ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Alymsys 25 mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate contains 25 mg of bevacizumab*.
Each 4 mL vial contains 100 mg of bevacizumab.
Each 16 mL vial contains 400 mg of bevacizumab.
For dilution and other handling recommendations, see section 6.6.

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

Excipient with known effect
Each 4 mL vial contains 1.6 mg of polysorbate 20.
Each 16 mL vial contains 6.4 mg of polysorbate 20.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Colourless to yellowish or brownish liquid with opalescence.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Alymsys in combination with paclitaxel is indicated for first-line treatment of adult patients with metastatic breast cancer. For further information as to human epidermal growth factor receptor 2 (HER2) status, please refer to section 5.1.

Alymsys in combination with capecitabine is indicated for first-line treatment of adult patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Alymsys in combination with capecitabine. For further information as to HER2 status, please refer to section 5.1.

Alymsys, in addition to platinum-based chemotherapy, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology.

Alymsys, in combination with erlotinib, is indicated for first-line treatment of adult patients with unresectable advanced, metastatic or recurrent non-squamous non-small cell lung cancer with Epidermal Growth Factor Receptor (EGFR) activating mutations (see section 5.1).

Alymsys in combination with interferon alfa-2a is indicated for first-line treatment of adult patients with advanced and/or metastatic renal cell cancer.

Alymsys, in combination with carboplatin and paclitaxel is indicated for the front line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics (FIGO) stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer. (see section 5.1).

Alymsys, in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel, is indicated for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.

Alymsys, in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin is indicated for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents (see Section 5.1).

Alymsys, in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix (see section 5.1).

4.2 Posology and method of administration

Do not shake the vial.

Alymsys must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products.

Posology

Metastatic carcinoma of the colon or rectum (mCRC)

The recommended dose of Alymsys, administered as an intravenous infusion, is either 5 mg/kg or 10 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks.

It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Metastatic breast cancer (mBC)

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

It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Non-small cell lung cancer (NSCLC)

First-line treatment of non-squamous NSCLC in combination with platinum-based chemotherapy
Alymsys is administered in addition to platinum-based chemotherapy for up to 6 cycles of treatment followed by Alymsys as a single agent until disease progression.

The recommended dose of Alymsys is 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

Clinical benefit in NSCLC patients has been demonstrated with both 7.5 mg/kg and 15 mg/kg doses (see section 5.1).

It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

First-line treatment of non-squamous NSCLC with EGFR activating mutations in combination with erlotinib
EGFR mutation testing should be performed prior to initiation of treatment with the combination of Alymsys and erlotinib. It is important that a well-validated and robust methodology is chosen to avoid false negative or false positive determinations.

The recommended dose of Alymsys when used in addition to erlotinib is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

It is recommended that the treatment with Alymsys in addition to erlotinib is continued until disease progression.

For the posology and method of administration of erlotinib, please refer to the full erlotinib prescribing information.

Advanced and/or metastatic renal cell cancer (mRCC)

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

It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Epithelial ovarian, fallopian tube and primary peritoneal cancer

Front-line treatment
Alymsys is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by continued use of Alymsys as single agent until disease progression or for a maximum of 15 months or until unacceptable toxicity, whichever occurs earlier.

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

Treatment of platinum-sensitive recurrent disease
Alymsys is administered in combination with either carboplatin and gemcitabine for 6 cycles and up to 10 cycles or in combination with carboplatin and paclitaxel for 6 cycles and up to 8 cycles, followed by continued use of Alymsys as single agent until disease progression. The recommended dose of Alymsys is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

Treatment of platinum-resistant recurrent disease
Alymsys is administered in combination with one of the following agents – paclitaxel, topotecan (given weekly) or pegylated liposomal doxorubicin. The recommended dose of Alymsys is 10 mg/kg of body weight given once every 2 weeks as an intravenous infusion. When Alymsys is administered in combination with topotecan (given on days 1-5, every 3 weeks), the recommended dose of Alymsys is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion. It is recommended that treatment be continued until disease progression or unacceptable toxicity (see section 5.1, study MO22224).

Cervical cancer

Alymsys is administered in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin or paclitaxel and topotecan.

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

It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity (see section 5.1).

Special populations

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

Renal impairment
The safety and efficacy have not been studied in patients with renal impairment (see section 5.2).

Hepatic impairment
The safety and efficacy have not been studied in patients with hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of bevacizumab in children aged less than 18 years old have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

There is no relevant use of bevacizumab in the paediatric population in the indications for treatment of cancers of the colon, rectum, breast, lung, ovary, fallopian tube, peritoneum, cervix and kidney.

Method of administration

Alymsys is for intravenous use. The initial 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.

It should not be administered as an intravenous push or bolus.

Dose reduction for adverse reactions is not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended as described in section 4.4.

Precautions to be taken before handling or administering the medicinal product

For instructions on dilution of the medicinal product before administration, see section 6.6. Alymsys infusions should not be administered or mixed with glucose solutions. It must not be mixed with other medicinal products except those mentioned in section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies.
- Pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

Traceability

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

Gastrointestinal (GI) perforations and fistulae (see section 4.8)

Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation when treated with bevacizumab. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Prior radiation is a risk factor for GI perforation in patients treated for persistent, recurrent or metastatic cervical cancer with bevacizumab and all patients with GI perforation had a history of prior radiation. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.

GI-vaginal fistulae in study GOG-0240

Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab are at increased risk of fistulae between the vagina and any part of the GI tract (Gastrointestinal-vaginal fistulae). Prior radiation is a major risk factor for the development of GI-vaginal fistulae and all patients with GI-vaginal fistulae had a history of prior radiation. Recurrence of cancer within the field of prior radiation is an additional important risk factor for the development of GI-vaginal fistulae.

Non-GI fistulae (see section 4.8)

Patients may be at increased risk for the development of fistulae when treated with bevacizumab. Permanently discontinue Alymsys in patients with tracheoesophageal (TE) fistula or any grade 4 fistula [US National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE v.3)]. Limited information is available on the continued use of bevacizumab in patients with other fistulae.

In cases of internal fistula not arising in the gastrointestinal tract, discontinuation of Alymsys should be considered.

Wound healing complications (see section 4.8)

Bevacizumab may adversely affect the wound healing process. Serious wound healing complications, including anastomotic complications, with a fatal outcome have been reported. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for elective surgery.

Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Alymsys therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

Hypertension (see section 4.8)

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

Monitoring of blood pressure is generally recommended during therapy.

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. Alymsys 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.

Posterior reversible encephalopathy syndrome (PRES) (see section 4.8)

There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with PRES, a rare neurologic disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of Alymsys. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known.

Proteinuria (see section 4.8)

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence suggesting that all grade (NCI-CTCAE v.3) proteinuria may be related to the dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of patients treated with bevacizumab. Therapy should be permanently discontinued in patients who develop nephrotic syndrome (NCI-CTCAE v.3).

Arterial thromboembolism (see section 4.8)

In clinical trials, the incidence of arterial thromboembolic reactions including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs) was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone.

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

Therapy should be permanently discontinued in patients who develop arterial thromboembolic reactions.

Venous thromboembolism (see section 4.8)

Patients may be at risk of developing venous thromboembolic reactions, including pulmonary embolism under bevacizumab treatment.

Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab in combination with paclitaxel and cisplatin may be at increased risk of venous thromboembolic events.

Alymsys should be discontinued in patients with life-threatening (grade 4) thromboembolic reactions, including pulmonary embolism (NCI-CTCAE v.3). Patients with thromboembolic reactions ≤ grade 3 need to be closely monitored (NCI-CTCAE v.3).

Haemorrhage

Patients treated with bevacizumab have an increased risk of haemorrhage, especially tumour-associated haemorrhage. Alymsys should be discontinued permanently in patients who experience grade 3 or 4 bleeding during bevacizumab therapy (NCI-CTCAE v.3) (see section 4.8).

Patients with untreated CNS metastases were routinely excluded from clinical trials with bevacizumab, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS

haemorrhage in such patients has not been prospectively evaluated in randomised clinical trials (see section 4.8). Patients should be monitored for signs and symptoms of CNS bleeding, and Alymsys treatment discontinued in cases of intracranial bleeding.

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

Pulmonary haemorrhage/haemoptysis

Patients with non-small cell lung cancer treated with bevacizumab may be at risk of serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis. Patients with recent pulmonary haemorrhage/ haemoptysis (> 2.5 mL of red blood) should not be treated with Alymsys.

Aneurysms and artery dissections

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

Congestive heart failure (CHF) (see section 4.8)

Reactions 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 hospitalisation. Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with Alymsys.

Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present.

In patients in AVF3694g who received treatment with anthracyclines and who had not received anthracyclines before, no increased incidence of all grade CHF was observed in the anthracycline + bevacizumab group compared to the treatment with anthracyclines only. CHF grade 3 or higher reactions were somewhat more frequent among patients receiving bevacizumab in combination with chemotherapy than in patients receiving chemotherapy alone. This is consistent with results in patients in other studies of metastatic breast cancer who did not receive concurrent anthracycline treatment (NCI-CTCAE v.3) (see section 4.8).

Neutropenia and infections (see section 4.8)

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. This has mainly been seen in combination with platinum- or taxane-based therapies in the treatment of NSCLC, mBC, and in combination with paclitaxel and topotecan in persistent, recurrent, or metastatic cervical cancer.

Hypersensitivity reactions (including anaphylactic shock) /infusion reactions (see section 4.8)

Patients may be at risk of developing infusion/hypersensitivity reactions (including anaphylactic shock). Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanised monoclonal antibody. If a

reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

Osteonecrosis of the jaw (ONJ) (see section 4.8)

Cases of ONJ have been reported in cancer patients treated with bevacizumab, the majority of whom had received prior or concomitant treatment with intravenous bisphosphonates, for which ONJ is an identified risk. Caution should be exercised when Alymsys and intravenous 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 Alymsys. In patients who have previously received or are receiving intravenous bisphosphonates invasive dental procedures should be avoided, if possible.

Intravitreal use

Alymsys is not formulated for intravitreal use.

Eye disorders

Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intravitreal use of bevacizumab compounded from vials approved for intravenous administration in cancer patients. These reactions included infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these reactions have resulted in various degrees of visual loss, including permanent blindness.

Systemic effects following intravitreal use

A reduction of circulating VEGF concentration has been demonstrated following intravitreal anti-VEGF therapy. Systemic adverse reactions including non-ocular haemorrhages and arterial thromboembolic reactions have been reported following intravitreal injection of VEGF inhibitors.

Ovarian failure/fertility

Bevacizumab may impair female fertility (see sections 4.6 and 4.8). Therefore fertility preservation strategies should be discussed with women of childbearing potential prior to starting treatment with bevacizumab.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

This medicine contains 1.6 mg of polysorbate 20 in each 100 mg/4 mL vial and 6.4 mg in each 400 mg/16 mL vial which is equivalent to 0.4 mg/mL. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of antineoplastic agents on bevacizumab pharmacokinetics

No clinically relevant interaction of co-administered chemotherapy on bevacizumab pharmacokinetics was observed based on the results of population pharmacokinetic analyses. There were neither statistically significant nor clinically relevant differences in bevacizumab clearance in patients receiving bevacizumab monotherapy compared to patients receiving bevacizumab in combination with

interferon alfa-2a, erlotinib or chemotherapies (IFL, 5-FU/LV, carboplatin/paclitaxel, capecitabine, doxorubicin or cisplatin/gemcitabine).

Effect of bevacizumab on the pharmacokinetics of other antineoplastic agents

No clinically relevant interaction of bevacizumab was observed on the pharmacokinetics of co-administered interferon alfa 2a, erlotinib (and its active metabolite OSI-420), or the chemotherapies irinotecan (and its active metabolite SN38), capecitabine, oxaliplatin (as determined by measurement of free and total platinum), and cisplatin. Conclusions on the impact of bevacizumab on gemcitabine pharmacokinetics cannot be drawn.

