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

Data presented in Table 2 are based on the experience with the recommended dose of bevacizumab in 788 patients treated with irinotecan/5-fluorouracil/leucovorin (IFL) in Study AVF2107g.

Table 2. 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* + bevacizumab (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%)
Gastrointestinal Disorders		
Abdominal pain NOS	20 (5.1%)	28 (7.1%)
Diarrhea NOS	98 (24.7%)	127(32.4%)
General Disorders & Administration Site Conditions		
Pain NOS	12 (3.0%)	20 (5.1%)
Vascular Disorders		
Thromboembolism (Arterial)**	3 (0.8%)	12 (3.1%)
Deep Vein Thrombosis	25 (6.3%)	35 (8.9%)

* IFL = irinotecan/5-fluorouracil/leucovorin (see Table 4 for treatment regimen)
** This represents a pooled list of thromboembolic events of arterial origin including myocardial infarction, cerebrovascular accident, transient ischemic 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-fluorouracil/leucovorin (5-FU/LV) + bevacizumab combination (Arm 3) and concurrently enrolled patients in IFL + placebo arm (Arm 1) and IFL + bevacizumab arm (Arm 2) is shown in Table 3.

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

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

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

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

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

MedDRA System Organ Class Adverse Event	Arm 1 5-FU/LV + Placebo (n = 104)	Arm 2 5-FU/LV + bevacizumab (n = 100)
Subjects with at least one adverse event	74 (71.2%)	87 (87.0%)
Cardiac Disorders		
Hypertension	3 (2.9%)	16 (16.0%)
General Disorders & Administration Site Conditions		
Asthenia	12 (11.5%)	17 (17.0%)
Pain NOS	2 (1.9%)	6 (6.0%)
Infections & Infestations		
Abscess	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 ischemia 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.
5-FU/LV = 5-fluorouracil/leucovorin

Table 5. Adverse Events of all Grades (NCI-CTC) during Randomized Therapy (Events with ≥ 10% Higher Incidence in Arm 2 compared to Arm 1) in Study AVF2192g

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

Note: Data are unadjusted for the differential time on treatment.
Median duration of safety observation was 23 weeks for Arm 1 and 31 weeks for Arm 2.
5-FU/LV = 5-fluorouracil/leucovorin

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

Table 6. All NCI−CTC Grade 3−5 Non−Hematologic* and Grade 4−5 Hematologic* Adverse Events (ie, regardless of drug relationship) Occurring in ≥ 1% of Patients in Study E4599 (NSCLC)

Toxicity Category and Term	Control Arm Carboplatin/Paclitaxel (n = 441)	Treatment Arm Bevacizumab + Carboplatin/Paclitaxel (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%)

Table 6. All NCI−CTC Grade 3−5 Non−Hematologic* and Grade 4−5 Hematologic* Adverse Events (ie, regardless of drug relationship) Occurring in ≥ 1% of Patients in Study E4599 (NSCLC)

Toxicity Category and Term	Control Arm Carboplatin/Paclitaxel (n = 441)	Treatment Arm Bevacizumab + Carboplatin/Paclitaxel (n = 427)
Infection-Other	1 (0.2%)	5 (1.2%)
Neurology		
Neuropathy−Sensory	48 (10.9%)	39 (9.1%)
Dizziness / Lightheadedness	8 (1.8%)	14 (3.3%)
Confusion	10 (2.3%)	11 (2.6%)
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%)
Musculoskeletal		
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 7 below includes adverse events that occurred with ≥ 2% increased frequency in the bevacizumab group over the control arm.

Table 7. Adverse Events That Occurred with ≥ 2% Difference in Rates between Treatment Arms: Treated Patients, Study E4599 (NSCLC)

NCI-CTC Category Term[a]	No. (%) of Patients	
	Control Arm Carboplatin / Paclitaxel (n = 441)	Treatment Arm 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%)

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 8. Adverse Events (ie, 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)
Body as a Whole			
Asthenia	22 (68.8%)	24 (75.0%)	26 (76.5%)
Headache	3 (9.4%)	10 (31.3%)	16 (47.1%)
Pain	13 (40.6%)	13 (40.6%)	14 (41.2%)
Chest Pain	9 (28.1%)	6 (18.8%)	12 (35.3%)
Infection	8 (25.0%)	10 (31.3%)	12 (35.3%)
Fever	4 (12.5%)	11(34.4%)	11 (32.4%)
Abdominal Pain	3 (9.4%)	4 (12.5%)	8 (23.5%)
Back Pain	2 (6.3%)	5 (15.6%)	4 (11.8%)
Chills	3 (9.4%)	4 (12.5%)	4 (11.8%)
Reaction Unevaluable	1 (3.1%)	4 (12.5%)	0 (0.0%)
Moniliasis	0 (0.0%)	0 (0.0%)	3 (8.8%)
Cellulitis	0 (0.0%)	2 (6.3%)	2 (5.9%)
Abscess	0 (0.0%)	0 (0.0%)	2 (5.9%)
Accidental Injury	1 (3.1%)	1 (3.1%)	2 (5.9%)
Mucous Membrane Disorder	2 (6.3%)	1 (3.1%)	2 (5.9%)
Allergic Reaction	2 (6.3%)	1 (3.1%)	0 (0.0%)
Cardiovascular			
Hypertension	1 (3.1%)	5 (15.6%)	6 (17.6%)
Hemorrhage	0 (0.0%)	4 (12.5%)	0 (0.0%)
Hypotension	1 (3.1%)	4 (12.5%)	3 (8.8%)
Vasodilatation	3 (9.4%)	4 (12.5%)	4 (11.8%)
Syncope	2 (6.3%)	2 (6.3%)	4 (11.8%)
Cerebrovascular Accident	0 (0.0%)	0 (0.0%)	2 (5.9%)
Deep Thrombophlebitis	0 (0.0%)	1 (3.1%)	2 (5.9%)
Phlebitis	1 (3.1%)	0 (0.0%)	2 (5.9%)
Tachycardia	1 (3.1%)	1 (3.1%)	2 (5.9%)
Thrombosis	0 (0.0%)	0 (0.0%)	2 (5.9%)
Heart Arrest	2 (6.3%)	0 (0.0%)	0 (0.0%)
Digestive			
Nausea	15 (46.9%)	16 (50.0%)	17 (50.0%)
Anorexia	8 (25.0%)	9 (28.1%)	14 (41.2%)
Constipation	13 (40.6%)	13 (40.6%)	14 (41.2%)
Diarrhea	6 (18.8%)	9 (28.1%)	14 (41.2%)
Dyspepsia	7 (21.9%)	8 (25.0%)	6 (17.6%)
Stomatitis	3 (9.4%)	5 (15.6%)	8 (23.5%)
Vomiting	6 (18.8%)	6 (18.8%)	8 (23.5%)
Oral Moniliasis	0 (0.0%)	3 (9.4%)	1 (2.9%)

Table 8. Adverse Events (ie, 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)
Dysphagia	2 (6.3%)	1 (3.1%)	3 (8.8%)
Flatulence	2 (6.3%)	1 (3.1%)	3 (8.8%)
Rectal Disorder	0 (0.0%)	0 (0.0%)	3 (8.8%)
Nausea and Vomiting	0 (0.0%)	2 (6.3%)	0 (0.0%)
Cheilitis	0 (0.0%)	0 (0.0%)	2 (5.9%)
Liver Function Tests Abnormal	1 (3.1%)	1 (3.1%)	2 (5.9%)
Rectal Hemorrhage	1 (3.1%)	1 (3.1%)	2 (5.9%)
Ulcerative Stomatitis	0 (0.0%)	0 (0.0%)	2 (5.9%)
Hemic and Lymphatic			
Leukopenia	10 (31.3%)	15 (46.9%)	19 (55.9%)
Anemia	7 (21.9%)	6 (18.8%)	10 (29.4%)
Thrombocytopenia	5 (15.6%)	2 (6.3%)	7 (20.6%)
Ecchymosis	0 (0.0%)	0 (0.0%)	4 (11.8%)
Hypochromic Anemia	1 (3.1%)	1 (3.1%)	2 (5.9%)
Metabolic/Nutrition			
Peripheral Edema	6 (18.8%)	7 (21.9%)	5 (14.7%)
Hyperglycemia	3 (9.4%)	4 (12.5%)	7 (20.6%)
Weight Loss	0 (0.0%)	2 (6.3%)	6 (17.6%)
Alkaline Phosphatase Increased	1 (3.1%)	0 (0.0%)	3 (8.8%)
Dehydration	2 (6.3%)	1 (3.1%)	3 (8.8%)
Hypocalcemia	1 (3.1%)	2 (6.3%)	1 (2.9%)
Edema	0 (0.0%)	1 (3.1%)	2 (5.9%)
SGOT Increased	1 (3.1%)	0 (0.0%)	2 (5.9%)
SGPT Increased	2 (6.3%)	0 (0.0%)	2 (5.9%)
Musculoskeletal			
Arthralgia	16 (50.0%)	17 (53.1%)	14 (41.2%)
Myalgia	16 (50.0%)	9 (28.1%)	9 (26.5%)
Arthritis	2 (6.3%)	4 (12.5%)	0 (0.0%)
Bone Pain	0 (0.0%)	3 (9.4%)	2 (5.9%)
Leg Cramps	1 (3.1%)	1 (3.1%)	3 (8.8%)
Myasthenia	2 (6.3%)	1 (3.1%)	3 (8.8%)
Nervous			
Peripheral Neuritis	9 (28.1%)	8 (25.0%)	13 (38.2%)
Paresthesia	7 (21.9%)	9 (28.1%)	12 (35.3%)
Insomnia	14 (43.8%)	8 (25.0%)	5 (14.7%)
Depression	2 (6.3%)	5 (15.6%)	8 (23.5%)

Table 8. Adverse Events (ie, 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)
Anxiety	4 (12.5%)	3 (9.4%)	7 (20.6%)
Confusion	0 (0.0%)	2 (6.3%)	5 (14.7%)
Dizziness	4 (12.5%)	4 (12.5%)	5 (14.7%)
Neuropathy	9 (28.1%)	4 (12.5%)	5 (14.7%)
Somnolence	1 (3.1%)	0 (0.0%)	4 (11.8%)
Agitation	0 (0.0%)	2 (6.3%)	0 (0.0%)
Nervousness	2 (6.3%)	2 (6.3%)	2 (5.9%)
Amnesia	0 (0.0%)	0 (0.0%)	2 (5.9%)
Ataxia	1 (3.1%)	0 (0.0%)	2 (5.9%)
Emotional Lability	0 (0.0%)	1 (3.1%)	2 (5.9%)
Respiratory			
Cough Increased	8 (25.0%)	12 (37.5%)	17 (50.0%)
Epistaxis	2 (6.3%)	10 (31.3%)	15 (44.1%)
Dyspnea	11 (34.4%)	14 (43.8%)	14 (41.2%)
Hemoptysis	2 (6.3%)	9 (28.1%)	4 (11.8%)
Pharyngitis	3 (9.4%)	5 (15.6%)	9 (26.5%)
Rhinitis	0 (0.0%)	8 (25.0%)	7 (20.6%)
Voice Alteration	0 (0.0%)	5 (15.6%)	8 (23.5%)
Sinusitis	1 (3.1%)	3 (9.4%)	7 (20.6%)
Lung Disorder	3 (9.4%)	6 (18.8%)	6 (17.6%)
Bronchitis	1 (3.1%)	3 (9.4%)	4 (11.8%)
Hiccup	1 (3.1%)	2 (6.3%)	2 (5.9%)
Pleural Effusion	0 (0.0%)	2 (6.3%)	0 (0.0%)
Pneumonia	2 (6.3%)	2 (6.3%)	1 (2.9%)
Asthma	2 (6.3%)	1 (3.1%)	2 (5.9%)
Skin and Appendages			
Alopecia	17 (53.1%)	20 (62.5%)	22 (64.7%)
Rash	3 (9.4%)	11 (34.4%)	8 (23.5%)
Pruritus	0 (0.0%)	5 (15.6%)	2 (5.9%)
Sweating	3 (9.4%)	4 (12.5%)	4 (11.8%)
Acne	1 (3.1%)	0 (0.0%)	4 (11.8%)
Special Senses			
Taste Perversion	1 (3.1%)	3 (9.4%)	2 (5.9%)
Amblyopia	2 (6.3%)	0 (0.0%)	3 (8.8%)
Ear Pain	2 (6.3%)	1 (3.1%)	3 (8.8%)
Tinnitus	1 (3.1%)	2 (6.3%)	1 (2.9%)

Table 8. Adverse Events (ie, 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)
Urogenital			
Urinary Tract Infection	0 (0.0%)	1 (3.1%)	5 (14.7%)
Cystitis	0 (0.0%)	0 (0.0%)	3 (8.8%)
Urinary Incontinence	1 (3.1%)	0 (0.0%)	2 (5.9%)
Urinary Frequency	3 (9.4%)	0 (0.0%)	0 (0.0%)