Combination of bevacizumab and sunitinib malate

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

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

Combination with platinum- or taxane-based therapies (see sections 4.4 and 4.8)

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 and mBC.

Radiotherapy

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

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. Results from the randomised phase III studies, PACCE and CAIRO-2, in patients with mCRC suggest that the use of anti-EGFR monoclonal antibodies panitumumab and cetuximab, respectively, in combination with bevacizumab plus chemotherapy, is associated with decreased PFS and/or OS, and with increased toxicity compared with bevacizumab plus chemotherapy alone.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Women of childbearing potential have to use effective contraception during (and up to 6 months after) treatment.

Pregnancy

There are no clinical trial data on the use of bevacizumab in pregnant women. Studies in animals have shown reproductive toxicity including malformations (see section 5.3). IgGs are known to cross the placenta, and bevacizumab is anticipated to inhibit angiogenesis in the foetus, and thus is suspected to cause serious birth defects when administered during pregnancy. In the post-marketing setting, cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known

embryotoxic chemotherapeutics have been observed (see section 4.8). Alymsys is contraindicated in pregnancy (see section 4.3).

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 (see section 5.3), women must discontinue breast-feeding during therapy and not breast-feed for at least six months following the last dose of bevacizumab.

Fertility

Repeat dose toxicity studies in animals have shown that bevacizumab may have an adverse effect on female fertility (see section 5.3). In a phase III trial in the adjuvant treatment of patients with colon cancer, a substudy with premenopausal women has shown a higher incidence of new cases of ovarian failure in the bevacizumab group compared to the control group. After discontinuation of bevacizumab treatment, ovarian function recovered in the majority of patients. Long term effects of the treatment with bevacizumab on fertility are unknown.

4.7 Effects on ability to drive and use machines

Bevacizumab has no or negligible influence on the ability to drive and use machines. However, somnolence and syncope have been reported with bevacizumab use (see Table 1 in section 4.8). If patients are experiencing symptoms that affect their vision or concentration, or their ability to react, they should be advised not to drive and use machines until symptoms abate.

4.8 Undesirable effects

Summary of the safety profile

The overall safety profile of bevacizumab is based on data from over 5,700 patients with various malignancies, predominantly treated with bevacizumab in combination with chemotherapy in clinical trials.

The most serious adverse reactions were:

- Gastrointestinal perforations (see section 4.4).
- Haemorrhage, including pulmonary haemorrhage/haemoptysis, which is more common in non-small cell lung cancer patients (see section 4.4).
- Arterial thromboembolism (see section 4.4).

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

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

Tabulated list of adverse reactions

The adverse reactions listed in this section fall into the following frequency categories: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Tables 1 and 2 list adverse reactions associated with the use of bevacizumab in combination with different chemotherapy regimens in multiple indications, by MedDRA system organ class.

Table 1 provides all adverse reactions by frequency that were determined to have a causal relationship with bevacizumab through:

- comparative incidences noted between clinical trial treatment arms (with at least a 10% difference compared to the control arm for NCI-CTCAE grade 1-5 reactions or at least a 2% difference compared to the control arm for NCI-CTCAE grade 3-5 reactions,
- post-authorisation safety studies,
- spontaneous reporting,
- epidemiological studies\non-interventional or observational studies,
- or through an evaluation of individual case reports.

Table 2 provides the frequency of severe adverse reactions. Severe reactions are defined as adverse reactions with at least a 2% difference compared to the control arm in clinical trials for NCI-CTCAE grade 3-5 reactions. Table 2 also includes adverse reactions which are considered by the MAH to be clinically significant or severe.

Post-marketing adverse reactions are included in both Tables 1 and 2, where applicable. Detailed information about these post-marketing reactions are provided in Table 3.

Adverse reactions are added to the appropriate frequency category in the Tables below according to the highest incidence seen in any indication.

Within each frequency category, adverse reactions are presented in the order of decreasing seriousness.

Some of the adverse reactions are reactions commonly seen with chemotherapy; however, bevacizumab may exacerbate these reactions when combined with chemotherapeutic agents. Examples include palmar-plantar erythrodysaesthesia syndrome with pegylated liposomal doxorubicin or capecitabine, peripheral sensory neuropathy with paclitaxel or oxaliplatin, nail disorders or alopecia with paclitaxel, and paronychia with erlotinib.

Table 1. Adverse reactions by frequency

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Infections and infestations		Sepsis, Abscess[b,d], Cellulitis, Infection, Urinary tract infection		Necrotising fasciitis[a]		
Blood and lymphatic system disorders	Febrile neutropenia, Leukopenia, Neutropenia[b], Thrombocytopenia	Anaemia, Lymphopenia				
Immune system disorders		Hypersensitivity, Infusion reactions[a,b,d]		Anaphylactic shock		
Metabolism and nutrition disorders	Anorexia, Hypomagnesaemia, Hyponatraemia	Dehydration				
Nervous system disorders	Peripheral sensory neuropathy[b], Dysarthria, Headache, Dysguesia	Cerebrovascular accident, Syncope, Somnolence		Posterior reversible encephalopathy syndrome[a,b,d]	Hypertensive encephalopathy[a]	
Eye disorders	Eye disorder, Lacrimation increased					

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Cardiac disorders		Congestive heart failure[b,d], Supraventricular tachycardia				
Vascular disorders	Hypertension[b,d], Thromboembolism (venous)[b,d]	Thromboembolism (arterial)[b,d], Haemorrhage[b,d], Deep vein thrombosis				Renal thrombotic microangiopathy[a,b], Hyaline occlusive glomerular microangiopathy[a], Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders	Dyspnoea, Rhinitis, Epistaxis, Cough	Pulmonary haemorrhage/ Haemoptysis[b,d], Pulmonary embolism, Hypoxia, Dysphonia[a]				Pulmonary hypertension[a], Nasal septum perforation[a]
Gastrointestinal disorders	Rectal haemorrhage, Stomatitis, Constipation, Diarrhoea, Nausea, Vomiting, Abdominal pain	Gastrointestinal perforation[b,d], Intestinal perforation, Ileus, Intestinal obstruction, Recto-vaginal fistulae[d,e], Gastrointestinal disorder, Proctalgia				Gastrointestinal ulcer[a]
Hepatobiliary disorders						Gallbladder perforation[a,b]
Skin and subcutaneous tissue disorders	Wound healing complications[b,d], Exfoliative dermatitis, Dry skin, Skin discolouration	Palmar-plantar erythrodysaesthesia syndrome				
Musculoskeletal and connective tissue disorders	Arthralgia, Myalgia	Fistula[b,d], Muscular weakness, Back pain				Osteonecrosis of the jaw[a,b], Non-mandibular osteonecrosis[a,f]
Renal and urinary disorders	Proteinuria[b,d]					
Reproductive system and breast disorders	Ovarian failure[b,c,d]	Pelvic pain				
Congenital, familial, and genetic disorder						Foetal abnormalities[a,b]
General disorders and administration site conditions	Asthenia, Fatigue, Pyrexia, Pain, Mucosal inflammation	Lethargy				
Investigations	Weight decreased					

When events were noted as both all grade and grade 3-5 adverse drug reactions in clinical trials, the highest frequency observed in patients has been reported. Data are unadjusted for the differential time on treatment.

[a] For further information please refer to Table 3 "Adverse reactions reported in post-marketing setting".
[b] Terms represent a group of events that describe a medical concept rather than a single condition or MedDRA (Medical Dictionary for Regulatory Activities) preferred term. This group of medical terms may involve the same underlying pathophysiology (e.g. arterial thromboembolic reactions include cerebrovascular accident, myocardial infarction, transient ischaemic attack and other arterial thromboembolic reactions).
[c] Based on a substudy from NSABP C-08 with 295 patients.
[d] For additional information refer below within section "Description of selected serious adverse reactions".
[e] Recto-vaginal fistulae are the most common fistulae in the GI-vaginal fistula category.
[f] Observed in paediatric population only.

Table 2. Severe adverse reactions by frequency

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Infections and infestations		Sepsis, Cellulitis, Abscess[a,b], Infection, Urinary tract infection				Necrotising fasciitis[c]
Blood and lymphatic system disorders	Febrile neutropenia, Leukopenia, Neutropenia[a], Thrombocytopenia	Anaemia, Lymphopenia				
Immune system disorders		Hypersensitivity, Infusion reactions[a,b,c]		Anaphylactic shock		
Metabolism and nutrition disorders		Dehydration, Hyponatraemia				
Nervous system disorders	Peripheral sensory neuropathy[a]	Cerebrovascular accident, Syncope, Somnolence, Headache				Posterior reversible encephalopathy syndrome[a,b,c], Hypertensive encephalopathy[c]
Cardiac disorders		Congestive heart failure[a,b], Supraventricular tachycardia				
Vascular disorders	Hypertension[a,b]	Thromboembolism arterial[a,b], Haemorrhage[a,b], Thromboembolism (venous)[a,b], Deep vein thrombosis				Renal thrombotic microangiopathy[b,c], Hyaline occlusive glomerular microangiopathy[c], Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders		Pulmonary haemorrhage/ Haemoptysis[a,b], Pulmonary embolism, Epistaxis, Dyspnoea, Hypoxia				Pulmonary hypertension[c], Nasal septum perforation[c]
Gastrointestinal disorders	Diarrhoea, Nausea, Vomiting, Abdominal pain	Intestinal perforation, Ileus, Intestinal obstruction, Recto-vaginal fistulae[c,d], Gastrointestinal disorder, Stomatitis, Proctalgia				Gastrointestinal perforation[a,b], Gastrointestinal ulcer[c], Rectal haemorrhage

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Hepatobiliary disorders						Gallbladder perforation[b,c]
Skin and subcutaneous tissue disorders		Wound healing complications[a,b], Palmar-plantar erythrodysaesthesia syndrome				
Musculoskeletal and connective tissue disorders		Fistula[a,b], Myalgia, Arthralgia, Muscular weakness, Back pain				Osteonecrosis of the jaw[b,c]
Renal and urinary disorders		Proteinuria[a,b]				
Reproductive system and breast disorders		Pelvic pain				Ovarian failure[a,b]
Congenital, familial, and genetic disorder						Foetal abnormalities[a,c]
General disorders and administration site conditions	Asthenia, Fatigue	Pain, Lethargy, Mucosal inflammation				

Table 2 provides the frequency of severe adverse reactions. Severe reactions are defined as adverse reactions with at least a 2% difference compared to the control arm in clinical studies for NCI-CTCAE grade 3-5 reactions.
Table 2 also includes adverse reactions which are considered by the MAH to be clinically significant or severe. These clinically significant adverse reactions were reported in clinical trials but the grade 3-5 reactions did not meet the threshold of at least a 2% difference compared to the control arm. Table 2 also includes clinically significant adverse reactions that were observed only in the post-marketing setting, therefore, the frequency and NCI-CTCAE grade is not known. These clinically significant reactions have therefore been included in Table 2 within the column entitled “Frequency not known”.

[a] Terms represent a group of events that describe a medical concept rather than a single condition or MedDRA (Medical Dictionary for Regulatory Activities) preferred term. This group of medical terms may involve the same underlying pathophysiology (e.g. arterial thromboembolic reactions include cerebrovascular accident, myocardial infarction, transient ischaemic attack and other arterial thromboembolic reactions).

[b] For additional information refer below within section "Description of selected serious adverse reactions".

[c] For further information please refer to Table 3 “Adverse reactions reported in post-marketing setting”.

[d] Recto-vaginal fistulae are the most common fistulae in the GI-vaginal fistula category.

Description of selected serious adverse reactions

GI perforations and fistulae (see section 4.4)

Bevacizumab has been associated with serious cases of gastrointestinal perforation.

GI perforations have been reported in clinical trials with an incidence of less than 1% in patients with non-squamous non-small cell lung cancer, up to 1.3% in patients with metastatic breast cancer, up to 2.0% in patients with metastatic renal cell cancer or in patients with ovarian cancer, and up to 2.7% (including gastrointestinal fistula and abscess) in patients with metastatic colorectal cancer. From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), GI perforations (all grade) were reported in 3.2% of patients, all of whom had a history of prior pelvic radiation.

The occurrence of those events varied in type and severity, ranging from free air seen on the plain abdominal X-ray, which resolved without treatment, to intestinal perforation with abdominal abscess

and fatal outcome. In some cases, underlying intra-abdominal inflammation was present, either from gastric ulcer disease, tumour necrosis, diverticulitis, or chemotherapy-associated colitis.

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.

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 cancer.

GI-vaginal fistulae in study GOG-0240

In a trial of patients with persistent, recurrent or metastatic cervical cancer, the incidence of GI-vaginal fistulae was 8.3% in bevacizumab-treated patients and 0.9% in control patients, all of whom had a history of prior pelvic radiation. The frequency of GI-vaginal fistulae in the group treated with bevacizumab + chemotherapy was higher in patients with recurrence within the field of prior radiation (16.7%) compared with patients with no prior radiation and/ or no recurrence inside the field of prior radiation (3.6%). The corresponding frequencies in the control group receiving chemotherapy alone were 1.1% vs. 0.8%, respectively. Patients who develop GI-vaginal fistulae may also have bowel obstructions and require surgical intervention as well as diverting ostomies.

Non-GI fistulae (see section 4.4)

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

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (GOG-240), 1.8% of bevacizumab-treated patients and 1.4% of control patients were reported to have had non-gastrointestinal vaginal, vesical, or female genital tract fistulae.

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

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

Wound healing (see section 4.4)

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

In clinical trials of metastatic carcinoma of the colon or rectum, there was no increased risk of postoperative bleeding or wound healing complications observed in patients who underwent major surgery 28-60 days prior to starting bevacizumab. An increased incidence of post-operative bleeding or wound healing complication occurring within 60 days of major surgery was observed if the patient was being treated with bevacizumab at the time of surgery. The incidence varied between 10% (4/40) and 20% (3/15).

Serious wound healing complications, including anastomotic complications, have been reported, some of which had a fatal outcome.

In locally recurrent and metastatic breast cancer trials, grade 3-5 wound healing complications were observed in up to 1.1% of patients receiving bevacizumab compared with up to 0.9% of patients in the control arms (NCI-CTCAE v.3).

In clinical trials of ovarian cancer, grade 3-5 wound healing complications were observed in up to 1.8% of patients in the bevacizumab arm versus 0.1% in the control arm (NCI-CTCAE v.3).

Hypertension (see section 4.4)

In clinical trials, with the exception of study JO25567, the overall incidence of hypertension (all grades) ranged up to 42.1% in the bevacizumab-containing arms compared with up to 14% in the control arms. The overall incidence of NCI-CTC grade 3 and 4 hypertension in patients receiving bevacizumab ranged from 0.4% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of patients treated with bevacizumab and chemotherapy compared to up to 0.2% of patients treated with the same chemotherapy alone.

In study JO25567, all grade hypertension was observed in 77.3% of the patients who received bevacizumab in combination with erlotinib as first-line treatment for non-squamous NSCLC with EGFR activating mutations, compared to 14.3% of patients treated with erlotinib alone. Grade 3 hypertension was 60.0% in patients treated with bevacizumab in combination with erlotinib compared to 11.7% in patients treated with erlotinib alone. There were no grade 4 or 5 hypertension events.

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 bevacizumab treatment or hospitalisation.

Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal.

The risk of bevacizumab-associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy.

Posterior reversible encephalopathy syndrome (see section 4.4)

There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with PRES, a rare neurological disorder. Presentation may include seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. The clinical presentation of PRES is often nonspecific, and therefore the diagnosis of PRES requires confirmation by brain imaging, preferably MRI.

In patients developing PRES, early recognition of symptoms with prompt treatment of specific symptoms including control of hypertension (if associated with severe uncontrolled hypertension) is recommended in addition to discontinuation of bevacizumab therapy. Symptoms usually resolve or improve within days after treatment discontinuation, although some patients have experienced some neurologic sequelae. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known.

Across clinical trials, 8 cases of PRES have been reported. Two of the eight cases did not have radiological confirmation via MRI.

Proteinuria (see section 4.4)

In clinical trials, proteinuria has been reported within the range of 0.7% to 54.7% of patients receiving bevacizumab.

Proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome, with the great majority as grade 1 proteinuria (NCI-CTCAE v.3). Grade 3 proteinuria was reported in up to 10.9% of treated patients. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of treated patients. Testing for proteinuria is recommended prior to start of Alymsys therapy. In most clinical trials urine protein levels of ≥ 2 g/24 hrs led to the holding of bevacizumab until recovery to < 2 g/24 hrs.

Haemorrhage (see section 4.4)

In clinical trials across all indications the overall incidence of NCI-CTCAE v.3 grade 3-5 bleeding reactions ranged from 0.4% to 6.9% in bevacizumab treated patients, compared with up to 4.5% of patients in the chemotherapy control group.

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), grade 3-5 bleeding reactions have been reported in up to 8.3% of patients treated with bevacizumab in combination with paclitaxel and topotecan compared with up to 4.6% of patients treated with paclitaxel and topotecan.

The haemorrhagic reactions that have been observed in clinical trials were predominantly tumour-associated haemorrhage (see below) and minor mucocutaneous haemorrhage (e.g. epistaxis).

Tumour-associated haemorrhage (see section 4.4)

Major or massive pulmonary haemorrhage/haemoptysis has been observed primarily in trials in patients with non-small cell lung cancer (NSCLC). Possible risk factors include squamous cell histology, treatment with antirheumatic/anti-inflammatory substances, 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 phase III trials, while patients with unknown tumour histology were included.

In patients with NSCLC excluding predominant squamous histology, all grade reactions were seen with a frequency of up to 9.3% when treated with bevacizumab plus chemotherapy compared with up to 5% in the patients treated with chemotherapy alone. Grade 3-5 reactions have been observed in up to 2.3% of patients treated with bevacizumab plus chemotherapy as compared with < 1% with chemotherapy alone (NCI-CTCAE v.3). Major or massive pulmonary haemorrhage/haemoptysis can occur suddenly and up to two thirds of the serious pulmonary haemorrhages resulted in a fatal outcome.

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

Tumour-associated haemorrhage was also seen rarely in other tumour types and locations, including cases of central nervous system (CNS) bleeding in patients with CNS metastases (see section 4.4).

The incidence of CNS bleeding in patients with untreated CNS metastases receiving bevacizumab has not been prospectively evaluated in randomised clinical trials. In an exploratory retrospective analysis of data from 13 completed randomised trials in patients with various tumour types, 3 patients out of 91 (3.3%) with brain metastases experienced CNS bleeding (all grade 4) when treated with bevacizumab, compared to 1 case (grade 5) out of 96 patients (1%) that were not exposed to bevacizumab. In two subsequent studies in patients with treated brain metastases (which included around 800 patients), one case of grade 2 CNS haemorrhage was reported in 83 subjects treated with bevacizumab (1.2%) at the time of interim safety analysis (NCI-CTCAE v.3).

Across all clinical trials, mucocutaneous haemorrhage has been seen in up to 50% of bevacizumab-treated patients. These were most commonly NCI-CTCAE v.3 grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in the bevacizumab treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous haemorrhage (e.g. epistaxis) may be dose-dependent.

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

Thromboembolism (see section 4.4)

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

In clinical trials, the overall incidence of arterial thromboembolic reactions ranged up to 3.8% in the bevacizumab-containing arms compared with up to 2.1% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving bevacizumab compared to 0.5% in patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischaemic attacks) were reported in up to 2.7% of patients treated with bevacizumab in combination with chemotherapy compared to up to 0.5% of patients treated with chemotherapy alone. Myocardial infarction was reported in up to 1.4% of patients treated with bevacizumab in combination with chemotherapy compared to up to 0.7% of patients treated with chemotherapy alone.

In one clinical trial evaluating bevacizumab in combination with 5-fluorouracil/folinic acid, AVF2192g, patients with metastatic colorectal cancer who were not candidates for treatment with irinotecan were included. In this trial arterial thromboembolic reactions were observed in 11% (11/100) of patients compared to 5.8% (6/104) in the chemotherapy control group.

Venous thromboembolism
The incidence of venous thromboembolic reactions in clinical trials was similar in patients receiving bevacizumab in combination with chemotherapy compared to those receiving the control chemotherapy alone. Venous thromboembolic reactions include deep venous thrombosis, pulmonary embolism and thrombophlebitis.

In clinical trials across indications, the overall incidence of venous thromboembolic reactions ranged from 2.8% to 17.3% of bevacizumab-treated patients compared with 3.2% to 15.6% in the control arms.

Grade 3-5 (NCI-CTCAE v.3) venous thromboembolic reactions have been reported in up to 7.8% of patients treated with chemotherapy plus bevacizumab compared with up to 4.9% in patients treated with chemotherapy alone (across indications, excluding persistent, recurrent, or metastatic cervical cancer).

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), grade 3-5 venous thromboembolic events have been reported in up to 15.6% of patients treated with bevacizumab in combination with paclitaxel and cisplatin compared with up to 7.0% of patients treated with paclitaxel and cisplatin.

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

Congestive heart failure (CHF)

In clinical trials with bevacizumab, congestive heart failure (CHF) was observed in all cancer indications studied to date, but occurred predominantly in patients with metastatic breast cancer. In four phase III trials (AVF2119g, E2100, BO17708 and AVF3694g) in patients with metastatic breast cancer CHF grade 3 (NCI-CTCAE v.3) or higher was reported in up to 3.5% of patients treated with bevacizumab in combination with chemotherapy compared with up to 0.9% in the control arms. For patients in study AVF3694g who received anthracyclines concomitantly with bevacizumab, the incidences of grade 3 or higher CHF for the respective bevacizumab and control arms were similar to those in the other studies in metastatic breast cancer: 2.9% in the anthracycline + bevacizumab arm and 0% in the anthracycline + placebo arm. In addition, in study AVF3694g the incidences of all grade

CHF were similar between the anthracycline + bevacizumab (6.2%) and the anthracycline + placebo arms (6.0%).

Most patients who developed CHF during mBC trials showed improved symptoms and/or left ventricular function following appropriate medical therapy.

In most clinical trials of bevacizumab, patients with pre-existing CHF of NYHA (New York Heart Association) 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 should be considered for patients exposed to cumulative doxorubicin doses greater than 300 mg/m^2 when combined with bevacizumab.

Hypersensitivity reactions (including anaphylactic shock) /infusion reactions (see section 4.4 and *Post-marketing experience* below)

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

Infections

From a clinical trial in patients with persistent, recurrent, or metastatic cervical cancer (study GOG-0240), grade 3-5 infections have been reported in up to 24% of patients treated with bevacizumab in combination with paclitaxel and topotecan compared with up to 13% of patients treated with paclitaxel and topotecan.

Ovarian failure/fertility (see sections 4.4 and 4.6)

In NSABP C-08, a phase III trial of bevacizumab in adjuvant treatment of patients with colon cancer, the incidence of new cases of ovarian failure, defined as amenorrhoea lasting 3 or more months, FSH level ≥ 30 mIU/mL and a negative serum β-HCG pregnancy test, has been evaluated in 295 premenopausal women. New cases of ovarian failure were reported in 2.6% patients in the mFOLFOX-6 group compared to 39% in the mFOLFOX-6 + bevacizumab group. After discontinuation of bevacizumab treatment, ovarian function recovered in 86.2% of these evaluable women. Long term effects of the treatment with bevacizumab on fertility are unknown.