*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 9. 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 (68.8%)	24 (75.0%)	26 (76.5%)
Headache	3 (9.4%)	10 (31.3%)	16 (47.1%)
Chest Pain	9 (28.1%)	6 (18.8%)	12 (35.3%)
Infection	8 (25.0%)	10 (31.3%)	12 (35.3%)
Fever	4 (12.5%)	11 (34.4%)	11 (32.4%)
Abdominal Pain	3 (9.4%)	4 (12.5%)	8 (23.5%)
Back Pain	2 (6.3%)	5 (15.6%)	4 (11.8%)
Reaction Unevaluable	1 (3.1%)	4 (12.5%)	0 (0.0%)
Moniliasis	0 (0.0%)	0 (0.0%)	3 (8.8%)
Cellulitis	0 (0.0%)	2 (6.3%)	2 (5.9%)
Abscess	0 (0.0%)	0 (0.0%)	2 (5.9%)
Cardiovascular			
Hypertension	1 (3.1%)	5 (15.6%)	6 (17.6%)
Hemorrhage	0 (0.0%)	4 (12.5%)	0 (0.0%)
Hypotension	1 (3.1%)	4 (12.5%)	3 (8.8%)
Syncope	2 (6.3%)	2 (6.3%)	4 (11.8%)
Cerebrovascular Accident	0 (0.0%)	0 (0.0%)	2 (5.9%)
Deep Thrombophlebitis	0 (0.0%)	1 (3.1%)	2 (5.9%)
Thrombosis	0 (0.0%)	0 (0.0%)	2 (5.9%)
Digestive			
Anorexia	8 (25.0%)	9 (28.1%)	14 (41.2%)
Diarrhea	6 (18.8%)	9 (28.1%)	14 (41.2%)
Stomatitis	3 (9.4%)	5 (15.6%)	8 (23.5%)
Vomiting	6 (18.8%)	6 (18.8%)	8 (23.5%)
Oral Moniliasis	0 (0.0%)	3 (9.4%)	1 (2.9%)

Table 9. 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)
Rectal Disorder	0 (0.0%)	0 (0.0%)	3 (8.8%)
Nausea and Vomiting	0 (0.0%)	2 (6.3%)	0 (0.0%)
Cheilitis	0 (0.0%)	0 (0.0%)	2 (5.9%)
Ulcerative Stomatitis	0 (0.0%)	0 (0.0%)	2 (5.9%)
Hemic and Lymphatic			
Leukopenia	10 (31.3%)	15 (46.9%)	19 (55.9%)
Anemia	7 (21.9%)	6 (18.8%)	10 (29.4%)
Thrombocytopenia	5 (15.6%)	2 (6.3%)	7 (20.6%)
Ecchymosis	0 (0.0%)	0 (0.0%)	4 (11.8%)
Metabolic/Nutrition			
Hyperglycemia	3 (9.4%)	4 (12.5%)	7 (20.6%)
Weight Loss	0 (0.0%)	2 (6.3%)	6 (17.6%)
Alkaline Phosphatase Increased	1 (3.1%)	0 (0.0%)	3 (8.8%)
Edema	0 (0.0%)	1 (3.1%)	2 (5.9%)
Musculoskeletal			
Arthritis	2 (6.3%)	4 (12.5%)	0 (0.0%)
Bone Pain	0 (0.0%)	3 (9.4%)	2 (5.9%)
Leg Cramps	1 (3.1%)	1 (3.1%)	3 (8.8%)
Nervous			
Peripheral Neuritis	9 (28.1%)	8 (25.0%)	13 (38.2%)
Paresthesia	7 (21.9%)	9 (28.1%)	12 (35.3%)
Depression	2 (6.3%)	5 (15.6%)	8 (23.5%)
Anxiety	4 (12.5%)	3 (9.4%)	7 (20.6%)
Confusion	0 (0.0%)	2 (6.3%)	5 (14.7%)
Somnolence	1 (3.1%)	0 (0.0%)	4 (11.8%)
Agitation	0 (0.0%)	2 (6.3%)	0 (0.0%)
Amnesia	0 (0.0%)	0 (0.0%)	2 (5.9%)
Emotional Lability	0 (0.0%)	1 (3.1%)	2 (5.9%)
Respiratory			
Cough Increased	8 (25.0%)	12 (37.5%)	17 (50.0%)
Epistaxis	2 (6.3%)	10 (31.3%)	15 (44.1%)
Dyspnea	11 (34.4%)	14 (43.8%)	14 (41.2%)
Hemoptysis	2 (6.3%)	9 (28.1%)	4 (11.8%)
Pharyngitis	3 (9.4%)	5 (15.6%)	9 (26.5%)
Rhinitis	0 (0.0%)	8 (25.0%)	7 (20.6%)
Voice Alteration	0 (0.0%)	5 (15.6%)	8 (23.5%)
Sinusitis	1 (3.1%)	3 (9.4%)	7 (20.6%)
Lung Disorder	3 (9.4%)	6 (18.8%)	6 (17.6%)
Bronchitis	1 (3.1%)	3 (9.4%)	4 (11.8%)
Pleural Effusion	0 (0.0%)	2 (6.3%)	0 (0.0%)

Table 9. 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)
Skin and Appendages			
Alopecia	17 (53.1%)	20 (62.5%)	22 (64.7%)
Rash	3 (9.4%)	11 (34.4%)	8 (23.5%)
Pruritus	0 (0.0%)	5 (15.6%)	2 (5.9%)
Acne	1 (3.1%)	0 (0.0%)	4 (11.8%)
Special Senses			
Taste Perversion	1 (3.1%)	3 (9.4%)	2 (5.9%)
Urogenital			
Urinary Tract Infection	0 (0.0%)	1 (3.1%)	5 (14.7%)
Cystitis	0 (0.0%)	0 (0.0%)	3 (8.8%)

***** 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 bevacizumab groups over the active control group.

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Table 10. All Treatment-Related Adverse Events with a Frequency of ≥ 1% for both Treatment Arms in Study AVF4095g

Toxicity Category and Term	Control Arm Carboplatin + Gemcitabine + Placebo (n=233)	Treatment Arm Carboplatin + Gemcitabine + Bevacizumab (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 10. All Treatment-Related Adverse Events with a Frequency of ≥ 1% for both Treatment Arms in Study AVF4095g

Toxicity Category and Term	Control Arm Carboplatin + Gemcitabine + Placebo (n=233)	Treatment Arm Carboplatin + Gemcitabine + Bevacizumab (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%)

Table 10. All Treatment-Related Adverse Events with a Frequency of ≥ 1% for both Treatment Arms in Study AVF4095g

Toxicity Category and Term	Control Arm Carboplatin + Gemcitabine + Placebo (n=233)	Treatment Arm Carboplatin + Gemcitabine + Bevacizumab (n=247)
Myalgia	5 (2.1%)	9 (3.6%)
Pain In Extremity	4 (1.7%)	10 (4.0%)
Nervous System Disorders		
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%)
Dyspnea	7 (3.0%)	10 (4.0%)
Dyspnea 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%)
Rhinorrhea	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%)

Table 10. All Treatment-Related Adverse Events with a Frequency of ≥ 1% for both Treatment Arms in Study AVF4095g

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

The most frequent (≥ 20%) adverse events observed in the bevacizumab 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 bevacizumab 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 bevacizumab 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 11. Treatment-Emergent Adverse Events Occurring in ≥2% of Platinum-Sensitive Recurrent Ovarian Cancer Patients Treated with bevacizumab + Chemotherapy Compared to Those Treated with Chemotherapy Alone in Study AVF4095g

Toxicity Category and Term	Control Arm Carboplatin + Gemcitabine + Placebo (n=233)	Treatment Arm Carboplatin + Gemcitabine + Bevacizumab (n=247)
Blood And Lymphatic System Disorders		
Thrombocytopenia	119 (51.1%)	143 (57.9%)
Gastrointestinal Disorders		
Diarrhea	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%)
Hemorrhoids	6 (2.6%)	19 (7.7%)
Nausea	153 (65.7%)	179 (72.5%)
Oral Pain	3 (1.3%)	13 (5.3%)
Rectal Hemorrhage	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%)

Table 11. Treatment-Emergent Adverse Events Occurring in ≥2% of Platinum-Sensitive Recurrent Ovarian Cancer Patients Treated with bevacizumab + Chemotherapy Compared to Those Treated with Chemotherapy Alone in Study AVF4095g

Toxicity Category and Term	Control Arm Carboplatin + Gemcitabine + Placebo (n=233)	Treatment Arm Carboplatin + Gemcitabine + Bevacizumab (n=247)
Investigations		
Blood Pressure Increased	(0.0%)	7 (2.8%)
Hemoglobin Decreased	21 (9.0%)	30 (12.1%)
Metabolism And Nutrition Disorders		
Hyperglycemia	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%)
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%)

Table 11. Treatment-Emergent Adverse Events Occurring in ≥2% of Platinum-Sensitive Recurrent Ovarian Cancer Patients Treated with bevacizumab + Chemotherapy Compared to Those Treated with Chemotherapy Alone in Study AVF4095g

Toxicity Category and Term	Control Arm Carboplatin + Gemcitabine + Placebo (n=233)	Treatment Arm Carboplatin + Gemcitabine + Bevacizumab (n=247)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	43 (18.5%)	64 (25.9%)
Dysphonia	8 (3.4%)	33 (13.4%)
Dyspnea	56 (24.0%)	74 (30.0%)
Epistaxis	33 (14.2%)	135 (54.7%)
Oropharyngeal Pain	23 (9.9%)	40 (16.2%)
Rhinorrhea	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 12. All Treatment−Related Adverse Events with a Frequency of ≥ 1% in either Treatment Arms in Study M022224

System Organ Class/ Preferred Term	Control Arm Chemotherapy (n = 181)	Treatment Arm Chemotherapy + Bevacizumab (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%)
Esophagitis	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 12. All Treatment−Related Adverse Events with a Frequency of ≥ 1% in either Treatment Arms in Study M022224

System Organ Class/ Preferred Term	Control Arm Chemotherapy (n = 181)	Treatment Arm Chemotherapy + Bevacizumab (n = 179)
Localized 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%)
Dyspnea	0 (0.0%)	3 (1.7%)
Pulmonary Embolism	2 (1.1%)	3 (1.7%)
Skin and Subcutaneous Tissue Disorders		
Palmar−Plantar Erythrodysesthesia 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%)
Rash	1 (0.6%)	4 (2.2%)

Table 12. All Treatment−Related Adverse Events with a Frequency of ≥ 1% in either Treatment Arms in Study M022224

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

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

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

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

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

Among patients initially randomized to chemotherapy alone, 72 (40%) crossed over to receive single-agent bevacizumab after progression of disease. Median duration of bevacizumab monotherapy in this subgroup was 11.6 weeks (0 - 55 week range). Grade 3–5 adverse events occurred in 19/72 patients (26.4%). Sixteen patients (22.2%) experienced Grade 3 adverse events. Two patients (2.8%) experienced Grade 4 adverse events (transient ischemic attack and PRES). One patient (1.4%) experienced a Grade 5 GI hemorrhage.

Table 13. Treatment-Emergent Adverse Events Occurring in ≥ 2% of Platinum-Resistant Recurrent Ovarian Cancer Patients Treated with bevacizumab + Chemotherapy Compared to those Treated with Chemotherapy Alone (by chemotherapy cohort) in Study M022224

System Organ Class / Preferred Term	Control Arm Paclitaxel + Placebo (n = 55)	Treatment Arm Paclitaxel + Bevacizumab (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		
Hyperbilirubinemia	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%)
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%)

Table 13. Treatment-Emergent Adverse Events Occurring in ≥ 2% of Platinum-Resistant Recurrent Ovarian Cancer Patients Treated with bevacizumab + Chemotherapy Compared to those Treated with Chemotherapy Alone (by chemotherapy cohort) in Study M022224

System Organ Class / Preferred Term	Control Arm Paclitaxel + Placebo (n = 55)	Treatment Arm Paclitaxel + Bevacizumab (n = 60)
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%)
Paresthesia	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%)
Dyspnea	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		
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%)

Table 13. Treatment-Emergent Adverse Events Occurring in ≥ 2% of Platinum-Resistant Recurrent Ovarian Cancer Patients Treated with bevacizumab + Chemotherapy Compared to those Treated with Chemotherapy Alone (by chemotherapy cohort) in Study M022224

System Organ Class / Preferred Term	Control Arm Paclitaxel + Placebo (n = 55)	Treatment Arm Paclitaxel + Bevacizumab (n = 60)
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 Erythrodysesthesia Syndrome	8 (12.7%)	17 (27.4%)
Erythema	1 (1.6%)	4 (6.5%)
Dermatitis	2 (3.2%)	0 (0.0%)
Vascular Disorders		
Hypertension	4 (6.3%)	19 (30.6%)
Venous Thrombosis	0 (0.0%)	2 (3.2%)
Blood and Lymphatic System Disorders		
Neutropenia	25 (39.7%)	21 (36.8%)
Anemia	30 (47.6%)	17 (29.8%)
Leukopenia	13 (20.6%)	9 (15.8%)
Thrombocytopenia	12 (19.0%)	8 (14.0%)
Gastrointestinal Disorders		
Abdominal Pain	6 (9.5%)	7 (12.3%)
Nausea	3 (4.8%)	7 (12.3%)
Diarrhea	1 (1.6%)	6 (10.5%)