Laboratory abnormalities

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

Across clinical trials, the following grade 3 and 4 (NCI-CTCAE v.3) laboratory abnormalities occurred in patients treated with bevacizumab with at least a 2% difference compared to the corresponding control groups: hyperglycaemia, decreased haemoglobin, hypokalaemia, hyponatraemia, decreased white blood cell count, increased international normalised ratio (INR).

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

Other special populations

Elderly patients

In randomised clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic reactions, including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs). Other reactions with a higher frequency seen in patients over 65 were grade 3-4 leukopenia and thrombocytopenia (NCI-CTCAE v.3); and all grade neutropenia, diarrhoea, nausea, headache and fatigue as compared to those aged ≤ 65 years when treated with bevacizumab (see sections 4.4 and 4.8 under *Thromboembolism*). In one clinical trial, the incidence of hypertension of grade ≥ 3 was two-fold higher in patients aged > 65 years than in the younger age group (< 65 years). In a study of platinum-resistant recurrent ovarian cancer patients, alopecia, mucosal inflammation, peripheral sensory neuropathy, proteinuria and hypertension were also reported and occurred at a rate at least 5% higher in the CT + BV arm for bevacizumab-treated patients ≥ 65 years of age compared with bevacizumab-treated patients aged < 65 years.

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

Paediatric population

The safety and efficacy of bevacizumab in children less than 18 years old have not been established.

In study BO25041 of bevacizumab added to post-operative radiation therapy (RT) with concomitant and adjuvant temozolomide in paediatric patients with newly diagnosed supratentorial, infratentorial, cerebellar, or peduncular high-grade glioma, the safety profile was comparable with that observed in other tumour types in adults treated with bevacizumab.

In study BO20924 of bevacizumab with current standard of care in rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma, the safety profile of bevacizumab-treated children was comparable with that observed in adults treated with bevacizumab.

Alymsys is not approved for use in patients under the age of 18 years. In published literature reports, cases of non-mandibular osteonecrosis have been observed in patients under the age of 18 years treated with bevacizumab.

Post-marketing experience

Table 3. Adverse reactions reported in post-marketing setting

System organ class (SOC)	Reactions (frequency*)
Infections and infestations	Necrotising fasciitis, usually secondary to wound healing complications, gastrointestinal perforation or fistula formation (rare) (see also section 4.4)
Immune system disorders	Hypersensitivity reactions and infusion reactions (common); with the following possible co-manifestations: dyspnoea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting (see also section 4.4 and *Hypersensitivity reactions/infusion* reactions above) Anaphylactic shock (rare) (see also section 4.4)

System organ class (SOC)	Reactions (frequency*)
Nervous system disorders	Hypertensive encephalopathy (very rare) (see also section 4.4 and *Hypertension* in section 4.8) Posterior Reversible Encephalopathy Syndrome (PRES) (rare) (see also section 4.4)
Vascular disorders	Renal thrombotic microangiopathy with or without concomitant sunitinib use, and hyaline occlusive glomerular microangiopathy which may be clinically manifested as proteinuria (not known) . For further information on proteinuria see section 4.4 and *Proteinuria* in section 4.8
Respiratory, thoracic and mediastinal disorders	Nasal septum perforation (not known) Pulmonary hypertension (not known) Dysphonia (common)
Gastrointestinal disorders	Gastrointestinal ulcer (not known)
Hepatobiliary disorders	Gall bladder perforation (not known)
Musculoskeletal and connective tissue disorders	Cases of osteonecrosis of the jaw (ONJ) have been reported in patients treated with bevacizumab, most of which occurred in patients who had identified risk factors for ONJ, in particular exposure to intravenous bisphosphonates and/or a history of dental disease requiring invasive dental procedures (see also section 4.4)
	Cases of non-mandibular osteonecrosis have been observed in bevacizumab-treated paediatric patients (see section 4.8, Paediatric population)
Congenital, familial, and genetic disorder	Cases of foetal abnormalities in women treated with bevacizumab alone or in combination with known embryotoxic chemotherapeutics have been observed (see section 4.6)

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The highest dose tested in humans (20 mg/kg of body weight, intravenous every 2 weeks) was associated with severe migraine in several patients.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic and immunomodulating agents, antineoplastic agents, monoclonal antibodies and antibody drug conjugates, ATC code: L01FG01

Alymsys is a biosimilar medicinal product. Detailed information is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Mechanism of action

Bevacizumab binds to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt-1 (VEGFR-1) and

KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.

Pharmacodynamic effects

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

Clinical efficacy and safety

Metastatic carcinoma of the colon or rectum (mCRC)

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

- AVF2107g: A weekly schedule of irinotecan/bolus 5-fluorouracil/folinic acid (IFL) for a total of 4 weeks of each 6 week-cycle (Saltz regimen).
- AVF0780g: In combination with bolus 5-fluorouracil/folinic acid (5-FU/FA) for a total of 6 weeks of each 8 week-cycle (Roswell Park regimen).
- AVF2192g: In combination with bolus 5-FU/FA 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.

Three additional studies with bevacizumab have been conducted in mCRC patients: first-line (NO16966), second-line with no previous bevacizumab treatment (E3200), and second-line with previous bevacizumab treatment following disease progression in first-line (ML18147). In these studies, bevacizumab was administered at the following dosing regimens in combination with FOLFOX-4 (5-FU/LV/oxaliplatin), XELOX (capecitabine/oxaliplatin), and fluoropyrimidine/irinotecan and fluoropyrimidine/oxaliplatin:

- NO16966: Bevacizumab 7.5 mg/kg of body weight every 3 weeks in combination with oral capecitabine and intravenous oxaliplatin (XELOX) or bevacizumab 5 mg/kg every 2 weeks in combination with leucovorin plus 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4).
- E3200: Bevacizumab 10 mg/kg of body weight every 2 weeks in combination with leucovorin and 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4) in bevacizumab-naïve patients.
- ML18147: Bevacizumab 5.0 mg/kg of body weight every 2 weeks or bevacizumab 7.5 mg/kg of body weight every 3 weeks in combination with fluoropyrimidine/irinotecan or fluoropyrimidine/oxaliplatin in patients with disease progression following first-line treatment with bevacizumab. Use of irinotecan- or oxaliplatin-containing regimen was switched depending on first-line usage of either oxaliplatin or irinotecan.

AVF2107g
This was a phase III randomised, double-blind, active-controlled clinical trial evaluating bevacizumab in combination with IFL as first-line treatment for metastatic carcinoma of the colon or rectum. Eight hundred and thirteen patients were randomised to receive IFL + placebo (Arm 1) or IFL + bevacizumab (5 mg/kg every 2 weeks, Arm 2). A third group of 110 patients received bolus 5-FU/FA + bevacizumab (Arm 3). Enrolment in Arm 3 was discontinued, as pre-specified, once safety of bevacizumab with the IFL regimen was established and considered acceptable. All treatments were continued until disease progression. The overall mean age was 59.4 years; 56.6% of patients had an

ECOG performance status of 0, 43% had a value of 1 and 0.4% had a value of 2. 15.5% had received prior radiotherapy and 28.4% prior chemotherapy.

The primary efficacy variable of the trial was overall survival. The addition of bevacizumab to IFL resulted in statistically significant increases in overall survival, progression-free survival and overall response rate (see Table 4). The clinical benefit, as measured by overall 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.

The efficacy results of bevacizumab in combination with IFL-chemotherapy are displayed in Table 4.

Table 4. Efficacy results for trial AVF2107g

	AVF2107g	
	Arm 1 IFL + placebo	**Arm 2 IFL + bevacizumab[a]**
Number of patients	411	402
Overall survival		
Median time (months)	15.6	20.3
95% CI	14.29-16.99	18.46-24.18
Hazard ratio[b]	0.660 (p-value = 0.00004)	
Progression-free survival		
Median time (months)	6.2	10.6
Hazard ratio	0.54 (p-value < 0.0001)	
Overall response rate		
Rate (%)	34.8	44.8
	(p-value = 0.0036)	

[a] 5 mg/kg every 2 weeks.
[b] Relative to control arm.

Among the 110 patients randomised to Arm 3 (5-FU/FA + bevacizumab) prior to discontinuation of this arm, the median overall survival was 18.3 months and the median progression-free survival was 8.8 months.

AVF2192g
This was a phase II randomised, double-blind, active-controlled clinical trial evaluating the efficacy and safety of bevacizumab in combination with 5-FU/FA as first-line treatment for metastatic colorectal cancer in patients who were not optimal candidates for first-line irinotecan treatment. One hundred and five patients were randomised to 5-FU/FA + placebo arm and 104 patients to 5-FU/FA + bevacizumab (5 mg/kg every 2 weeks) arm. All treatments were continued until disease progression. The addition of bevacizumab 5 mg/kg every two weeks to 5-FU/FA resulted in higher objective response rates, significantly longer progression-free survival, and a trend in longer survival as compared to 5-FU/FA chemotherapy alone.

AVF0780g
This was a phase II randomised, active-controlled, open-labelled clinical trial investigating bevacizumab in combination with 5-FU/FA as first-line treatment of metastatic colorectal cancer. The median age was 64 years. 19% of the patients had received prior chemotherapy and 14% prior radiotherapy. Seventy-one patients were randomised to receive bolus 5-FU/FA or 5-FU/FA + bevacizumab (5 mg/kg every 2 weeks). A third group of 33 patients received bolus 5-FU/FA + 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 bevacizumab 5 mg/kg every two weeks to 5-FU/FA resulted in higher objective response rates, longer progression-free survival, and a trend in longer survival, compared with 5-FU/FA chemotherapy alone (see Table 5). These efficacy data are consistent with the results from trial AVF2107g.

The efficacy data from trials AVF0780g and AVF2192g investigating bevacizumab in combination with 5-FU/FA chemotherapy are summarised in Table 5.

Table 5. Efficacy results for trials AVF0780g and AVF2192g

	AVF0780g			AVF2192g	
	5-FU/FA	**5-FU/FA + bevacizumab[a]**	**5-FU/FA + bevacizumab[b]**	**5-FU/FA + placebo**	**5-FU/FA + bevacizumab**
Number of patients	36	35	33	105	104
Overall survival					
Median time (months)	13.6	17.7	15.2	12.9	16.6
95% CI				10.35 - 16.95	13.63 - 19.32
Hazard ratio[c]	-	0.52	1.01		0.79
p-value		0.073	0.978		0.16
Progression-free survival					
Median time (months)	5.2	9.0	7.2	5.5	9.2
Hazard ratio		0.44	0.69		0.5
p-value	-	0.0049	0.217		0.0002
Overall response rate					
Rate (percent)	16.7	40.0	24.2	15.2	26
95% 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 time (months)	NR	9.3	5.0	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.
NR = Not Reached.

NO16966
This was a phase III randomised, double-blind (for bevacizumab), clinical trial investigating bevacizumab 7.5 mg/kg in combination with oral capecitabine and intravenous oxaliplatin (XELOX), administered on a 3-weekly schedule; or bevacizumab 5 mg/kg in combination with leucovorin with 5-fluorouracil bolus, followed by 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule. The trial contained two parts: an initial unblinded 2-arm part (Part I) in which patients were randomised to two different treatment groups (XELOX and FOLFOX-4) and a subsequent 2 x 2 factorial 4-arm part (Part II) in which patients were randomised to four treatment groups (XELOX + placebo, FOLFOX-4 + placebo, XELOX + bevacizumab, FOLFOX-4 + bevacizumab). In Part II, treatment assignment was double-blind with respect to bevacizumab.