Table 13. Treatment-Emergent Adverse Events Occurring in ≥ 2% of Platinum-Resistant Recurrent Ovarian Cancer Patients Treated with bevacizumab + Chemotherapy Compared to those Treated with Chemotherapy Alone (by chemotherapy cohort) in Study M022224

System Organ Class / Preferred Term	Control Arm Paclitaxel + Placebo (n = 55)	Treatment Arm Paclitaxel + Bevacizumab (n = 60)
Constipation	7 (11.1%)	5 (8.8%)
Vomiting	7 (11.1%)	5 (8.8%)
Subileus	3 (4.8%)	4 (7.0%)
Abdominal Pain Upper	2 (3.2%)	3 (5.3%)
Ileus	0 (0.0%)	3 (5.3%)
Intestinal Obstruction	0 (0.0%)	2 (3.5%)
Toothache	0 (0.0%)	2 (3.5%)
Ascites	4 (6.3%)	1 (1.8%)
Abdominal Distension	3 (4.8%)	0 (0.0%)
General Disorders and Administration Site Conditions		
Fatigue	12 (19.0%)	14 (24.6%)
General Physical Health Deterioration	0 (0.0%)	2 (3.5%)
Mucosal Inflammation	3 (4.8%)	1 (1.8%)
Pyrexia	5 (7.9%)	1 (1.8%)
General Symptom	2 (3.2%)	0 (0.0%)
Infections and Infestations		
Infection	4 (6.3%)	8 (14.0%)
Urinary Tract Infection	6 (9.5%)	4 (7.0%)
Nasopharyngitis	0 (0.0%)	2 (3.5%)
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		
Dyspnea	4 (6.3%)	6 (10.5%)
Cough	0 (0.0%)	2 (3.5%)

PLD = pegylated liposomal doxorubicin

Malignant Glioma (WHO Grade IV)- Glioblastoma

Table 14. 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 Lomustine (n = 147)	Treatment Arm Bevacizumab + Lomustine (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%)
Diarrhea	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 (0.0%)	6 (2.2%)
Mouth Hemorrhage	0 (0.0%)	5 (1.8%)
Gastroesophageal Reflux Disease	2 (1.4%)	2 (0.7%)
Esophageal Pain	0 (0.0%)	4 (1.4%)
Dyspepsia	2 (1.4%)	1 (0.4%)
Hemorrhoids	0 (0.0%)	3 (1.1%)
Rectal Hemorrhage	0 (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%)
Edema Peripheral	2 (1.4%)	4 (1.4%)
Pyrexia	0 (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 (0.0%)	4 (1.4%)
Upper Respiratory Tract Infection	0 (0.0%)	3 (1.1%)
Injury, Poisoning and Procedural Complications		
Wound Complication	0 (0.0%)	5 (1.8%)
Wound Dehiscence	0 (0.0%)	4 (1.4%)
Investigations		
Weight Decreased	2 (1.4%)	9 (3.2%)
Gamma−Glutamyltransferase Increased	2 (1.4%)	3 (1.1%)

Table 14. 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 Lomustine (n = 147)	Treatment Arm Bevacizumab + Lomustine (n = 278)
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 (0.0%)	3 (1.1%)
Nervous System Disorders		
Headache	3 (2.0%)	12 (4.3%)
Peripheral Sensory Neuropathy	1 (0.7%)	11 (4.0%)
Dysgeusia	0 (0.0%)	7 (2.5%)
Dizziness	1 (0.7%)	5 (1.8%)
Hemorrhage Intracranial	0 (0.0%)	5 (1.8%)
Peripheral Motor Neuropathy	1 (0.7%)	3 (1.1%)
Respiratory, Thoracic and Mediastinal Disorders		
Epistaxis	1 (0.7%)	34 (12.2%)
Pulmonary Embolism	0 (0.0%)	13 (4.7%)
Dysphonia	0 (0.0%)	9 (3.2%)
Dyspnea	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 (0.0%)
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 (0.0%)	5 (1.8%)
Dermatitis Acneiform	0 (0.0%)	3 (1.1%)
Erythema	2 (1.4%)	0 (0.0%)
Vascular Disorders		
Hypertension	2 (1.4%)	65 (23.4%)
Embolism	0 (0.0%)	10 (3.6%)

All adverse events were collected in 425 patients enrolled in Study EORTC 26101 who received either lomustine alone or bevacizumab plus lomustine. All patients involved in the study had experienced first progression after radiation therapy concurrent/adjuvant chemotherapy for glioblastoma multiforme (GBM). Of patients who discontinued any study treatment due to adverse events, there were 21.9% in the bevacizumab plus lomustine arm, compared with 10.2% of patients in the lomustine arm. In patients receiving bevacizumab plus

lomustine (N=278), the most frequently reported adverse events (regardless of drug relationship) of any grade (≥20%) were fatigue (61.9%), hypertension (33.1%), headache (31.7%), nausea (24.5%) and seizures (23.7%). The most frequently reported adverse events of grade ≥ 3 and with an incidence rate of at least 2 % were hypertension (15.1%), seizure (6.1%), fatigue (5.0%), pulmonary embolism (4.7%), dyspnea (2.2%) and lung infection (2.2%).

9.3 Less Common Clinical Trial Adverse Reactions

Listing 1 Less Common NCI−CTC Grade 3−5 Non−Hematologic and Grade 4−5 Hematologic Clinical Trial Adverse Events (< 1%) in Study E4599 [NSCLC] 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.

Musculoskeletal: 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 [NSCLC] 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.

9.4 Further Information on Selected, Serious Adverse Drug Reactions

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

Cardiovascular

Hypertension **(see WARNINGS AND PRECAUTIONS)**

An increased incidence of hypertension (all Grades) of up to 43.7% has been observed in patients treated with bevacizumab compared with up to 14% in the comparator arm. In clinical trials across all indications the overall incidence of NCI-CTC Grade 3 and 4 hypertension in patients receiving bevacizumab ranged from 3.0% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of patients treated with bevacizumab compared to up to 0.2% patients treated with the same chemotherapy alone. The incidence of hypertension in platinum-sensitive ovarian cancer patients was greater in the bevacizumab 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 bevacizumab 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 bevacizumab or hospitalization. Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal. MVASI should be permanently discontinued in patients who develop hypertensive encephalopathy. Hypertensive encephalopathy is a complication of malignant hypertension. Signs and symptoms may include severe hypertension associated with headache, nausea, vomiting, convulsions, or confusion. Hypertensive encephalopathy may be reversible if treated by progressively reducing blood pressure to near normal ranges within several hours.

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

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. One patient in the treatment arm experienced Grade 3 PRES and 1 patient in the monotherapy crossover arm experienced Grade 4 PRES.

Thromboembolism (see **WARNINGS AND PRECAUTIONS**)

Arterial Thromboembolism

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

In clinical trials, the overall incidence ranged up to 5.9% in the bevacizumab containing arms and up to 1.7% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving bevacizumab in combination with chemotherapy compared to 0.5% of patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischemic attacks) were reported in up to 2.3% of bevacizumab treated patients versus 0.5% of patients in the control group: myocardial infarction was reported in 1.4% of bevacizumab treated versus 0.7% of patients in the observed control group.

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

In the study AVF4095g, 2.4% of the patients treated with bevacizumab 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 bevacizumab arm versus 0.0% in the chemotherapy arm). One patient in the bevacizumab 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 bevacizumab plus lomustine arm and the lomustine arm (11.5% vs. 10.9%). The most commonly reported ATE events (in > 1% of patients in either treatment arm) were hemiparesis (19 patients [6.8%] in the bevacizumab plus lomustine arm vs. 11 [7.5%] in the lomustine arm) and embolism (11 [4.0%] vs. 3 [2.0%]).

Venous Thromboembolism

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

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

In the study AVF4095g, 8.1% of the patients treated with bevacizumab 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 bevacizumab-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 MVASI in combination with chemotherapy versus chemotherapy alone.

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

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

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

In clinical trials with bevacizumab, 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 bevacizumab arm (2.0%) compared with the control arm (0.9%), and 12.6% of patients in the bevacizumab 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 bevacizumab in combination with capecitabine compared with 0.5% in patients treated with capecitabine alone. In study E2100, the incidence of CHF Grade 3 or higher was 2.2% in patients treated with bevacizumab in combination with paclitaxel compared with 0.3% in patients treated with paclitaxel. In study BO17708, the

incidence of CHF Grade 3 or higher ranged from 0 to 1.2% in patients treated with bevacizumab in combination with docetaxel compared to 0% in the docetaxel arm. In study AVF3694g, the incidence of CHF Grade 3 or higher was 2.0% in patients treated with bevacizumab in combination with taxanes, vs. 0% for taxanes alone, 2.9% for patients treated with bevacizumab plus anthracyclines vs. 0% for anthracyclines alone, and 1% for patients treated with bevacizumab plus capecitabine compared to 0.5% in patients treated with capecitabine alone.

Most patients showed improved symptoms and/or left ventricular function following appropriate medical therapy. In most clinical trials of bevacizumab, patients with pre-existing CHF of NYHA II – IV were excluded; therefore, no information is available on the risk of CHF in this population.

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

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

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

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

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer, 1.8% of bevacizumab treated patients and 1.4% of control patients were reported to have had non-gastrointestinal vaginal, vesical, or female genital tract fistulae. MVASI 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 (eg, tracheoesophageal, bronchopleural, and biliary fistulae) were observed across various indications. Fistulae have also been reported in post-marketing experience.

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

Gastrointestinal

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

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

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

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

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

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

A causal association of intra-abdominal inflammatory process and gastrointestinal perforation to bevacizumab has not been established.

Genitourinary

Ovarian Failure

The incidence of new cases of ovarian failure, defined as amenorrhea lasting 3 or more months, FSH level ≥ 30 mIU/mL and a negative serum β-HCG pregnancy test, has been evaluated in a substudy (see **WARNINGS AND PRECAUTIONS, Special Populations**). New cases of ovarian failure were reported more frequently in patients receiving bevacizumab (39.0% vs. 2.6%). Age did not seem to have an influence on development of an ovarian failure for patients randomized to the mFOLFOX6 (modified 5-fluorouracil/folinic acid, oxaliplatin) + bevacizumab arm compared with patients randomized to the mFOLFOX6 arm. Conclusions about age and risk of ovarian failure should be interpreted with caution, due to the small sample size of patients with ovarian failure in this substudy. After discontinuation of bevacizumab treatment, ovarian function recovered in a majority of women (86%). Long term effects of the treatment with bevacizumab on fertility are unknown.

Proteinuria (see **WARNINGS AND PRECAUTIONS**)

In clinical trials proteinuria was very common and has been reported in up to 38% of patients receiving bevacizumab. Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome. Grade 3 proteinuria was reported in up to 8.1% of treated patients, and Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4 % of treated patients. In the study AVF4095g, a higher proportion of patients in the bevacizumab 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 bevacizumab 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 bevacizumab in combination with chemotherapy experienced Grade ≥ 2 proteinuria. The Grade ≥ 2 proteinuria resolved in 74.2% (201 of 271) of patients. Bevacizumab was re-initiated in 41.7% (113 of 271) of patients. Of the 113 patients who re-initiated bevacizumab, 47.8% (54 of 113) experienced a second episode of Grade ≥2 proteinuria.

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

Hematologic

Hemorrhage (see **WARNINGS AND PRECAUTIONS**)

CNS Hemorrhage

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

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

Within 10 randomized controlled Phase III trials across the tumour indications advanced or metastatic colorectal cancer, renal cell cancer, non-small cell lung cancer, breast cancer and pancreatic cancer, representing a total of 8036 patients, the incidence of intracranial hemorrhage (all Grades)[6] 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 bevacizumab, compared to 0 to 4.5% of patients in the chemotherapy control group. The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumour-associated hemorrhage (see below) and minor mucocutaneous hemorrhage (eg, epistaxis).

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

Tumour-associated hemorrhage

Tumour associated hemorrhage was observed in bevacizumab studies. Major or massive pulmonary hemorrhage/hemoptysis has been observed primarily in studies in patients with non-small cell lung cancer. These events can occur suddenly and can present as major or massive pulmonary hemorrhage/hemoptysis. Possible risk factors include squamous cell histology, treatment with antirheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumour location and cavitation of tumours prior to or during therapy. The only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology. Patients with NSCLC of known squamous cell histology or mixed cell type with predominant squamous cell histology were excluded from subsequent studies, while patients with unknown tumour histology were included.

In patients with NSCLC excluding predominant squamous histology, all Grade pulmonary hemorrhage events were seen with a frequency of up to 9% when treated with bevacizumab plus chemotherapy compared with 5% in the patients treated with chemotherapy alone. Grade 3-5 pulmonary hemorrhage events have been observed in up to 2.3% of patients treated with bevacizumab plus chemotherapy as compared with <1% with chemotherapy alone. Grade 3-5

[6] 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.