Approximately 350 patients were randomised into each of the 4 trial arms in the Part II of the trial.

Table 6. Treatment regimens in trial NO16966 (mCRC)

	Treatment	Starting dose	Schedule
FOLFOX-4 or	Oxaliplatin	85 mg/m^2 intravenous 2 h	Oxaliplatin on day 1

	Treatment	Starting dose	Schedule
FOLFOX-4 + bevacizumab	Leucovorin 5-Fluorouracil	200 mg/m^2 intravenous 2 h 400 mg/m^2 intravenous bolus, 600 mg/m^2 intravenous 22 h	Leucovorin on day 1 and 2 5-fluorouracil intravenous bolus/infusion, each on days 1 and 2
	Placebo or bevacizumab	5 mg/kg intravenous 30-90 min	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX + bevacizumab	Oxaliplatin Capecitabine	130 mg/m^2 intravenous 2 h 1,000 mg/m^2 oral bid	Oxaliplatin on day 1 Capecitabine oral bid for 2 weeks (followed by 1 week off treatment)
	Placebo or bevacizumab	7.5 mg/kg intravenous 30-90 min	Day 1, prior to XELOX, q 3 weeks
5-Fluorouracil: intravenous bolus injection immediately after leucovorin			

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

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

- Superiority of the bevacizumab-containing arms versus the chemotherapy alone arms in the overall comparison was demonstrated in terms of progression-free survival in the ITT population (Table 7).

Secondary PFS analyses, based on 'on-treatment'-based response assessments, confirmed the significantly superior clinical benefit for patients treated with bevacizumab (analyses shown in Table 7), consistent with the statistically significant benefit observed in the pooled analysis.

Table 7. Key efficacy results for the superiority analysis (ITT population, trial NO16966)

Endpoint (months)	FOLFOX-4 or XELOX + placebo (n = 701)	FOLFOX-4 or XELOX + bevacizumab (n = 699)	p-value
Primary endpoint			
Median PFS**	8.0	9.4	0.0023
Hazard ratio (97.5% CI)[a]	0.83 (0.72 - 0.95)		
Secondary endpoints			
Median PFS (on treatment)**	7.9	10.4	< 0.0001
Hazard ratio (97.5% CI)	0.63 (0.52 - 0.75)		
Overall response rate (invest. assessment)**	49.2%	46.5%	
Median overall survival*	19.9	21.2	0.0769
Hazard ratio (97.5% CI)	0.89 (0.76 - 1.03)		

* Overall survival analysis at clinical cut-off 31 January 2007.
** Primary analysis at clinical cut-off 31 January 2006.
[a] Relative to control arm.

In the FOLFOX treatment subgroup, the median PFS was 8.6 months in placebo and 9.4 months in bevacizumab-treated patients, HR = 0.89, 97.5% CI = [0.73; 1.08]; p-value = 0.1871, the corresponding results in the XELOX treatment subgroup being 7.4 vs. 9.3 months, HR = 0.77, 97.5% CI = [0.63; 0.94]; p-value = 0.0026.

The median overall survival was 20.3 months in placebo and 21.2 months in bevacizumab-treated patients in the FOLFOX treatment subgroup, HR = 0.94, 97.5% CI = [0.75; 1.16]; p-value = 0.4937, the corresponding results in the XELOX, treatment subgroup being 19.2 vs. 21.4 months, HR = 0.84, 97.5% CI = [0.68; 1.04]; p-value = 0.0698.

ECOG E3200
This was a phase III randomised, active-controlled, open-label trial investigating bevacizumab 10 mg/kg in combination with leucovorin with 5-fluorouracil bolus and then 5-fluorouracil infusion, with intravenous oxaliplatin (FOLFOX-4), administered on a 2-weekly schedule in previously-treated patients (second-line) with advanced colorectal cancer. In the chemotherapy arms, the FOLFOX-4 regimen used the same doses and schedule as shown in Table 6 for trial NO16966.

The primary efficacy parameter of the trial was overall survival, defined as the time from randomisation to death from any cause. Eight hundred and twenty-nine patients were randomised (292 FOLFOX-4, 293 bevacizumab + FOLFOX-4 and 244 bevacizumab monotherapy). The addition of bevacizumab to FOLFOX-4 resulted in a statistically significant prolongation of survival. Statistically significant improvements in progression-free survival and objective response rate were also observed (see Table 8).

Table 8. Efficacy results for trial E3200

	E3200	
	FOLFOX-4	**FOLFOX-4 + bevacizumab[a]**
Number of patients	292	293
Overall survival		
Median (months)	10.8	13.0
95% CI	10.12 - 11.86	12.09 - 14.03
Hazard ratio[b]	0.751 (p-value = 0.0012)	
Progression-free survival		
Median (months)	4.5	7.5
Hazard ratio	0.518 (p-value < 0.0001)	
Objective response rate		
Rate	8.6%	22.2%
	(p-value < 0.0001)	

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

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

ML18147
This was a phase III randomised, controlled, open-label trial investigating bevacizumab 5.0 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks in combination with fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone in patients with mCRC who have progressed on a first-line bevacizumab-containing regimen.

Patients with histologically confirmed mCRC and disease progression were randomised 1:1 within 3 months after discontinuation of bevacizumab first-line therapy to receive

fluoropyrimidine/oxaliplatin- or fluoropyrimidine/irinotecan-based chemotherapy (chemotherapy switched depending on first-line chemotherapy) with or without bevacizumab. Treatment was given until progressive disease or unacceptable toxicity. The primary outcome measure was overall survival defined as the time from randomisation until death from any cause.

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

Table 9. Efficacy results for study ML18147 (ITT population)

	ML18147	
	Fluoropyrimidine/irinotecan or Fluoropyrimidine/oxaliplatin based chemotherapy	**Fluoropyrimidine/irinotecan or Fluoropyrimidine/oxaliplatin based chemotherapy + bevacizumab[a]**
Number of patients	410	409
Overall survival		
Median (months)	9.8	11.2
Hazard ratio (95% confidence interval)	0.81 (0.69, 0.94) (p-value = 0.0062)	
Progression-free survival		
Median (months)	4.1	5.7
Hazard ratio (95% confidence interval)	0.68 (0.59, 0.78) (p-value < 0.0001)	
Objective response rate (ORR)		
Patients included in analysis	406	404
Rate	3.9%	5.4%
	(p-value = 0.3113)	

[a] 5.0 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks.

Statistically significant improvements in progression-free survival were also observed. Objective response rate was low in both treatment arms and the difference was not significant.

Study E3200 used a 5 mg/kg/week equivalent dose of bevacizumab in bevacizumab-naïve patients, while study ML18147 used a 2.5 mg/kg/week equivalent dose of bevacizumab in bevacizumab-pretreated patients. A cross-trial comparison of the efficacy and safety data is limited by differences between these studies, most notably in patient populations, previous bevacizumab exposure and chemotherapy regimens. Both the 5 mg/kg/week and 2.5 mg/kg/week equivalent doses of bevacizumab provided a statistically significant benefit with regards to OS (HR 0.751 in study E3200; HR 0.81 in study ML18147) and PFS (HR 0.518 in study E3200; HR 0.68 in study ML18147). In terms of safety, there was a higher overall incidence of grade 3-5 AEs in study E3200 relative to study ML18147.

Metastatic breast cancer (mBC)

Two large Phase III trials were designed to investigate the treatment effect of bevacizumab in combination with two individual chemotherapy agents, as measured by the primary endpoint of PFS. A clinically meaningful and statistically significant improvement in PFS was observed in both trials.

Summarised below are PFS results for the individual chemotherapy agents included in the indication:

- Study E2100 (paclitaxel)
  - Median PFS increase 5.6 months, HR 0.421 (p < 0.0001, 95% CI 0.343; 0.516)
- Study AVF3694g (capecitabine)
  - Median PFS increase 2.9 months, HR 0.69 (p = 0.0002, 95% CI 0.56; 0.84)

Further details of each study and the results are provided below.

ECOG E2100
Trial E2100 was an open-label, randomised, active controlled, multicentre clinical trial evaluating bevacizumab in combination with paclitaxel for locally recurrent or metastatic breast cancer in patients who had not previously received chemotherapy for locally recurrent and metastatic disease. Patients were randomised to paclitaxel alone (90 mg/m^2 intravenous over 1 hour once weekly for three out of four weeks) or in combination with bevacizumab (10 mg/kg intravenous infusion every two weeks). Prior hormonal therapy for the treatment of metastatic disease was allowed. Adjuvant taxane therapy was allowed only if it was completed at least 12 months prior to trial entry. Of the 722 patients in the trial, the majority of patients had HER2-negative disease (90%), with a small number of patients with unknown (8%) or confirmed HER2-positive status (2%), who had previously been treated with or were considered unsuitable for trastuzumab therapy. Furthermore, 65% of patients had received adjuvant chemotherapy including 19% prior taxanes and 49% prior anthracyclines. Patients with central nervous system metastases, including previously treated or resected brain lesions, were excluded.

In trial E2100, patients were treated until disease progression. In situations where early discontinuation of chemotherapy was required, treatment with bevacizumab as a single agent continued until disease progression. The patient characteristics were similar across the trial arms. The primary endpoint of this trial was progression free survival (PFS), based on trial investigators' assessment of disease progression. In addition, an independent review of the primary endpoint was also conducted. The results of this trial are presented in Table 10.

Table 10. Trial E2100 efficacy results

Progression-free survival				
	Investigator assessment*		IRF assessment	
	Paclitaxel (n = 354)	Paclitaxel/ bevacizumab (n = 368)	Paclitaxel (n = 354)	Paclitaxel/ bevacizumab (n = 368)
Median PFS (months)	5.8	11.4	5.8	11.3
HR (95% CI)	0.421 (0.343; 0.516)		0.483 (0.385; 0.607)	
p-value	< 0.0001		< 0.0001	
Response rates (for patients with measurable disease)				
	Investigator assessment		IRF assessment	
	Paclitaxel (n = 273)	Paclitaxel/ bevacizumab (n = 252)	Paclitaxel (n = 243)	Paclitaxel/ bevacizumab (n = 229)
% pts with objective response	23.4	48.0	22.2	49.8
p-value	< 0.0001		< 0.0001	

* Primary analysis

Overall survival		
	Paclitaxel (n = 354)	Paclitaxel/ bevacizumab (n = 368)
Median OS (months)	24.8	26.5
HR (95% CI)	0.869 (0.722; 1.046)	

p-value	0.1374

The clinical benefit of bevacizumab as measured by PFS was seen in all pre-specified subgroups tested (including disease-free interval, number of metastatic sites, prior receipt of adjuvant chemotherapy and oestrogen receptor (ER) status).

AVF3694g
Study AVF3694g was a Phase III, multicentre, randomised, placebo-controlled trial designed to evaluate the efficacy and safety of bevacizumab in combination with chemotherapy compared to chemotherapy plus placebo as first-line treatment for patients with HER2-negative metastatic or locally recurrent breast cancer.

Chemotherapy was chosen at the investigator's discretion prior to randomisation in a 2:1 ratio to receive either chemotherapy plus bevacizumab or chemotherapy plus placebo. The choices of chemotherapy included capecitabine, taxane (protein-bound paclitaxel, docetaxel), and anthracycline-based agents (doxorubicin/ cyclophosphamide, epirubicin/ cyclophosphamide, 5-fluorouracil/ doxorubicin/ cyclophosphamide, 5-fluorouracil/epirubicin/cyclophosphamide) given every three weeks (q3w). Bevacizumab or placebo was administered at a dose of 15 mg/kg q3w.