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)[7] 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 bevacizumab clinical trials, mucocutaneous hemorrhages were seen in up to 50% of patients treated with bevacizumab. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any change in the bevacizumab treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous hemorrhage (eg, epistaxis) may be dose-dependent.

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

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

An increased rate of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia, in some cases with a fatal outcome, was identified for patients treated with some myelotoxic/myelosuppressive chemotherapy regimens in combination with bevacizumab compared to chemotherapy alone. These increases were seen mainly in patients with non-small cell lung cancer, from ECOG4599 treated with carboplatin + paclitaxel in combination with bevacizumab (26.2% in the bevacizumab containing arm vs. 17.2% in the chemotherapy arm), and also in combination with myelosuppressive chemotherapy agents used to treat metastatic colorectal cancer (19.7% in the bevacizumab arm vs. 13.6% in the chemotherapy arm of AVF2107g). In study AVF4095g, incidences of infection were reported at 58.3% (144/247) in the bevacizumab 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 bevacizumab clinical trials, the frequencies of patients experiencing death due to neutropenia and infection occurring within 21 days after last study treatment dose of bevacizumab were generally low. In metastatic colorectal carcinoma trials, the frequency of fatal cases of neutropenia and infection was 0.9% and 1.3% in patients treated with bevacizumab plus chemotherapy and treated with chemotherapy alone, respectively. Events occurring in the bevacizumab treated patients included sepsis, necrotizing fasciitis, peritoneal abscess, and peritonitis. In study AVF3708, a non-comparative trial that led to approval of bevacizumab in recurrent glioblastoma multiforme, 1 of 163 patients (0.6%) treated with bevacizumab died of neutropenic infection. In non-small cell lung carcinoma trials, the frequencies of patients experiencing death due to neutropenia and infection were 1.0% and 0.3% in patients treated with chemotherapy plus bevacizumab and chemotherapy only, respectively. Events occurring in

[7] 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.

the bevacizumab 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 bevacizumab arm, Grade 3-5 infection was 7.9%. Of the overall infection cases, one was fatal.

Thrombocytopenia

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

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

In Study AVF4095g, thrombocytopenia of any Grade (57.9%, 143/247) and Grade ≥ 3 (40.1%, 99/247) was observed with bevacizumab. 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 bevacizumab-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 bevacizumab arm versus 4.9 months in the chemotherapy arm, and time to resolution was longer in the bevacizumab arm (2.3 months) compared with that in the chemotherapy arm (0.8 months).

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

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

Infusion reactions reported in clinical trials and post-marketing experience include hypertension, hypertensive crises associated with neurologic signs and symptoms, wheezing, oxygen desaturation, Grade 3 hypersensitivity, chest pain, headaches, rigors, and diaphoresis. In study AVF4095g, anaphylactic and hypersensitivity reactions of any Grade were reported for a higher percentage of patients receiving bevacizumab 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 bevacizumab 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 bevacizumab was 3.3% and 3.4% in patients treated with bevacizumab + chemotherapy and in patients treated with chemotherapy alone respectively.

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

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

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

In a platinum-sensitive recurrent ovarian cancer trial, a total of five patients in the bevacizumab 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 hemorrhage in the bevacizumab arm and acute myocardial infarction in the chemotherapy arm). In the bevacizumab arm, additional causes of death occurring later than 21 days after the last bevacizumab study treatment dose included sepsis, respiratory failure, and unspecified adverse events. Furthermore, another patient in the bevacizumab arm and two patients in the chemotherapy arm died of unknown causes. In a platinum-resistant recurrent ovarian cancer trial, nine patients in the bevacizumab arm versus six patients in the chemotherapy arm died due to adverse events. In the bevacizumab + chemotherapy arm, the causes of death were aspiration pneumonia (2 patients), sepsis (2 patients), cardiac arrest, cardiopulmonary failure, gastrointestinal disorder, general physical health deterioration, and shock. In the chemotherapy arm, the causes of death were septic shock (2 patients), cardiac failure, multi-organ failure, peritonitis, and GI hemorrhage (latter occurred after the patient started crossover bevacizumab monotherapy).

Peri-Operative Conditions

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

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

Across metastatic colorectal cancer clinical trials there was no increased risk of post-operative bleeding or wound healing complications observed in patients who underwent major surgery between 28-60 days prior to starting bevacizumab therapy. An increased incidence of post-operative bleeding or wound healing complications occurring within 60 days of major surgery was observed, if the patient was being treated with bevacizumab at the time of surgery. The incidence varied between 10% (4/40) and 20% (3/15). 4/247 (1.6%) patients treated with bevacizumab 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 bevacizumab use, some of which had a fatal outcome (see **WARNINGS AND PRECAUTIONS, Peri-Operative Considerations,** Wound Healing).

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

Immunogenicity

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

Nasal Septum Perforations

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

Special Populations and Conditions

Gender:

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

Geriatrics:

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

In study AVF4095g, the safety profile of the bevacizumab in platinum-sensitive recurrent ovarian cancer patients, ≥ 65 years of age is consistent with the known overall safety profile of bevacizumab 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 bevacizumab as compared to those aged ≤ 65 years treated with bevacizumab.

9.5 Abnormal Hematologic and Clinical Chemistry Findings

Laboratory Abnormalities

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

Across clinical trials, the following Grade 3 and 4 laboratory abnormalities were seen with an increased (≥ 2%) incidence in patients treated with bevacizumab compared to those in the control groups: hyperglycemia, decreased hemoglobin, hypokalemia, hyponatremia, decreased white blood cell count, thrombocytopenia, increased PT prothrombin time and normalized 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 MVASI. The observed increase in serum creatinine was not associated with a higher incidence of clinical manifestations of renal impairment in patients treated with bevacizumab.

9.6 Post-Market Adverse Reactions

System Organ Class	Reactions (frequency)[1]
Body as a whole	Polyserositis
Gastrointestinal disorders	Gastrointestinal ulcer (frequency not known), intestinal necrosis, anastomotic ulceration
Cardiovascular	Mesenteric venous occlusion
Congenital, familial and genetic disorders	Cases of fetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see **WARNINGS AND PRECAUTIONS**).
Hepatobiliary disorders	Gallbladder perforation (frequency not known)
Immune system disorders	Hypersensitivity reactions, including anaphylactic reaction, infusion reactions (frequency not known); possibly associated with the following co-manifestations: dyspnea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting. (see **WARNINGS AND PRECAUTIONS**, and **ADVERSE REACTIONS**)
Nervous system disorders	Hypertensive encephalopathy (very rare) Posterior Reversible Encephalopathy Syndrome (PRES) (rare) (see **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 **WARNINGS AND PRECAUTIONS**, and **ADVERSE REACTIONS**) Arterial (including aortic) aneurysms, dissections, and rupture
Musculoskeletal and Connective Tissue disorders	Cases of Osteonecrosis of the Jaw (ONJ) have been observed in bevacizumab treated patients mainly in association with prior or concomitant use of bisphosphonates. Cases of osteonecrosis at sites other than the jaw, have been observed in bevacizumab treated pediatric patients (see **WARNINGS AND PRECAUTIONS, Pediatric**)**.
Infections and Infestations	Necrotizing fasciitis (rare), usually secondary to wound healing complications, gastrointestinal perforation or fistula formation (see **WARNINGS AND PRECAUTIONS**)

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

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

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

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

10 DRUG INTERACTIONS

10.1 Overview

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

10.2 Drug-Drug Interactions

In study AVF2107g, irinotecan concentrations were similar in patients receiving IFL (irinotecan/5-fluorouracil/leucovorin) alone and in combination with bevacizumab. Concentrations of SN38, the active metabolite of irinotecan, were analyzed in a subset of patients, ie, approximately 30 per treatment arms. Concentrations of SN38 were on average 33% higher in patients receiving IFL in combination with bevacizumab compared with IFL alone. Due to high inter-patient variability and limited sampling, it is unclear if the observed increase in SN38 levels was due to bevacizumab. There was a small increase in diarrhea and leukopenia adverse events (known adverse drug reactions of irinotecan), and also more dose reductions of irinotecan were reported in the patients treated with IFL + bevacizumab. Patients who develop severe diarrhea, leukopenia or neutropenia with MVASI and irinotecan combination therapy should have irinotecan dose modifications as specified in the irinotecan product information.

Sunitinib Malate

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

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

The safety and efficacy of MVASI 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.

Epidermal growth factor receptor (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 MVASI has not been established in approved indications.

11 ACTION AND CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Bevacizumab is a recombinant humanized monoclonal antibody that selectively binds to and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab contains human framework regions with antigen binding regions of a humanized murine antibody that binds to VEGF. Bevacizumab is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system and is purified by a process that includes specific viral inactivation and removal steps. Bevacizumab consists of 1320 amino acids and has a molecular weight of approximately 149 000 Daltons.

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

11.2 Pharmacodynamics

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

11.3 Pharmacokinetics

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

Distribution:

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

Metabolism:

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

Elimination:

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

albumin (≤ 29 g/dL) and high alkaline phosphatase (≥ 484 U/L) (both markers of disease severity), bevacizumab clearance was approximately 20% faster than in patients with median laboratory values.

Special Populations and Conditions

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

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

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

12 STORAGE, STABILITY AND DISPOSAL

Store vials in a refrigerator at 2ºC to 8ºC. Keep vial in the outer carton in order to protect from light.

Do not freeze. Do not shake.

MVASI does not contain any antimicrobial preservative; therefore, care must be taken to ensure the sterility of the prepared 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.

After aseptic dilution in IV bags containing 0.9% sodium chloride solution, chemical and physical in-use stability has been demonstrated for up to 35 days at 2°C to 8°C, followed by up to 48 hours at up to 30°C.

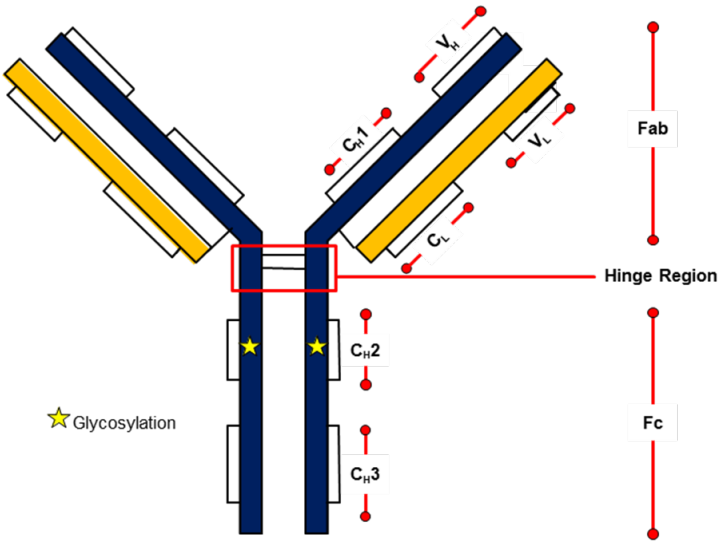
Disposal of unused/expired medicines

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	Bevacizumab for injection
Chemical name:	recombinant, humanized anti-VEGF monoclonal antibody
Molecular formula and molecular mass:	bevacizumab is a highly purified, approximately 149 000 dalton antibody that includes 1 320 amino acids.
Structural formula:	

Heavy chains are shown in blue and light chains are shown in orange

Black lines represent disulfide bonds.

VH is the variable domain of the heavy chain

CH1, CH2, and CH3 are the constant domains of the heavy chain

VL is the variable domain of the light chain

CL is the constant domain of the light chain

Physicochemical properties	Concentrate for solution for infusion: clear to slightly opalescent, colourless to yellow, sterile, pH 6.2 solution for intravenous infusion

14 COMPARATIVE CLINICAL TRIALS

14.1 Comparative Trial Design and Study Demographics

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

- A pivotal comparative pharmacokinetic (PK) phase 1 study in healthy subjects
- A pivotal comparative efficacy and safety study in subjects with locally advanced, metastatic or recurrent non-squamous NSCLC

A summary of the designs and subject demographics of the clinical studies is presented in Table 15.

Table 15. Trial Design and Study Demographics

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects and Gender	Healthy Subject or Diagnosis of Subjects
PK similarity	20110216	PK similarity, safety, and immunogenicity of MVASI compared with AVASTIN (US) and AVASTIN (EU), and bridging between AVASTIN (US) and AVASTIN (EU)	Phase 1 randomized, single-blind, single-dose, 3-arm, parallel-group study	MVASI vs AVASTIN (US) vs AVASTIN (EU) 3 mg/kg IV infusion Duration of treatment: Single dose; 85 days	202 (68 MVASI, 67 AVASTIN [US], 67 AVASTIN [EU]) Male: 202	Healthy male subjects between 18 to 45 years of age
Efficacy and Safety	20120265	Efficacy, safety, and immunogenicity of MVASI vs AVASTIN (EU)	Phase 3 randomized, double-blind, active-controlled study Patients were randomized 1:1 to receive 6 cycles of MVASI or AVASTIN in combination with platinum-based chemotherapy (Q3W paclitaxel [200 mg/m^2] and carboplatin [AUC=6.0] for 4 and up to 6 cycles	MVASI vs AVASTIN (EU) 15 mg/kg IV infusion every 3 weeks Duration of treatment: 19 weeks	642 (328 MVASI, 314 AVASTIN) Male: 384 Female: 258	Men and women ≥ 18 to < 80 years of age Stage IV/ recurrent non-squamous NSCLC; measurable disease per RECIST v1.1

AVASTIN (EU) = AVASTIN sourced from the European Union; AVASTIN (US) = AVASTIN sourced from the United States; CSR = clinical study report; IV = intravenous; NSCLC = non-small cell lung cancer; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumours.

14.2 Comparative Study Results

14.2.1 Comparative Bioavailability Studies

14.2.1.1 Pharmacokinetics

Comparative Pharmacokinetic Study

Study 20110216

This was a randomized, single-blind, single-dose, 3-arm, parallel group study in healthy adult male subjects. The primary objective of this study was to demonstrate the PK similarity of MVASI to AVASTIN (US) and AVASTIN (EU) assessed by the PK parameters AUC_{inf} and C_{max}.

In Study 20110216, 202 eligible subjects received a single 3 mg/kg dose of MVASI or AVASTIN (US or EU) in a ratio of 1:2. Subjects returned periodically for safety evaluations, PK sample collections and antidrug antibody (ADA) tests until Day 85.

Study Results

When comparing PK parameters of MVASI versus AVASTIN (EU), the point estimate for C_{max} was 103%, and the 90% confidence intervals (CIs) of the ratios of geometric means for AUC_{inf} and AUC_{last} were fully contained within the pre-defined bounds of 80% to 125%.

Table 16. Summary of Statistical Assessment of MVASI and AVASTIN (EU) Pharmacokinetic Parameters

Parameter (unit)	Geometric LS Mean		LS Mean Ratio	90% CI of the Ratio
	MVASI [N]	EU AVASTIN [N]		
AUC_{last} (mcg·h/mL)	28200 [62]	29400 [64]	96%	(92.0%, 100.4%)
AUC_{Inf} (mcg·h/mL)	29400 [66]	30600 [66]	96%	(91.6%, 100.6%)
C_{max} (mcg/mL)	87.2 [67]	84.7 [64]	103%	
T_{max} (h)	1.50 [67]	3.94 [64]		
$T_{1/2}$ (days)	17.7 [66]	18.5 [66]		

Abbreviations: CI = confidence interval; LS = least squares; N = number of subjects with evaluable parameters

14.2.2 Comparative Safety and Efficacy

14.2.2.1 Efficacy

Study 20120265: Non-small Cell Lung Cancer (NSCLC)

The study was a randomized, double-blind, active-controlled study in adult subjects with non-squamous NSCLC receiving first-line chemotherapy with carboplatin and paclitaxel. The primary endpoint was the objective response rate (ORR) (defined by the Response Evaluation Criteria in Solid Tumours [RECIST] v1.1). The primary study hypothesis was that there was no clinically meaningful difference between MVASI and AVASTIN for ORR. The hypothesis was tested by comparing the 2-sided 95% confidence interval (CI) of the risk ratio in ORR between MVASI and AVASTIN with an equivalence margin of 0.67, 1.5.

Study Results

Comparability between MVASI and AVASTIN was demonstrated since the two-sided 95% confidence interval of the risk ratio in ORR was entirely contained within the interval of 0.67 to 1.5 (Table 17).

Table 17. Summary of Objective Response Rate – Primary Efficacy (Intent-to-treat Population) (Study 20120265)

	MVASI (N = 328)	AVASTIN (N = 314)
Best overall response [n (%)]		
Complete response (CR)	2 (0.6)	2 (0.6)
Partial response (PR)	126 (38.4)	129 (41.1)
Stable disease (SD)	144 (43.9)	137 (43.6)
Progressive disease (PD)	21 (6.4)	18 (5.7)
Not evaluable (NE)	35 (10.7)	28 (8.9)
Objective response rate (ORR)[a] [n (%)]		
Yes	128 (39.0)	131 (41.7)
95% CI (%)	(33.7, 44.5)	(36.2, 47.4)
Risk ratio (MVASI/AVASTIN)[b]	0.93	
95% CI for risk ratio[b]	(0.77, 1.12)	

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; RECIST = Response Evaluation Criteria in Solid Tumours

Note: Objective response is determined by an independent, blinded radiologist. Subjects without any post-baseline tumour assessment are included in the NE category per RECIST 1.1.

[a] Objective response rate is defined as the percentage of subjects with an objective response. Objective response is defined as a best overall response of partial response or complete response as defined by RECIST v 1.1.

[b] Point estimate and confidence interval are estimated using a generalized linear model adjusted for the randomization stratification factors geographic region, ECOG performance status, and sex.

14.2.2.2 Safety

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

14.2.2.3 Immunogenicity

In study 20120265 in NSCLC, immunogenicity was evaluated at baseline, week 7, week 13, and week 19. An electrochemiluminescent (ECL) immunoassay was used to detect antibodies capable of binding MVASI or AVASTIN®.

In this study, 324 and 309 subjects were administered MVASI or AVASTIN®, respectively, up to 19 weeks. The incidence of subjects developing binding antibodies at any time point during the study was 1.4% (4 of 294 subjects) for those receiving MVASI and 2.5% (7 of 284 subjects) for those receiving AVASTIN® (Table 18). Among the subjects with positive binding ADAs, no subject in either treatment group tested positive for neutralizing antibodies.

Table 18. Incidence of binding Anti-drug antibodies (ADAs) to bevacizumab at each time point (Study 20120265)

Time point	MVASI (N = 324) n/n' (%)	AVASTIN® (N = 309) n/n' (%)
Week 0 (baseline)	0/315 (0.0)	3/303 (1.0)
Week 7[a]	2/286 (0.7)	2/279 (0.7)
Week 13[a]	3/294 (1.0)	3/283 (1.1)
Week 19[a]	4/294 (1.4)	6/284 (2.1)
Overall Week 19[a]	4/294 (1.4)	7/284 (2.5)

n': number of patient with available ADA samples at each time point
[a] Binding antibody positive post-baseline with a negative or no result at baseline

15 COMPARATIVE NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY

15.1 Comparative Non-Clinical Pharmacodynamics

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

A comprehensive biofunctional similarity assessment, summarized in Table 19, was designed to demonstrate similarity between MVASI and AVASTIN (US and EU) by evaluating the biological activity and immunochemical properties of MVASI relative to AVASTIN (US) and AVASTIN (EU) in in vitro and in vivo functional assays. The biological functions that contribute to the clinical efficacy of bevacizumab are mediated by the neutralization of vascular endothelial growth factor type A (VEGF-A).

Primary biofunctional assays comparing MVASI and AVASTIN were performed that included potency (proliferation inhibition in human umbilical vein endothelial cells [HUVEC]), VEGF-A binding (enzyme-linked immunosorbent assay [ELISA]), neonatal fragment crystallizable (Fc) receptor (FcRn) binding, Fc gamma receptor Type IIIa (FcγRIIIa) (158V) binding, FcγRIIIa (158F) binding, and C1q binding activities. Secondary biofunctional assays included VEGF-A binding (surface plasmon resonance [SPR]), induction of VEGF receptor 2 (VEGFR2) tyrosine kinase (RTK) autophosphorylation; specificity against vascular endothelial growth factor receptor C (VEGF-C) and vascular endothelial growth factor receptor D (VEGF-D); lack of the effector functions (ADCC and CDC) in multiple cell lines; and comparative binding to additional Fc gamma receptors (FcγRIa, FcγRIIa [131H], FcγRIIb, and FcγRIIIb). In all of these assessments, results demonstrated the similarity of MVASI to AVASTIN (US) and to AVASTIN (EU).

A number of in vivo studies were conducted to explore additional downstream activities of VEGF-A including vascular growth, vascular permeability, and support of tumour growth. Similarity in the ability to inhibit tumour growth and tumour-associated vascularization was demonstrated in 2 different xenograft tumour models, and similarity in the ability to inhibit VEGF-induced vascular permeability was demonstrated in a single, specialized in vivo model. Additional in vivo assessments characterized the PK (as well as toxicology) of MVASI compared to AVASTIN.

Results from the in vitro and in vivo assays together demonstrate the functional similarity between MVASI and AVASTIN (US and EU).

Table 19. Biofunctional and Nonclinical Pharmacology Studies Comparing MVASI with AVASTIN

Method	Relevant Activity
Primary Characterization Assays	
Inhibition of proliferation in HUVEC	VEGF-A
VEGF-A binding by ELISA	VEGF-A
FcγRIIIa (158V) binding	FcR
FcγRIIIa (158F) binding	FcR
FcRn binding	FcR
C1q binding	C1q
Additional Characterization Assays	
VEGF-A binding kinetics and affinity by SPR	VEGF-A
Inhibition of VEGFR-2 RTK autophosphorylation	VEGF-A
Specificity by VEGFR-2 RTK autophosphorylation	VEGF-C and VEGF-D
Lack of ADCC activity in Calu-6, DLD-1, and SKOV-3	VEGF-A and FcR
Lack of CDC activity in Calu-6, DLD-1, and SKOV-3	VEGF-A and C1q
FcγRIa binding	FcR
FcγRIIa (131H) binding	FcR
FcγRIIb binding	FcR
FcγRIIIb binding	FcR
In Vivo Models	
Tumour growth in xenograft (A431) model	VEGF-A
Vasculature in xenograft (A431) model	VEGF-A
Tumour growth in xenograft (Colo205) model	VEGF-A
Vasculature in xenograft (Colo205) model	VEGF-A
Inhibition of rhu VEGF-induced vascular permeability	VEGF-A

A431 = human epithelial carcinoma cells; ADCC = antibody dependent cell mediated cytotoxicity; C1q = first subcomponent of the C1 complex of the classical pathway of complement activation; Calu-6 = lung epithelial carcinoma cells; CDC = complement dependent cytotoxicity; Colo205 = human colon cancer cells; DLD-1 = adenocarcinoma cells; Fc = fragment crystallizable; FcR = Fc receptor; FcRn = neonatal Fc receptor; FcγRIa = Fc gamma receptor Type Ia; FcγRIIa = Fc gamma receptor Type IIa; FcγRIIIa = Fc gamma receptor Type IIIa; HUVEC = human umbilical vein endothelial cells; rhu = recombinant human; RTK = receptor tyrosine kinase; SKOV-3 = ovarian carcinoma cells; SPR = surface plasmon resonance; VEGF = vascular endothelial growth factor; VEGF A = vascular endothelial growth factor type A; VEGF-C = vascular endothelial growth factor type C; VEGF-D = vascular endothelial growth factor type D; VEGFR-2 = vascular endothelial growth factor receptor 2

15.2 Comparative Toxicology

MVASI is a biosimilar where the animal toxicology properties of bevacizumab have already been characterized for the reference product AVASTIN®. This section summarizes the comparative toxicity studies that were conducted to compare MVASI to AVASTIN®.

One comparative 1-month, repeat-dose, terminal study in cynomolgus monkeys (Study 114831) was conducted to evaluate whether the nonclinical safety and toxicokinetics of MVASI and AVASTIN (US) were similar (Table 20).

Table 20. Overview of Toxicology Program

Study Title	Sex and Species	Dosing Regimen	Test Article	GLP
1-month terminal comparative repeat-dose study	Cynomolgus monkeys	50 mg/kg IV twice weekly	MVASI / AVASTIN (US)	Yes

GLP = Good Laboratory Practice; IV = intravenous

In Study 114831, after 1 month of repeated administration, MVASI and AVASTIN (US) were well tolerated. There were no observed effects on clinical signs, body weight, food consumption, physiologic measurements, ophthalmic or electrocardiogram examinations, hematology, serum chemistry, coagulation, urinalysis, or macroscopic observations. Overall, average ovary-to-body weights were slightly reduced for MVASI and AVASTIN (US) compared to historical controls; however, it was hard to ascribe any treatment differences to either product due to considerable variation in the weight of female reproductive organs as a result of differences in age/sexual maturity and effects of the normal reproductive cycle. Consistent with previous bevacizumab studies, the finding of physeal dysplasia was observed via light microscopy in the femur of all animals dosed with either MVASI or AVASTIN (US) (mild in severity). Toxicokinetic profiles were similar between MVASI and AVASTIN (US) (Table 21) and there were no apparent sex differences. No ADAs were detected in either group; however, high levels of circulating drug may have interfered with the detection of ADAs.

Overall, the toxicity and toxicokinetic profiles were comparable between MVASI and AVASTIN (US), and no unexpected toxicities were observed with MVASI.