This study included a blinded treatment phase, an optional open-label post-progression phase, and a survival follow-up phase. During the blinded treatment phase, patients received chemotherapy and medicinal product (bevacizumab or placebo) every 3 weeks until disease progression, treatment-limiting toxicity, or death. On documented disease progression, patients who entered the optional open-label phase could receive open-label bevacizumab together with a wide-range of second line therapies.

Statistical analyses were performed independently for 1) patients who received capecitabine in combination with bevacizumab or placebo; 2) patients who received taxane-based or anthracycline-based chemotherapy in combination with bevacizumab or placebo. The primary endpoint of the study was PFS by investigator assessment. In addition, the primary endpoint was also assessed by an independent review committee (IRC).

The results of this study from the final protocol defined analyses for progression free survival and response rates for the independently powered capecitabine cohort of Study AVF3694g are presented in Table 11 Results from an exploratory overall survival analysis which include an additional 7 months of follow-up (approximately 46% of patients had died) are also presented. The percentage of patients who received bevacizumab in the open-label phase was 62.1% in the capecitabine + placebo arm and 49.9% in the capecitabine + bevacizumab arm.

Table 11 Efficacy results for study AVF3694g: – Capecitabine[a] and bevacizumab/Placebo (Cap + bevacizumab/Pl)

Progression-free survival[b]				
	Investigator Assessment		IRC Assessment	
	Cap + Pl (n = 206)	Cap + bevacizumab (n = 409)	Cap + Pl (n = 206)	Cap + bevacizumab (n = 409)
Median PFS (months)	5.7	8.6	6.2	9.8
Hazard ratio vs placebo arm (95% CI)	0.69 (0.56; 0.84)		0.68 (0.54; 0.86)	
p-value	0.0002		0.0011	
Response rate (for patients with measurable disease)[b]				
	Cap + Pl (n = 161)		Cap + bevacizumab (n = 325)	
% pts with objective response	23.6		35.4	
p-value	0.0097			

Overall survival[b]	
HR (95% CI)	0.88 (0.69; 1.13)
p-value (exploratory)	0.33

[a] 1000 mg/m^2 oral twice daily for 14 days administered every 3 weeks

[b] Stratified analysis included all progression and death events except those where non-protocol therapy (NPT) was initiated prior to documented progression; data from those patients were censored at the last tumour assessment prior to starting NPT.

An unstratified analysis of PFS (investigator assessed) was performed that did not censor for non-protocol therapy prior to disease progression. The results of these analyses were very similar to the primary PFS results.

Non-small cell lung cancer (NSCLC)

First-line treatment of non-squamous NSCLC in combination with platinum-based chemotherapy.

The safety and efficacy of bevacizumab, in addition to platinum-based chemotherapy, in the first-line treatment of patients with non-squamous non-small cell lung cancer (NSCLC), was investigated in trials E4599 and BO17704. An overall survival benefit has been demonstrated in trial E4599 with a 15 mg/kg/q3wk dose of bevacizumab. Trial BO17704 has demonstrated that both 7.5 mg/kg/q3wk and 15 mg/kg/q3wk bevacizumab doses increase progression-free survival and response rate.

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

Patients were randomised to platinum-based chemotherapy (paclitaxel 200 mg/m^2) and carboplatin AUC = 6.0, both by intravenous 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 intravenous 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 randomised to the two arms.

During the trial, 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 12.

Table 12. Efficacy results for trial 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)	
Progression-free survival		
Median (months)	4.8	6.4
Hazard ratio	0.65 (p < 0.0001) 95% CI (0.56; 0.76)	
Overall response rate		
Rate (percent)	12.9	29.0 (p < 0.0001)

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.

BO17704
Trial BO17704 was a randomised, double-blind phase III trial of bevacizumab in addition to cisplatin and gemcitabine versus placebo, cisplatin and gemcitabine in patients with locally advanced (stage IIIB with supraclavicular lymph node metastases or with malignant pleural or pericardial effusion), metastatic or recurrent non-squamous NSCLC, who had not received prior chemotherapy. The primary endpoint was progression-free survival, secondary endpoints for the trial included the duration of overall survival.

Patients were randomised to platinum-based chemotherapy, cisplatin 80 mg/m^2 intravenous infusion on day 1 and gemcitabine 1,250 mg/m^2 intravenous infusion on days 1 and 8 of every 3-week cycle for up to 6 cycles (CG) with placebo or CG with bevacizumab at a dose of 7.5 or 15 mg/kg intravenous infusion day 1 of every 3-week cycle. In the bevacizumab-containing arms, patients could receive bevacizumab as a single agent every 3 weeks until disease progression or unacceptable toxicity. Trial results show that 94% (277 / 296) of eligible patients went on to receive single agent bevacizumab at cycle 7. A high proportion of patients (approximately 62%) went on to receive a variety of non-protocol specified anti-cancer therapies, which may have impacted the analysis of overall survival.

The efficacy results are presented in Table 13.

Table 13. Efficacy results for trial BO17704

	Cisplatin/Gemcitabine + placebo	**Cisplatin/Gemcitabine + bevacizumab 7.5 mg/kg q 3 weeks**	**Cisplatin/Gemcitabine + bevacizumab 15 mg/kg q 3 weeks**
Number of patients	347	345	351
Progression-free survival			
Median (months)	6.1	6.7 (p = 0.0026)	6.5 (p = 0.0301)
Hazard ratio		0.75 [0.62; 0.91]	0.82 [0.68; 0.98]
Best overall response rate[a]	20.1%	34.1% (p < 0.0001)	30.4% (p = 0.0023)
Overall survival			
Median (months)	13.1	13.6 (p = 0.4203)	13.4 (p = 0.7613)
Hazard ratio		0.93 [0.78; 1.11]	1.03 [0.86, 1.23]

[a] patients with measurable disease at baseline

First-line treatment of non-squamous NSCLC with EGFR activating mutations in combination with erlotinib

JO25567
Study JO25567 was a randomised, open-label, multi-centre phase II study conducted in Japan to evaluate the efficacy and safety of bevacizumab used in addition to erlotinib in patients with non-squamous NSCLC with EGFR activating mutations (exon 19 deletion or exon 21 L858R mutation) who had not received prior systemic therapy for stage IIIB/IV or recurrent disease.

The primary endpoint was progression-free survival (PFS) based on independent review assessment. Secondary endpoints included overall survival, response rate, disease control rate, duration of response, and safety.

EGFR mutation status was determined for each patient prior to patient screening and 154 patients were randomised to receive either erlotinib + bevacizumab (erlotinib 150 mg oral daily + bevacizumab [15 mg/kg intravenous every 3 weeks]) or erlotinib monotherapy (150 mg oral daily) until disease progression (PD) or unacceptable toxicity. In the absence of PD, discontinuation of one component of study treatment in the erlotinib + bevacizumab arm did not lead to discontinuation of the other component of study treatment as specified in the study protocol.

The efficacy results of the study are presented in Table 14.

Table 14. Efficacy results for study JO25567

	Erlotinib N = 77[#]	**Erlotinib + bevacizumab N = 75[#]**
PFS^ (months)		
Median	9.7	16.0
HR (95% CI)	0.54 (0.36; 0.79)	
p-value	0.0015	
Overall response rate		
Rate (n)	63.6% (49)	69.3% (52)
p-value	0.4951	
Overall survival* (months)		
Median	47.4	47.0
HR (95% CI)	0.81 (0.53; 1.23)	
p-value	0.3267	

[#] A total of 154 patients (ECOG Performance Status 0 or 1) were randomised. However, two of the randomised patients discontinued the study before receiving any study treatment.

^ Blinded independent review (protocol-defined primary analysis).

* Exploratory analysis; final OS analysis at clinical cut-off on 31 October 2017, approx. 59% of patients had died.

CI, confidence interval; HR, Hazard ratio from unstratified Cox regression analysis; NR, not reached.

Advanced and/or metastatic renal cell cancer (mRCC)

Bevacizumab in combination with interferon alfa-2a for the first-line treatment of advanced and/ or metastatic renal cell cancer (BO17705)

This was a phase III randomised double-blind trial conducted to evaluate the efficacy and safety of bevacizumab in combination with interferon (IFN) alfa-2a versus IFN alfa-2a alone as first-line treatment in mRCC. The 649 randomised patients (641 treated) had Karnofsky Performance Status (KPS) of ≥ 70%, no CNS metastases and adequate organ function. Patients were nephrectomised for primary renal cell carcinoma. Bevacizumab 10 mg/kg was given every 2 weeks until disease progression. IFN alfa-2a was given up to 52 weeks or until disease progression at a recommended starting dose of 9 MIU three times a week, allowing a dose reduction to 3 MIU three times a week in 2 steps. Patients were stratified according to country and Motzer score and the treatment arms were shown to be well balanced for the prognostic factors.

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

The efficacy results are presented in Table 15.

Table 15. Efficacy results for trial BO17705

	BO17705	
	Placebo + IFN[a]	**BV[b]+ IFN[a]**
Number of patients	322	327
Progression-free survival		
Median (months)	5.4	10.2
Hazard ratio 95% CI	0.63 0.52, 0.75 (p-value < 0.0001)	
Objective response rate (%) in patients with measurable disease		
N	289	306
Response rate	12.8%	31.4%
	(p-value < 0.0001)	

[a] Interferon alfa-2a 9 MIU 3x/week.
[b] Bevacizumab 10 mg/kg q 2 wk.

Overall survival		
Median (months)	21.3	23.3
Hazard ratio 95% CI	0.91 0.76, 1.10 (p-value 0.3360)	

An exploratory multivariate Cox regression model using backward selection indicated that the following baseline prognostic factors were strongly associated with survival independent of treatment: gender, white blood cell count, platelets, body weight loss in the 6 months prior to trial entry, number of metastatic sites, sum of longest diameter of target lesions, Motzer score. Adjustment for these baseline factors resulted in a treatment hazard ratio of 0.78 (95% CI [0.63; 0.96], p = 0.0219), indicating a 22% reduction in the risk of death for patients in the bevacizumab + IFN alfa-2a arm compared to IFN alfa-2a arm.

Ninety-seven (97) patients in the IFN alfa-2a arm and 131 patients in the bevacizumab arm reduced the dose of IFN alfa-2a from 9 MIU to either 6 or 3 MIU three times a week as pre-specified in the protocol. Dose reduction of IFN alfa-2a did not appear to affect the efficacy of the combination of bevacizumab and IFN alfa-2a based on PFS event free rates over time, as shown by a subgroup analysis. The 131 patients in the bevacizumab + IFN alfa-2a arm who reduced and maintained the IFN alfa-2a dose at 6 or 3 MIU during the trial, exhibited at 6, 12 and 18 months PFS event free rates of 73, 52 and 21% respectively, as compared to 61, 43 and 17% in the total population of patients receiving bevacizumab + IFN alfa-2a.

AVF2938
This was a randomised, double-blind, phase II clinical trial investigating bevacizumab 10 mg/kg in a 2 weekly schedule with the same dose of bevacizumab in combination with 150 mg daily erlotinib, in patients with metastatic clear cell RCC. A total of 104 patients were randomised to treatment in this trial, 53 to bevacizumab 10 mg/kg every 2 weeks plus placebo and 51 to bevacizumab 10 mg/kg every 2 weeks plus erlotinib 150 mg daily. The analysis of the primary endpoint showed no difference between the bevacizumab + placebo arm and the bevacizumab + erlotinib arm (median PFS 8.5 versus 9.9 months). Seven patients in each arm had an objective response. The addition of erlotinib to bevacizumab did not result in an improvement in OS (HR = 1.764; p = 0.1789), duration of objective response (6.7 vs. 9.1 months) or time to symptom progression (HR = 1.172; p = 0.5076).