Table 21. Mean Toxicokinetic Parameters in Cynomolgus Monkeys After IV Administration (Single-dose and Twice-weekly) of MVASI or AVASTIN (US) (Study 114831)

	C_{max} (mcg/mL)		AUC_{0-72} (mcg•hr/mL)	
Dose and Test Article	Day 1	Day 25	Day 1	Day 25
50 mg/kg MVASI	1,420	3,750	60,400	196,000
50 mg/kg AVASTIN (US)	1,340	3,400	53,500	182,000

AUC_{0-72} = area under the concentration-time curve from time 0 to 72 hours; C_{max} = maximum observed concentration; IV = intravenous

16 CLINICAL TRIALS – REFERENCE BIOLOGIC DRUG

Clinical Efficacy

Metastatic Colorectal Cancer

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

- AVF2107g: A weekly schedule of irinotecan/bolus 5-fluorouracil/leucovorin (IFL regimen) for a total of 4 weeks of each 6 week cycle
- AVF0780g: In combination with bolus 5-fluorouracil/leucovorin (5 FU/LV) for a total of 6 weeks of each 8 week cycle (Roswell Park regimen);
- AVF2192g: In combination with bolus 5-fluorouracil/leucovorin (5-FU/LV) for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen) in patients who were not optimal candidates for first-line irinotecan treatment.

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

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

This was a phase III randomized, double blind, active controlled clinical trial evaluating bevacizumab in combination with IFL as first line treatment for metastatic carcinoma of the colon or rectum. Eight hundred thirteen patients were randomized to receive IFL + placebo (Arm 1) or IFL + bevacizumab (5 mg/kg every 2 weeks, Arm 2) (see Table 22). A third group of 110 patients received bolus 5 FU/LV + bevacizumab (Arm 3). Enrollment in Arm 3 was discontinued, as pre-specified, once safety of bevacizumab with the IFL regimen was established and considered acceptable.

Table 22. Treatment Regimens in Study AVF2107g

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

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

The primary efficacy parameter of the trial was duration of survival. The addition of bevacizumab to IFL resulted in a statistically significant increase in overall survival (see Table 23 and Figure 1). The clinical benefit of bevacizumab, as measured by survival, was seen in all pre- specified patient subgroups, including those defined by age, sex, performance status, location of primary tumour, number of organs involved, and duration of metastatic disease (see Figure 3).

The efficacy results of bevacizumab in combination with IFL chemotherapy are displayed in Table 23, Figure 1 and Figure 2 (Kaplan Meier plots for duration of survival and progression free survival).

Table 23. Efficacy Results for Study AVF2107g

	Arm 1 IFL + Placebo	**Arm 2 IFL + bevacizumab[a]**
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[b] (95% CI)		0.66 (0.54; 0.81)
p-value		0.00004
Progression-free Survival		
Median (months)	6.2	10.6
95% confidence interval (CI)	5.59 - 7.66	9.03 - 11.04
Hazard Ratio[b] (95% CI)		0.54 (0.45; 0.66)
p-value		< 0.00001
Overall Response Rate		
Rate (%)	34.8	44.8
95% confidence interval (CI)	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

[a] 5 mg/kg every 2 weeks; [b] Relative to control arm
IFL = irinotecan/5-fluorouracil/leucovorin

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

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

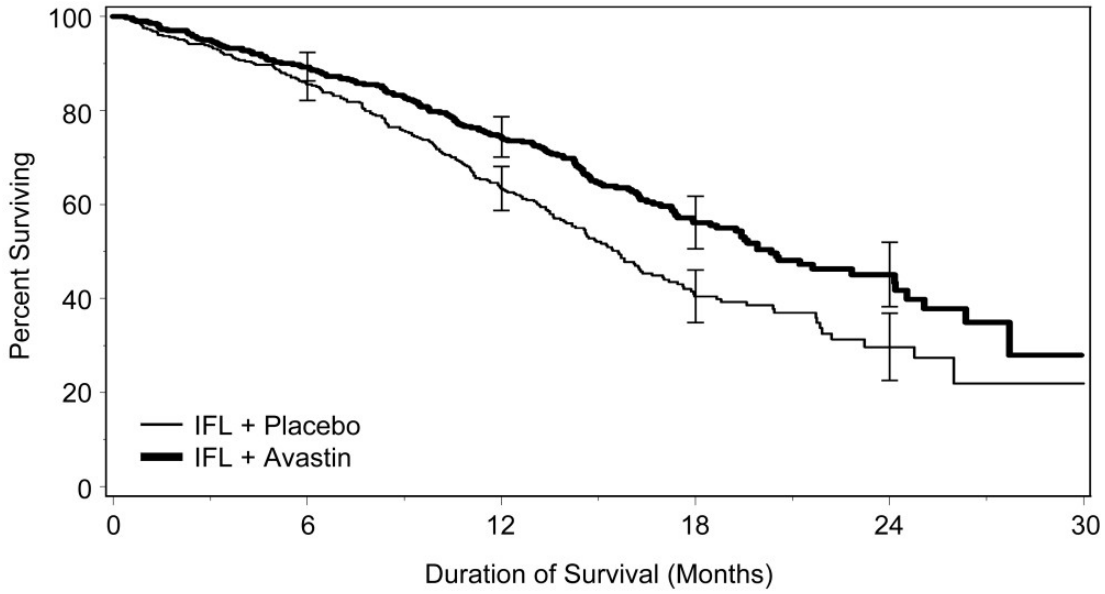


Figure 2. Progression Free Survival during First-Line Therapy in Study AVF2107g

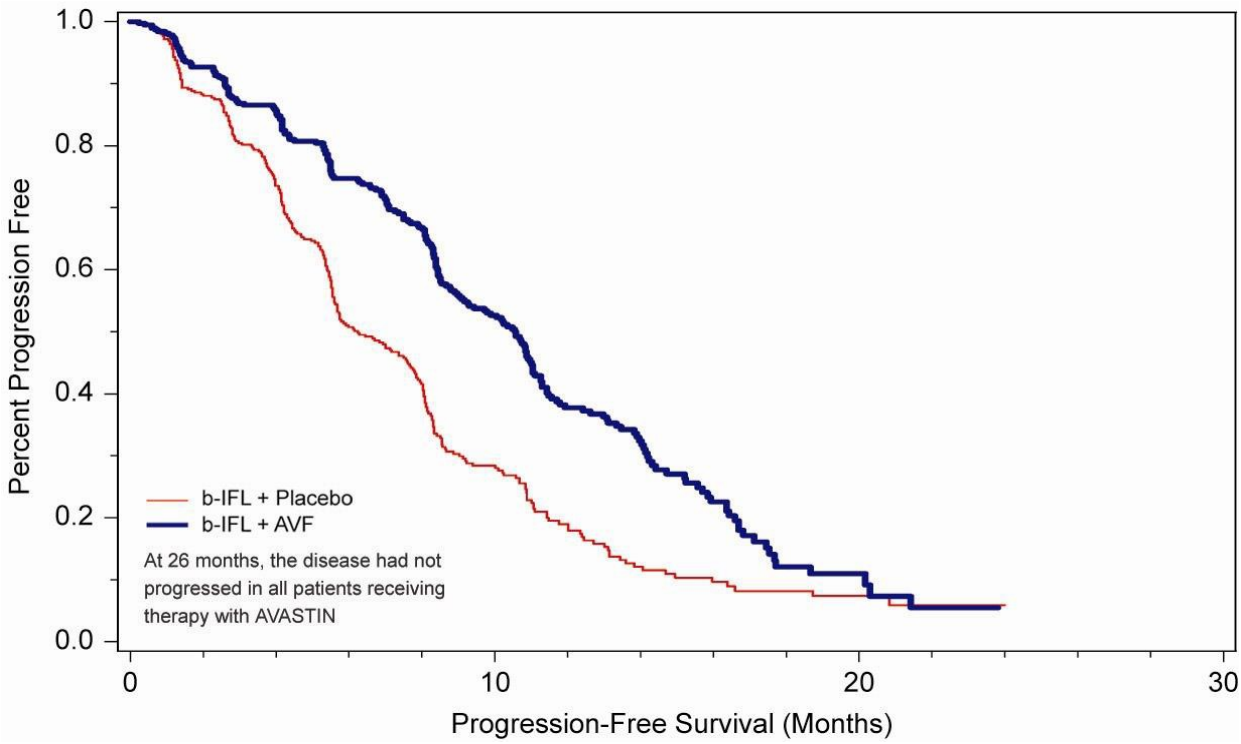
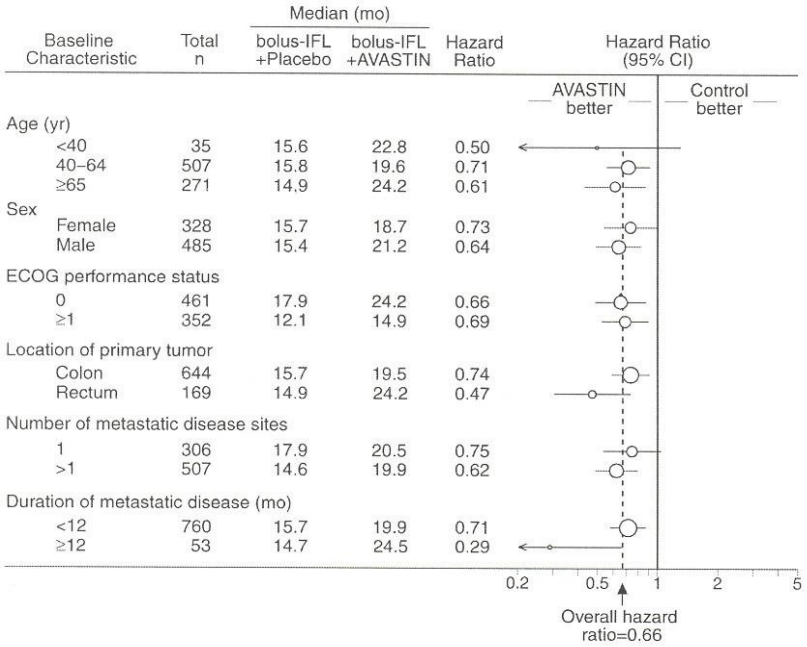


Figure 3. Duration of Survival by Baseline Risk Factor in Study AVF2107g



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

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

This was a phase II randomized, active-controlled, open-labelled clinical trial investigating bevacizumab in combination with 5 FU/Leucovorin as first-line treatment for metastatic colorectal cancer in patients who were not optimal candidates for first-line irinotecan treatment. Patients had to be either more susceptible to irinotecan toxicity (≥ 65 years, prior radiotherapy to pelvis or abdomen) or less likely to benefit from irinotecan treatment (PS ≥ 1, baseline albumin < 3.5 g/dl) in order to be eligible for enrolment. One hundred and five patients were randomized to 5 FU/LV + placebo arm and 104 patients randomized to 5 FU/LV + bevacizumab (5 mg/kg every 2 weeks). All treatments were continued until disease progression. The overall age was 71 years; 28.2% of patients had an ECOG performance status of 0, 65.1% had a value of 1 and 6.7% had a value of 2. The addition of bevacizumab 5 mg/kg every two weeks to 5 FU/LV resulted in higher objective response rates, significantly longer progression free survival, and a trend in longer survival, compared with 5 FU/LV chemotherapy alone (see Table 24). These efficacy data were consistent with the results observed in studies AVF2107g and AVF0780g.

Table 24. 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-week 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-week cycle
	bevacizumab	5 mg/kg IV	Every 2 weeks

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

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

This was a phase II randomized, active-controlled, open-labelled clinical trial investigating bevacizumab in combination with 5-FU/LV as first-line treatment of metastatic colorectal cancer. Seventy-one patients were randomized to receive bolus 5-FU/LV or 5-FU/LV + bevacizumab (5 mg/kg every 2 weeks). A third group of 33 patients received bolus 5-FU/LV + bevacizumab (10 mg/kg every 2 weeks). Patients were treated until disease progression. The primary endpoints of the trial were objective response rate and progression free survival. The addition of 5 mg/kg every two weeks of bevacizumab to 5-FU/LV resulted in higher objective response rates, longer progression free survival, and a trend in longer survival, compared with 5-FU/LV chemotherapy alone (see Table 25). This efficacy data is consistent with the results from study AVF2107g.

Table 25. Efficacy results for Study AVF0780g and AVF2192g

	AVF0780g			AVF2192g	
	5-FU/LV	**5-FU/LV bevacizumab[a]**	**5-FU/LV bevacizumab[b]**	**5-FU/LV placebo**	**5-FU/LV bevacizumab**
Number of Patients	36	35	33	105	104
Overall Survival					
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] (95% CI)		0.52 (0.25; 1.08)	1.01 (0.53; 1.91)		0.79 (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 (95% CI)		0.44 (0.24; 0.8)	0.69 (0.38; 1.25)		0.5 (0.34; 0.73)
p-value		0.0049	0.217		0.0002
Overall Response Rate					
Rate (%)	16.7	40	24.2	15.2	26
95% Confidence Interval (CI)	7.0 - 33.5	24.4 - 57.8	11.7 - 42.6	9.2 - 23.9	18.1 - 35.6
p-value		0.029	0.43		0.055
Duration of Response					
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

[a] 5 mg/kg every 2 weeks; [b] 10 mg/kg every 2 weeks; [c] Relative to control arm
5-FU/LV = 5-fluorouracil/leucovorin; NR = Not reached

Adjuvant Colon Cancer (aCC)

BO17920

This was a phase III randomized open-label, 3-arm study evaluating the efficacy and safety of bevacizumab administered at a dose equivalent to 2.5 mg/kg/week on either a 2-weekly schedule in combination with FOLFOX4, or on a 3-weekly schedule in combination with XELOX versus FOLFOX4 alone as adjuvant chemotherapy in 3451 patients with high-risk stage II and stage III colon carcinoma.

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

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

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

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

Study E4599

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

Patients were randomized to platinum-based chemotherapy (paclitaxel 200 mg/m^2 and carboplatin AUC = 6.0, both by IV infusion) (PC) on day 1 of every 3-week cycle for up to 6 cycles or PC in combination with bevacizumab at a dose of 15 mg/kg IV infusion day 1 of every 3- week cycle. After completion of six cycles of carboplatin-paclitaxel chemotherapy or upon premature discontinuation of chemotherapy, patients on the bevacizumab + carboplatin–paclitaxel arm continued to receive bevacizumab as a single agent every 3 weeks until disease progression. 878 patients were randomized to the two arms.

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

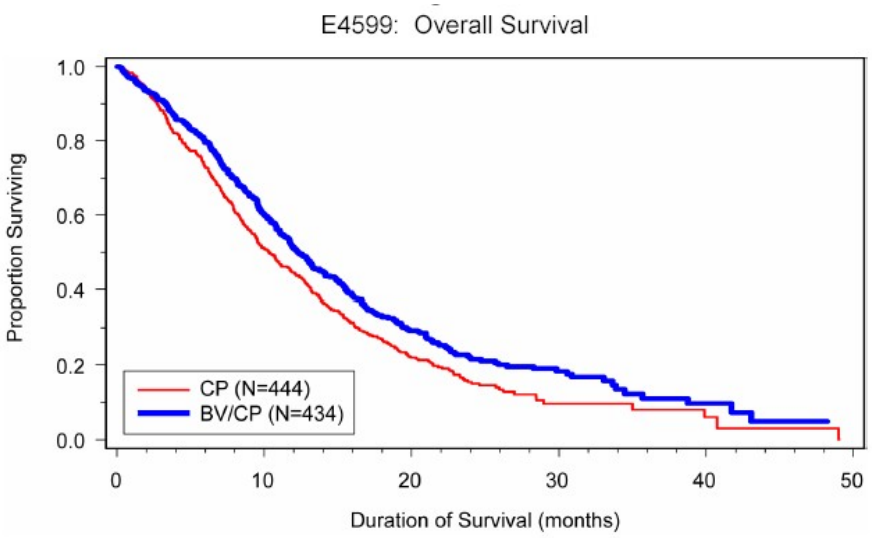
During the study, of the patients who received trial treatment, 32.2% (136/422) of patients received 7-12 administrations of bevacizumab and 21.1% (89/422) of patients received 13 or more administrations of bevacizumab.

The primary endpoint was duration of survival. Results are presented in Table 26.

Table 26. Efficacy Results for Study E4599

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

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



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

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

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

Table 27. 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%)

CP = carboplatin/paclitaxel; Bv15+CP = 15 mg/kg/q3w bevacizumab + carboplatin/paclitaxel

Study AVF0757g

The design for the pivotal phase III trial (study E4599) was based on the findings from an earlier supporting phase II study AVF0757g. In this randomized, multicentre, 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. Primary efficacy endpoints were time to disease progression (TTP) and best confirmed response rate as assessed both by the investigator and by a blinded independent review facility (IRF). Though not statistically significant based on the IRF assessment, there was a trend for improvement in TTP (7.0 vs 6.0 months) and the response rate (40% vs 31%) for patients in the 15 mg/kg arm compared with the control arm. There was not a statistically significant difference in survival between patients in the 15 mg/kg arm and the control arm (14.4 vs 13.3 months), however, 19 out of 32 patients randomized to the control arm crossed over to receive bevacizumab following disease progression.

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

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

Study AVF4095g

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

Bevacizumab was administered in combination with carboplatin and gemcitabine for 6 to10 cycles followed by continued use of bevacizumab 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/m^2 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/m^2 on Days 1 and 8) and concurrent bevacizumab (15 mg/kg Day 1) every 3 weeks for 6 and up to 10 cycles followed by bevacizumab (15 mg/kg every 3 weeks) alone until disease progression or unacceptable toxicity

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 28.

Table 28. Efficacy Results from Study AVF4095g

	Placebo + C/G (n = 242)	bevacizumab + C/G (n = 242)
Progression-free survival		
	Investigator Assessment [1]	
Median PFS (months)	8.4	12.4
Hazard ratio	0.484	
(95% CI)	[0.388, 0.605]	
p-value	<0.0001	
Objective response rate		
	Investigator Assessment	
% pts with objective response	57.4 %	78.5 %
p-value	<0.0001	
Overall survival (Interim)[2]		
Median OS (months)	29.9	35.5
Hazard ratio	0.751	
(95% CI)	[0.537, 1.052]	
p-value	0.094	
Overall survival (Final)[3]		
Median OS (months)	32.9	33.6
Hazard ratio	0.952	
(95% CI)	[0.771, 1.176]	
p-value	0.6479	

C = carboplatin; G = gemcitabine

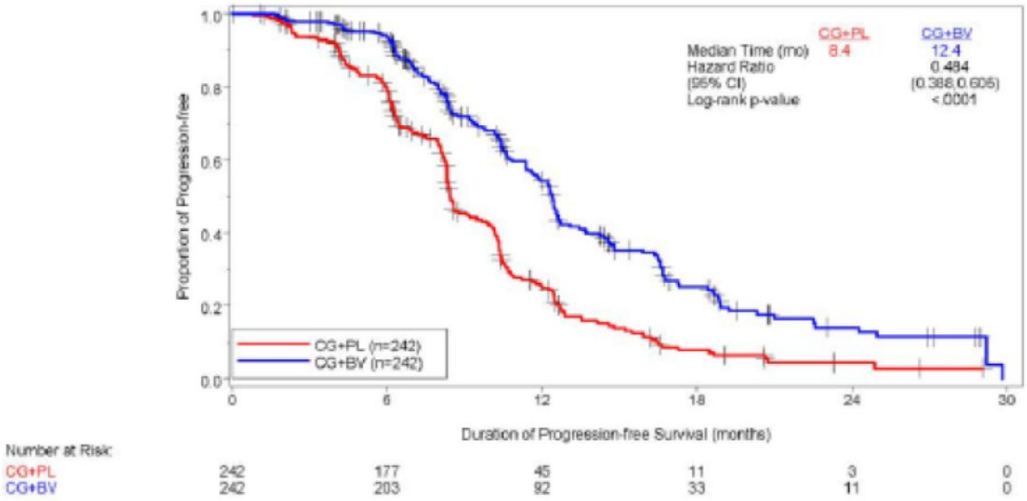
[1] Primary analysis

[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.



Number at Risk

CG+PL	242	177	45	11	3	0
CG+BV	242	203	92	33	11	0

BV = bevacizumab; CG = carboplatin+gemcitabine; PL = placebo.

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

Study MO22224 (AURELIA)

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

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

- CT Arm (chemotherapy alone):
  - Paclitaxel 80 mg/m^2 as a 1-hour IV infusion on Days 1, 8, 15, and 22 every 4 weeks.
  - Topotecan 4 mg/m^2 as a 30 minute IV infusion on Days 1, 8, and 15 every 4 weeks. Alternatively, a 1.25 mg/m^2 dose could be administered over 30 minutes on Days 1–5 every 3 weeks.
  - PLD 40 mg/m^2 as a 1 mg/min IV infusion on Day 1 only every 4 weeks. After Cycle 1, the drug could be delivered as a 1 hour infusion.
- CT+BV Arm (chemotherapy plus bevacizumab):
  - The chosen chemotherapy was combined with bevacizumab 10 mg/kg IV every 2 weeks (or bevacizumab 15 mg/kg every 3 weeks if used in combination with topotecan 1.25 mg/m^2 on Days 1–5 on a every 3 weeks schedule).

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 (ie, progression while on preceding platinum therapy) were excluded.

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

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

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

The addition of bevacizumab to chemotherapy demonstrated a statistically significant improvement in investigator assessed PFS, which was supported by a retrospective independent review analysis. Study results for the intent to treat (ITT) population are presented in Table 29 and Figure 6. Results for the separate chemotherapy cohorts are presented in Table 30.

Table 29. Efficacy Results from Study MO22224 (AURELIA)

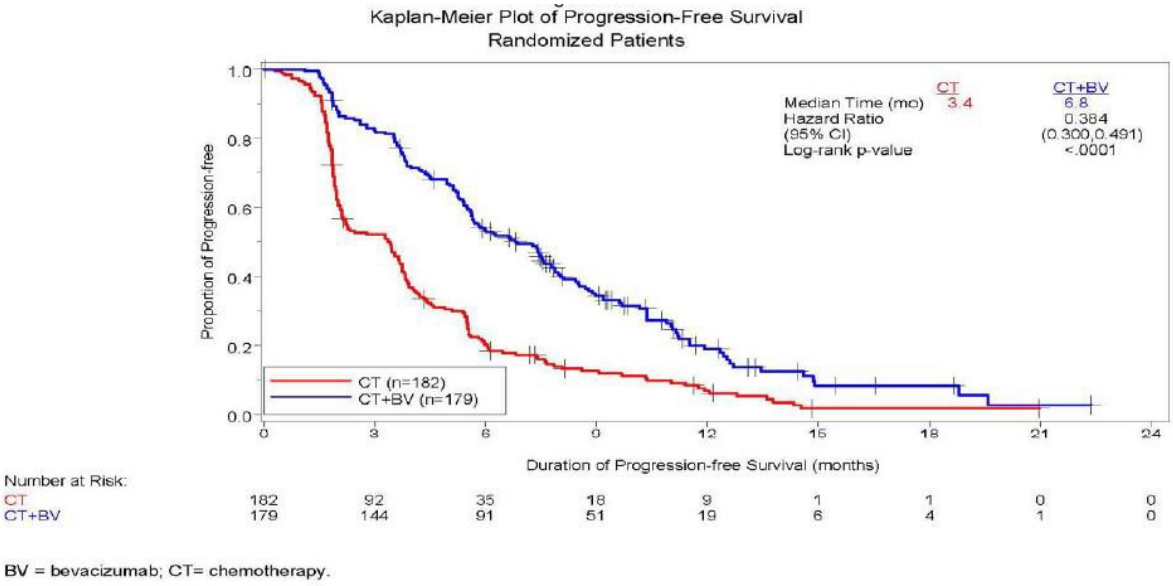
	Investigator Assessment	
	CT (n = 182)	**CT + BV (n = 179)**
Primary Endpoint		
Progression-Free Survival		
No. (%) patients with event	168 (92.3%)	140 (78.2%)
Median (months)	3.4	6.8
Hazard ratio* (95% CI)	0.384 (0.300, 0.491)	
p-value**	< 0.0001	
Secondary Endpoints		
Objective Response Rate		
No. patients with measurable disease at baseline	144	142
No. (%) patients with objective response	18 (12.5%)	40 (28.2%)
Median duration of response (months)	5.4	9.4
Overall Survival (final analysis)		
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 30. Efficacy Results in Chemotherapy Cohorts from Study MO22224 (AURELIA)

Efficacy Parameter	Paclitaxel		Topotecan		PLD	
	CT[b] (N = 55)	CT[b]+ bevacizumab (N = 60)	CT[b] (N = 63)	CT[b]+ bevacizumab (N = 57)	CT[b] (N = 64)	CT[b]+ bevacizumab (N = 62)
PFS per Investigator						
No. (%) of subjects with an event	50 (90.9%)	39 (65.0%)	57 (90.5%)	45 (78.9%)	61 (95.3%)	56 (90.3%)
Median (months) (95% CI)	3.9 (3.5, 5.5)	9.6 (7.8, 11.5)	2.1 (1.9, 2.3)	6.2 (5.3, 7.6)	3.5 (1.9, 3.9)	5.1 (3.9, 6.3)
Hazard Ratio (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)
Hazard Ratio (95% CI)[a]	0.64 (0.41, 1.01)		1.12 (0.73, 1.73)		0.94 (0.63, 1.42)	
Objective Response Rate						
Number of Patients with Measurable Disease at Baseline	43	45	50	46	51	51
Rate, % (95% CI)	30 (17, 44)	53 (39, 68)	2 (0, 6)	17 (6, 28)	8 (0, 15)	16 (6, 26)
Median of Response Duration (months)	6.8	11.6	NE	5.2	4.6	8.0