AVF0890
This was a randomised phase II trial conducted to compare the efficacy and safety of bevacizumab versus placebo. A total of 116 patients were randomised to receive bevacizumab 3 mg/kg every 2 weeks (n = 39), 10 mg/kg every 2 weeks; (n = 37), or placebo (n = 40). An interim analysis showed there was a significant prolongation of the time to progression of disease in the 10 mg/kg group as compared with the placebo group (hazard ratio, 2.55; p < 0.001). There was a small difference, of

borderline significance, between the time to progression of disease in the 3 mg/kg group and that in the placebo group (hazard ratio, 1.26; p = 0.053). Four patients had objective (partial) response, and all of these had received the 10 mg/kg dose bevacizumab; the ORR for the 10 mg/kg dose was 10%.

Epithelial ovarian, fallopian tube and primary peritoneal cancer

Front-line treatment of ovarian cancer

The safety and efficacy of bevacizumab in the front-line treatment of patients with epithelial ovarian, fallopian tube or primary peritoneal cancer were studied in two phase III trials (GOG-0218 and BO17707) that evaluated the effect of the addition of bevacizumab to carboplatin and paclitaxel compared to the chemotherapy regimen alone.

GOG-0218
The GOG-0218 study was a phase III multicentre, randomised, double-blind, placebo-controlled, three arm study evaluating the effect of adding bevacizumab to an approved chemotherapy regimen (carboplatin and paclitaxel) in patients with advanced (stages IIIB, IIIC and IV according to FIGO staging version dated 1988) epithelial ovarian, fallopian tube or primary peritoneal cancer.

Patients who had received prior therapy with bevacizumab or prior systemic anti-cancer therapy for ovarian cancer (e.g. chemotherapy, monoclonal antibody therapy, tyrosine kinase inhibitor therapy, or hormonal therapy) or previous radiotherapy to the abdomen or pelvis were excluded from the study.

A total of 1,873 patients were randomised in equal proportions to the following three arms:

- CPP arm: Five cycles of placebo (started cycle 2) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles followed by placebo alone, for a total of up to 15 months of therapy
- CPB15 arm: Five cycles of bevacizumab (15 mg/kg q3w started cycle 2) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles followed by placebo alone, for a total of up to 15 months of therapy
- CPB15+ arm: Five cycles of bevacizumab (15 mg/kg q3w started cycle 2) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles followed by continued use of bevacizumab (15 mg/kg q3w) as single agent for a total of up to 15 months of therapy.

The majority of patients included in the study were white (87% in all three arms); the median age was 60 years in CPP and CPB15 arms and 59 years in CPB15+ arm; and 29% of patients in CPP or CPB15 and 26% in CPB15+ were over 65 years of age. Overall, approximately 50% of patients had a GOG PS of 0 at baseline, 43% a GOG PS score of 1, and 7% a GOG PS score of 2. Most patients had EOC (82% in CPP and CPB15, 85% in CPB15+) followed by PPC (16% in CPP, 15% in CPB15, 13% in CPB15+) and FTC (1% in CPP, 3% in CPB15, 2% in CPB15+). The majority of patients had serous adenocarcinoma histologic type (85% in CPP and CPB15, 86% in CPB15+). Overall, approximately 34% of patients were FIGO stage III optimally debulked with gross residual disease, 40% stage III sub-optimally debulked, and 26% were stage IV patients.

The primary endpoint was PFS based on investigator's assessment of disease progression based on radiological scans or CA-125 levels, or symptomatic deterioration per protocol. In addition, a pre-specified analysis of the data censoring for CA-125 progression events was conducted, as well as an independent review of PFS as determined by radiological scans.

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (carboplatin and paclitaxel) alone in the front-line setting, patients who received bevacizumab at a dose of 15 mg/kg q3w in combination with chemotherapy and continued to receive bevacizumab alone (CPB15+), had a clinically meaningful and statistically significant improvement in PFS.

In patients who only received bevacizumab in combination with chemotherapy and did not continue to receive bevacizumab alone (CPB15), no clinically meaningful benefit in PFS was observed.

The results of this study are summarised in Table 16.

Table 16. Efficacy results from study GOG-0218

Progression-free survival[1]			
	CPP (n = 625)	CPB15 (n = 625)	CPB15+ (n = 623)
Median PFS (months)	10.6	11.6	14.7
Hazard ratio (95% CI)[2]		0.89 (0.78, 1.02)	0.70 (0.61, 0.81)
p-value[3,4]		0.0437	< 0.0001
Objective response rate[5]			
	CPP (n = 396)	CPB15 (n = 393)	CPB15+ (n = 403)
% pts with objective response	63.4	66.2	66.0
p-value		0.2341	0.2041
Overall survival[6]			
	CPP (n = 625)	CPB15 (n = 625)	CPB15+ (n = 623)
Median OS (months)	40.6	38.8	43.8
Hazard ratio (95% CI)[2]		1.07 (0.91, 1.25)	0.88 (0.75, 1.04)
p-value[3]		0.2197	0.0641

1 Investigator assessed GOG protocol-specified PFS analysis (neither censored for CA-125 progressions nor censored for NPT prior to disease progression) with data cut-off date of 25 February, 2010.
2 Relative to the control arm; stratified hazard ratio.
3 One-sided log-rank p-value.
4 Subject to a p-value boundary of 0.0116.
5 Patients with measurable disease at baseline.
6 Final overall survival analysis performed when 46.9% of the patients had died.

Pre-specified PFS analyses were conducted, all with a cut-off date of 29 September 2009. The results of these pre-specified analyses are as follows:

- The protocol-specified analysis of investigator assessed PFS (without censoring for CA-125 progression or non-protocol therapy [NPT]) shows a stratified hazard ratio of 0.71 (95% CI: 0.61-0.83, 1-sided log-rank p-value < 0.0001) when CPB15+ is compared with CPP, with a median PFS of 10.4 months in the CPP arm and 14.1 months in the CPB15+ arm.
- The primary analysis of investigator assessed PFS (censoring for CA-125 progressions and NPT) shows a stratified hazard ratio of 0.62 (95% CI: 0.52-0.75, 1-sided log-rank p-value < 0.0001) when CPB15+ is compared with CPP, with a median PFS of 12.0 months in the CPP arm and 18.2 months in the CPB15+ arm.
- The analysis of PFS as determined by the independent review committee (censoring for NPT) shows a stratified hazard ratio of 0.62 (95% CI: 0.50-0.77, 1-sided log-rank p-value < 0.0001) when CPB15+ is compared with CPP, with a median PFS of 13.1 in the CPP arm and 19.1 months in the CPB15+ arm.

PFS subgroup analyses by disease stage and debulking status are summarised in Table 17. These results demonstrate robustness of the analysis of PFS as shown in Table 16.

Table 17. PFS[1] results by disease stage and debulking status from study GOG-0218

Randomised patients stage III optimally debulked disease[2,3]			
	CPP (n = 219)	CPB15 (n = 204)	CPB15+ (n = 216)
Median PFS (months)	12.4	14.3	17.5
Hazard ratio (95% CI)[4]		0.81 (0.62, 1.05)	0.66 (0.50, 0.86)
Randomised patients with stage III sub-optimally debulked disease[3]			
	CPP (n = 253)	CPB15 (n = 256)	CPB15+ (n = 242)
Median PFS (months)	10.1	10.9	13.9
Hazard ratio (95% CI)[4]		0.93 (0.77, 1.14)	0.78 (0.63, 0.96)
Randomised patients with stage IV disease			
	CPP (n = 153)	CPB15 (n = 165)	CPB15+ (n = 165)
Median PFS (months)	9.5	10.4	12.8
Hazard ratio (95% CI)[4]		0.90 (0.70, 1.16)	0.64 (0.49, 0.82)

1 Investigator assessed GOG protocol-specified PFS analysis (neither censored for CA-125 progressions nor censored for NPT prior to disease progression) with data cut-off date of 25 February, 2010.
2 With gross residual disease.
3 3.7% of the overall randomised patient population had stage IIIB disease.
4 Relative to the control arm.

BO17707 (ICON7)
BO17707 was a phase III, two-arm, multicentre, randomised, controlled, open-label study comparing the effect of adding bevacizumab to carboplatin plus paclitaxel in patients with FIGO stage I or IIA (grade 3 or clear cell histology only; n = 142), or FIGO stage IIB-IV (all grades and all histological types, n = 1,386) epithelial ovarian, fallopian tube or primary peritoneal cancer following surgery (NCI-CTCAE v.3). FIGO staging version dated 1988 was used in this trial.

Patients who had received prior therapy with bevacizumab or prior systemic anti-cancer therapy for ovarian cancer (e.g. chemotherapy, monoclonal antibody therapy, tyrosine kinase inhibitor therapy, or hormonal therapy) or previous radiotherapy to the abdomen or pelvis were excluded from the study.

A total of 1,528 patients were randomised in equal proportions to the following two arms:

- CP arm: Carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles of 3 weeks duration.
- CPB7.5+ arm: Carboplatin (AUC 6) and paclitaxel (175 mg/ m^2) for 6 cycles of 3 weeks plus bevacizumab (7.5 mg/kg q3w) for up to 12 months (bevacizumab was started at cycle 2 of chemotherapy if treatment was initiated within 4 weeks of surgery or at cycle 1 if treatment was initiated more than 4 weeks after surgery).

The majority of patients included in the study were white (96%), the median age was 57 years in both treatment arms, 25% of patients in each treatment arm were 65 years of age or over, and approximately 50% of patients had an ECOG PS of 1; 7% of patients in each treatment arm had an ECOG PS of 2. The majority of patients had EOC (87.7%) followed by PPC (6.9%) and FTC (3.7%) or a mixture of the three origins (1.7%). Most patients were FIGO stage III (both 68%) followed by FIGO stage IV (13% and 14%), FIGO stage II (10% and 11%) and FIGO stage I (9% and 7%). The majority of the patients in each treatment arm (74% and 71%) had poorly differentiated (grade 3) primary tumours at baseline. The incidence of each histologic sub-type of EOC was similar between the treatment arms; 69% of patients in each treatment arm had serous adenocarcinoma histologic type.

The primary endpoint was PFS as assessed by the investigator using RECIST.

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

The results of this study are summarised in Table 18.

Table 18. Efficacy results from study BO17707 (ICON7)

Progression-free survival		
	CP (n = 764)	CPB7.5+ (n = 764)
Median PFS (months)[2]	16.9	19.3
Hazard ratio [95% CI][2]	0.86 [0.75; 0.98] (p-value = 0.0185)	
Objective response rate[1]		
	CP (n = 277)	CPB7.5+ (n = 272)
Response rate	54.9%	64.7%
	(p-value = 0.0188)	
Overall survival[3]		
	CP (n = 764)	CPB7.5+ (n = 764)
Median (months)	58.0	57.4
Hazard ratio [95% CI]	0.99 [0.85; 1.15] (p-value = 0.8910)	

[1] In patients with measurable disease at baseline.
[2] Investigator assessed PFS analysis with data cut-off date of 30 November 2010.
[3] Final overall survival analysis performed when 46.7% of the patients had died with data cut-off date of 31 March 2013.

The primary analysis of investigator assessed PFS with a data cut-off date of 28 February 2010 shows an unstratified hazard ratio of 0.79 (95% CI: 0.68-0.91, 2-sided log-rank p-value 0.0010) with a median PFS of 16.0 months in the CP arm and 18.3 months in the CPB7.5+ arm.

PFS subgroup analyses by disease stage and debulking status are summarised in Table 19. These results demonstrate robustness of the primary analysis of PFS as shown in Table 18.