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

Malignant Glioma (WHO Grade IV) - Glioblastoma

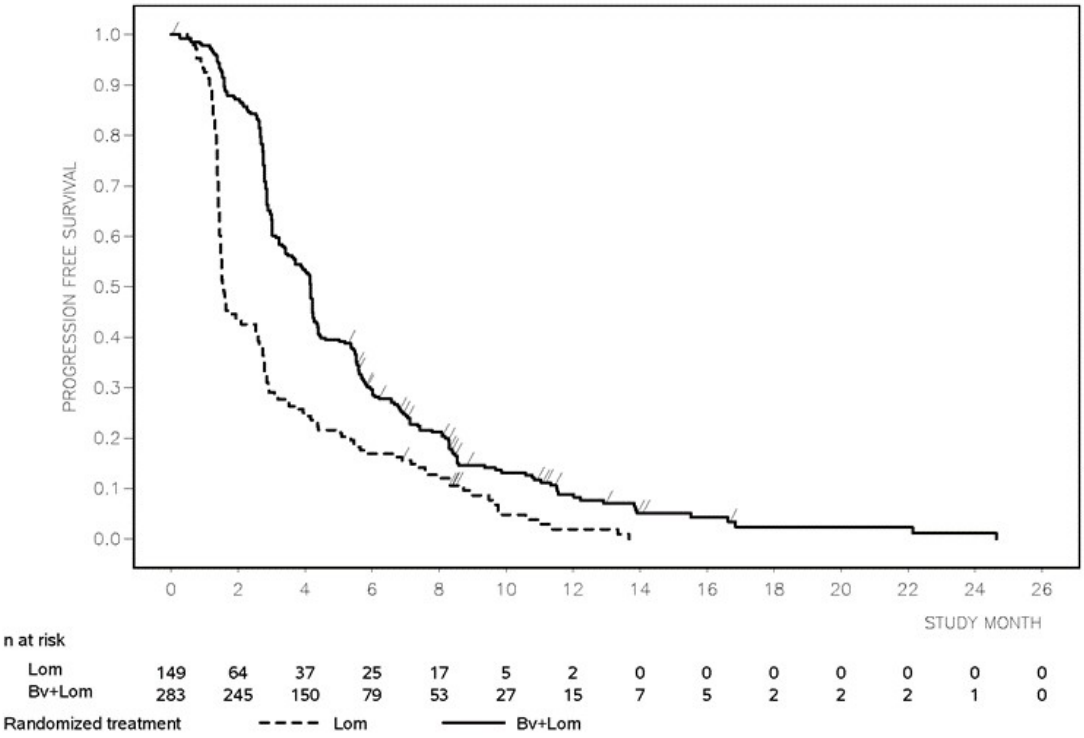
Study EORTC 26101

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

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

There was no difference in OS (HR=0.91, p = 0.4578); therefore, all secondary outcome measures can be interpreted as descriptive only. PFS was shown to be longer among patients receiving bevacizumab plus lomustine compared to those receiving lomustine alone; the unblinded investigator-assessed results were a median PFS of 4.2 months vs. 1.5 months [HR 0.52 (95% CI 0.41, 0.64)]. The results are presented in Figure 7. Among the 399 patients with measurable disease, ORR was 26% in those receiving bevacizumab plus lomustine and 6% in those receiving only lomustine. A retrospective PFS analysis was conducted on subjects with available diagnostic information (91.2% and 95.3% of subjects receiving bevacizumab + lomustine and lomustine alone, respectively) by a blinded central review and results were a median PFS of 2.8 months vs. 1.5 months [HR 0.53 (95% CI 0.42, 0.66)].

Figure 7. Investigator-Assessed Progression-Free Survival in Study EORTC 26101



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

Pediatric Studies

Study BO20924 (Bernie)

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

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

Study BO25041 (Herby)

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

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

17 SUPPORTING PRODUCT MONOGRAPHS

1. Avastin® (bevacizumab), Submission Control No.: 259188, Product Monograph, Hoffmann-La Roche Limited. April 29, 2022.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr MVASI®

Pronounced *em vah' see*

bevacizumab

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

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

Serious Warnings and Precautions

- **Eye Disorders**

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

- **Gastrointestinal Perforations**

  MVASI treatment can cause gastrointestinal perforation, (hole in the stomach or bowel) which can be fatal.

  MVASI treatment should be stopped if this happens. Gastrointestinal perforation can happen at any time during treatment: symptoms include abdominal pain, constipation, and vomiting.

- **Wound Healing Complications**

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

- **Hemorrhage**

  Treatment with MVASI 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 bevacizumab 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 MVASI. Treatment with MVASI should be permanently stopped if serious bleeding occurs (ie, requiring medical attention).

What is MVASI used for?

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

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

Recurrent Platinum-Sensitive Ovarian Cancer: MVASI 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.

Recurrent Platinum-Resistant Ovarian Cancer: MVASI is used in combination with a specific type of chemotherapy (paclitaxel, topotecan, or pegylated liposomal doxorubicin) for the treatment of people diagnosed with recurrent, platinum-resistant, epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens. Recurrent platinum-resistant ovarian cancer is the type of cancer that progresses within 6 months after the last time the patient responded to a chemotherapy regimen containing a platinum agent.

Recurrent Glioblastoma: MVASI 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 MVASI work?

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

What are the ingredients in MVASI?

- The medicinal ingredient is called bevacizumab.
- The non-medicinal ingredients are (in alphabetical order): α,α-trehalose dihydrate, polysorbate 20, sodium phosphate and water for injection.

MVASI comes in the following dosage forms:

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

- 100 mg/4 mL (25 mg/mL)
- 400 mg/16 mL (25 mg/mL)

Do not use MVASI if:

MVASI should not be used by people who are allergic to it or any of its ingredients or by people whose cancer has spread to their central nervous system (to their brain or spine). MVASI 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 MVASI. Talk about any health conditions or problems you may have, including if you:

- have high blood pressure
- plan to have surgery or have had surgery in the last 28 days
- have ever had a heart attack or stroke
- are pregnant or plan to become pregnant
- are breast feeding
- have any allergies to this drug or its ingredients
- have any illnesses or diseases affecting your kidneys
- have heart failure or weakened heart muscles
- have ever coughed up blood or observed abnormal vaginal bleeding
- are diabetic.

Other warnings you should know about:

MVASI 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 MVASI and for at least 6 months after your last dose of MVASI. If you become pregnant during treatment with MVASI, tell your doctor immediately.

MVASI 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 MVASI.

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 MVASI:

- Drugs that may interact with MVASI include: irinotecan and sunitinib malate. Your doctor may adjust the dose of irinotecan if you have side effects known to be related to it. The safety and effectiveness of MVASI in combination with sunitinib malate has not been established, therefore this combination is not recommended.
- Tell your doctor if you are using platinum- or taxane-based therapies for lung cancer. These therapies in combination with MVASI may increase the risk of severe side effects.

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

How to take MVASI?

Dosage and frequency of administration

The dose of MVASI needed depends on your body weight and the kind of cancer to be treated. If you have:

- Metastatic Colorectal Cancer, you will receive 5 mg/kg of your body weight once every 2 weeks.
- Metastatic Lung Cancer, you will receive 15 mg/kg of your body weight once every 3 weeks.
- Ovarian Cancer (Platinum-sensitive recurrent disease), you will receive 15 mg/kg of your body weight once every 3 weeks.
- Ovarian Cancer (Platinum-resistant recurrent disease), you will receive 10 mg/kg or 15 mg/kg of your body weight once every 2 or 3 weeks.
- Recurrent Glioblastoma, you will receive 10 mg/kg of your body weight once every 2 weeks.

Your doctor will prescribe a dose of MVASI that is right for you.

A doctor or nurse will give you a diluted MVASI solution by intravenous infusion (a drip in your vein). The first infusion will be given to you over 90 minutes. If this is well-tolerated the second infusion may be given over 60 minutes. Later infusions may be given to you over 30 minutes. The number of infusions that you receive will depend on how you are responding to treatment; you should continue to receive this medicine until MVASI fails to stop your tumour growing. Your doctor will discuss this with you.

Usual Dose:

Metastatic Colorectal Cancer:

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

Metastatic Lung Cancer:

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

Ovarian Cancer (Platinum-sensitive recurrent disease):

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

Ovarian Cancer (Platinum-resistant recurrent disease):

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

Recurrent Glioblastoma:

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

Overdose:

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

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

Missed Dose:

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

What are possible side effects from using MVASI?

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

Very Common (more than 1 in 10 patients):

- High blood pressure
- Diarrhea
- Vomiting
- Abdominal pain
- Constipation
- Nausea
- Lack of energy or strength
- Loss of appetite
- Pain (including joint pain)
- Bleeding (from the nose or rectum)
- Sores in the mouth
- Shortness of breath
- Runny nose
- Dry, scaling skin or changes in skin colour
- Changes in the sense of taste
- Eye problems (for example: excessive tearing, blurred vision, an experience of discomfort or pain to the eyes due to light exposure)

- A decrease in certain white blood cells in the blood that help fight off infection
- Decrease in the number of red blood cells (anemia)
- Difficulty in sleeping
- Fever, chills or excessive sweating
- Headache
- Abnormal urine test (protein in the urine)
- Tingling sensation or numbness in toes and fingers
- Bronchitis (an inflammation of the main air passages to the lungs)
- Bruising
- Change in moods
- Infections (mouth, throat, sinus, lungs or urine infections)
- Excess of sugar in the blood
- Weight loss
- Widening of the blood vessels
- Low levels of sodium and magnesium in the blood
- Coughing
- Tiredness

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

- Pain (including muscle pain, chest pain, heart pain (angina), back pain, and pain in the pelvis and anal regions)
- Stroke/heart attack
- Blood clots
- Perforation of the gut (hole in the stomach or bowel)
- Altered voice such as hoarseness
- Swelling and numbness of the hand and feet
- Urinary (bladder or kidney) infection
- Infections of the skin or deeper layers under the skin
- Fistula (abnormal tube like connection between internal parts of the body that are not normally connected) such as between the stomach and intestines (gastrointestinal fistula), in patients with metastatic colorectal cancer, and recurrent ovarian cancer and between the vagina and the gut in patients with cervical cancer (unauthorized use)
- Allergic reactions
- Nephrotic syndrome (a type of kidney disorder)

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

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

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

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

Frequency unknown:

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

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

Changes in your blood and urine tests done by your doctor may occur while you are receiving MVASI. 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 MVASI for cancer treatment, the following side effects may occur when MVASI 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 hospitalization, eg, heart attack, stroke, and high blood pressure.

Serious side effects and what to do about them		
Symptom / effect	**Talk to your healthcare professional in all cases**	**Stop taking drug and get immediate medical help**
VERY COMMON (more than 1 in 10 patients)		
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		
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		
Bronchitis (an inflammation of the main air passages to the lungs)	✓	
Excess of sugar in the blood	✓	
• Symptoms may include frequent hunger, frequent thirst, frequent urination		
Infections (mouth, throat, sinus, lungs or urine infections)	✓	

Serious side effects and what to do about them		
Symptom / effect	**Talk to your healthcare professional in all cases**	**Stop taking drug and get immediate medical help**
Weakened heart muscle/loss of the heart's pumping ability • Symptoms may include shortness of breath, fatigue, persistent coughing or wheezing, increased heart rate, swelling in the feet or ankles	✓	
Low levels of sodium and magnesium in the blood	✓	
Coughing	✓	
COMMON (less than 1 in 10 patients but more than 1 in 100 patients)		
Perforation of the gut (leakage of the bowel) • Symptoms include: sudden onset of abdominal pain, abdominal tenderness with vomiting, high fever		✓
Allergic reactions • Symptoms include difficulty in breathing, chest pain, redness or flushing of the skin, rash, shivering, nausea, vomiting	✓	
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 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		✓
Pain • in the pelvis and anal regions	✓	
Fistula • Abnormal tube-like connection between internal organs and skin or other tissues that are not normally connected, including connections between the vagina and the gut in patients with cervical cancer (unauthorized use)		✓
Nephrotic syndrome (a type of kidney disorder) • Symptoms include swelling in the face, arms, legs, belly area, foamy appearance of urine and poor appetite	✓	

Serious side effects and what to do about them		
Symptom / effect	**Talk to your healthcare professional in all cases**	**Stop taking drug and get immediate medical help**
UNCOMMON (less than 1 in 100 patients but more than 1 in 1000 patients)		
Non-gastrointestinal perforations and fistulae • Depending on the organs involved the symptoms could be as follows: leakage of urine, abnormal and bad odor in the genital area, abdominal pain, vomiting, fever, gradually increasing/worsening of shortness of breath (dyspnea), cough, chest pain, yellowish discoloration of the skin etc.	✓	✓
Posterior Reversible Encephalopathy Syndrome (PRES) • Symptoms include headache, confusion, seizures and visual loss		✓

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

Reporting Side Effects

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

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

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

Storage:

Store vials in a refrigerator at 2ºC to 8ºC. Do not freeze. Do not shake.

Keep vial in the outer carton in order to protect from light.

Keep out of the reach and sight of children.

If you want more information about MVASI:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.amgen.ca, or by calling 1-866-502-6436.

This leaflet was prepared by Amgen Canada Inc.

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