Table 19. PFS[1] results by disease stage and debulking status from study BO17707 (ICON7)

Randomised patients stage III optimally debulked disease[2,3]		
	CP (n = 368)	CPB7.5+ (n = 383)
Median PFS (months)	17.7	19.3
Hazard ratio (95% CI)[4]		0.89 (0.74, 1.07)
Randomised patients with stage III sub-optimally debulked disease[3]		
	CP (n = 154)	CPB7.5+ (n= 140)
Median PFS (months)	10.1	16.9
Hazard ratio (95% CI)[4]		0.67 (0.52, 0.87)
Randomised patients with stage IV disease		
	CP (n = 97)	CPB7.5+ (n = 104)
Median PFS (months)	10.1	13.5

Hazard ratio (95% CI)[4]		0.74 (0.55, 1.01)

[1] Investigator assessed PFS analysis with data cut-off date of 30 November 2010.
[2] With or without gross residual disease.
[3] 5.8% of the overall randomised patient population had stage IIIB disease.
[4] Relative to the control arm.

Recurrent ovarian cancer
The safety and efficacy of bevacizumab in the treatment of recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer was studied in three phase III trials (AVF4095g, MO22224 and GOG-0213) with different patient populations and chemotherapy regimens.

- AVF4095g evaluated the efficacy and safety of bevacizumab in combination with carboplatin and gemcitabine followed by bevacizumab as a single agent in patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer.
- GOG-0213 evaluated the efficacy and safety of bevacizumab in combination with carboplatin and paclitaxel, followed by bevacizumab as a single agent in patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer.
- MO22224 evaluated the efficacy and safety of bevacizumab in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin in patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer.

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 randomised, double-blind, placebo-controlled trial (AVF4095g). The study compared the effect of adding bevacizumab to carboplatin and gemcitabine chemotherapy and continuing bevacizumab as a single agent to progression, to carboplatin and gemcitabine alone.

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

A total of 484 patients with measurable disease were randomised 1:1 to either:
- Carboplatin (AUC 4, day 1) and gemcitabine (1,000 mg/m^2 on days 1 and 8) and concurrent placebo every 3 weeks for 6 and up to 10 cycles followed by placebo (every 3 weeks) alone until disease progression or unacceptable toxicity.
- Carboplatin (AUC 4, day 1) and gemcitabine (1,000 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 modified RECIST 1.0. Additional endpoints included objective response, duration of response, overall survival and safety. An independent review of the primary endpoint was also conducted.

The results of this study are summarised in Table 20.

Table 20. Efficacy results from study AVF4095g

Progression-free survival				
	Investigator assessment		IRC assessment	
	Placebo + C/G (n = 242)	Bevacizumab + C/G (n = 242)	Placebo + C/G (n = 242)	Bevacizumab + C/G (n = 242)
Not censored for NPT				

Median PFS (months)	8.4	12.4	8.6	12.3
Hazard ratio (95% CI)	0.524 [0.425, 0.645]		0.480 [0.377, 0.613]	
p-value	< 0.0001		< 0.0001	
Censored for NPT				
Median PFS (months)	8.4	12.4	8.6	12.3
Hazard ratio (95% CI)	0.484 [0.388, 0.605]		0.451 [0.351, 0.580]	
p-value	< 0.0001		< 0.0001	
Objective response rate				
	Investigator assessment		IRC assessment	
	Placebo + C/G (n = 242)	Bevacizumab + C/G (n = 242)	Placebo + C/G (n = 242)	Bevacizumab + C/G (n = 242)
% pts with objective response	57.4%	78.5%	53.7%	74.8%
p-value	< 0.0001		< 0.0001	
Overall survival				
	Placebo + C/G (n = 242)		Bevacizumab + C/G (n = 242)	
Median OS (months)	32.9		33.6	
Hazard ratio (95% CI)	0.952 [0.771, 1.176]			
p-value	0.6479			

PFS subgroup analyses depending on recurrence since last platinum therapy are summarised in Table 21.

Table 21. Progression-free survival by time from last platinum therapy to recurrence

	Investigator assessment	
Time from last platinum therapy to recurrence	**Placebo + C/G (n = 242)**	**Bevacizumab + C/G (n = 242)**
6 – 12 months (n = 202)		
Median	8.0	11.9
Hazard ratio (95% CI)	0.41 (0.29-0.58)	
> 12 months (n = 282)		
Median	9.7	12.4
Hazard ratio (95% CI)	0.55 (0.41-0.73)	

GOG-0213

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

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

- CP arm: Carboplatin (AUC5) and paclitaxel (175 mg/m^2 intravenous) every 3 weeks for 6 and up to 8 cycles.
- CPB arm: Carboplatin (AUC5) and paclitaxel (175 mg/m^2 intravenous) and concurrent bevacizumab (15 mg/kg) every 3 weeks for 6 and up to 8 cycles, followed by bevacizumab

(15 mg/kg every 3 weeks) alone until disease progression or unacceptable toxicity.

Most patients in both the CP arm (80.4%) and the CPB arm (78.9%) were white. The median age was 60.0 years in the CP arm and 59.0 years in the CPB arm. The majority of patients (CP: 64.6%; CPB: 68.8%) were in the age category < 65 years. At baseline, most patients in both treatment arms had a GOG PS of 0 (CP: 82.4%: CPB; 80.7%) or 1 (CP: 16.7%: CPB; 18.1%). A GOG PS of 2 at baseline was reported in 0.9% of patients in the CP arm and in 1.2% of patients in the CPB arm.

The primary efficacy endpoint was overall survival (OS). The main secondary efficacy endpoint was progression-free survival (PFS). Results are presented in Table 22.

Table 22. Efficacy results[1,2] from study GOG-0213

Primary endpoint		
Overall survival (OS)	CP (n = 336)	CPB (n = 337)
Median OS (months)	37.3	42.6
Hazard ratio (95% CI) (eCRF)[a]	0.823 [CI: 0.680, 0.996]	
p-value	0.0447	
Hazard ratio (95% CI) (registration form)[b]	0.838 [CI: 0.693, 1.014]	
p-value	0.0683	
Secondary endpoint		
Progression-free survival (PFS)	CP (n = 336)	CPB (n = 337)
Median PFS (months)	10.2	13.8
Hazard ratio (95% CI)	0.613 [CI: 0.521, 0.721]	
p-value	< 0.0001	

1 Final analysis

2 Tumour assessments and response evaluations were determined by the investigators using the GOG RECIST criteria (Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228Y247).

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

b stratified by the duration of treatment free-interval prior to enrolling onto this study per the registration form, and secondary surgical debulking status Yes/No.

The trial met its primary objective of OS improvement. Treatment with bevacizumab at 15 mg/kg every 3 weeks in combination with chemotherapy (carboplatin and paclitaxel) for 6 and up to 8 cycles, followed by bevacizumab until disease progression or unacceptable toxicity resulted, when data were derived from eCRF, in a clinically meaningful and statistically significant improvement in OS compared to treatment with carboplatin and paclitaxel alone.

MO22224

Study MO22224 evaluated the efficacy and safety of bevacizumab in combination with chemotherapy for platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal 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 (paclitaxel, topotecan, or pegylated liposomal doxorubicin (PLD) alone or in combination with bevacizumab:

CT Arm (chemotherapy alone):

- Paclitaxel 80 mg/m^2 as a 1-hour intravenous infusion on Days 1, 8, 15, and 22 every 4 weeks.
- Topotecan 4 mg/m^2 as a 30-minute intravenous 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 intravenous 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 intravenous 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 every 3 weeks).

Eligible patients had epithelial ovarian, fallopian tube or primary peritoneal cancer that progressed within < 6 months of previous platinum therapy consisting of a minimum of 4 platinum therapy cycles. Patients should have had a life expectancy of ≥ 12 weeks and no prior radiotherapy to the pelvis or abdomen. Most patients were FIGO Stage IIIC or Stage IV. The majority of patients in both arms had an ECOG Performance Status (PS) of 0 (CT: 56.4% vs. CT + BV: 61.2%). The percentage of patients with an ECOG PS of 1 or ≥ 2 was 38.7% and 5.0% in the CT arm, and 29.8% and 9.0% in the CT + BV arm. Information on race exists for 29.3% of patients and nearly all patients were white. The median age of patients was 61.0 (range: 25-84) years. A total of 16 patients (4.4%) were > 75 years old. The overall rates of discontinuation due to adverse events were 8.8% in the CT arm and 43.6% in the CT + BV arm (mostly due to Grade 2-3 adverse events) and the median time to discontinuation in the CT + BV arm was 5.2 months compared to 2.4 months in the CT arm. The rates of discontinuation due to adverse events in the subgroup of patients > 65 years old were 8.8% in the CT arm and 50.0% in the CT + BV arm. The HR for PFS was 0.47 (95% CI: 0.35, 0.62) and 0.45 (95% CI: 0.31, 0.67) for the < 65 and ≥ 65 subgroups, respectively.

The primary endpoint was progression-free survival, with secondary endpoints including objective response rate and overall survival. Results are presented in Table 23.

Table 23. Efficacy Results from Study MO22224

Primary Endpoint		
Progression-Free Survival*		
	CT (n=182)	CT + BV (n=179)
Median (months)	3.4	6.7
Hazard ratio (95% CI)	0.379 [0.296, 0.485]	
p-value	< 0.0001	
Secondary Endpoints		
Objective Response Rate**		
	CT (n=144)	CT + BV (n=142)
% patients with objective response	18 (12.5%)	40 (28.2%)
p-value	0.0007	
Overall Survival (final analysis)***		
	CT (n=182)	CT + BV (n=179)
Median OS (months)	13.3	16.6
Hazard Ratio (95% CI)	0.870 [0.678, 1.116]	
p-value	0.2711	

All analyses presented in this table are stratified analyses.

* Primary analysis was performed with a data cut-off date of 14 November 2011.

** Randomised Patients with Measurable Disease at Baseline.

*** The final analysis of overall survival was performed when 266 deaths, which account for 73.7% of enrolled patients, were observed.

The trial met its primary objective of PFS improvement. Compared to patients treated with chemotherapy (paclitaxel, topotecan or PLD) alone in the recurrent platinum-resistant setting, patients who received bevacizumab at a dose of 10 mg/kg every 2 weeks (or 15 mg/kg every 3 weeks if used in combination with 1.25 mg/m^2 topotecan on Days 1-5 every 3 weeks) in combination with chemotherapy and continued to receive bevacizumab until disease progression or unacceptable toxicity, had a statistically significant improvement in PFS. The exploratory PFS and OS analyses by chemotherapy cohort (paclitaxel, topotecan and PLD) are summarised in Table 24.

Table 24. Exploratory PFS and OS analyses by chemotherapy cohort

	CT	**CT + BV**
Paclitaxel	n=115	
Median PFS (months)	3.9	9.2
Hazard ratio (95% CI)	0.47 [0.31, 0.72]	
Median OS (months)	13.2	22.4
Hazard ratio (95% CI)	0.64 [0.41, 0.99]	
Topotecan	n=120	
Median PFS (months)	2.1	6.2
Hazard ratio (95% CI)	0.28 [0.18, 0.44]	
Median OS (months)	13.3	13.8
Hazard ratio (95% CI)	1.07 [0.70, 1.63]	
PLD	n=126	
Median PFS (months)	3.5	5.1
Hazard ratio (95% CI)	0.53 [0.36, 0.77]	
Median OS (months)	14.1	13.7
Hazard ratio (95% CI)	0.91 [0.61, 1.35]	

Cervical cancer

GOG-0240
The efficacy and safety of bevacizumab in combination with chemotherapy (paclitaxel and cisplatin or paclitaxel and topotecan) in the treatment for patients with persistent, recurrent or metastatic carcinoma of the cervix was evaluated in study GOG-0240, a randomised, four-arm, open label, multi-centre phase III trial.

A total of 452 patients were randomised to receive either:

- Paclitaxel 135 mg/m^2 intravenous over 24 hours on day 1 and cisplatin 50 mg/m^2 intravenous on day 2, every 3 weeks (q3w); or
  Paclitaxel 175 mg/m^2 intravenous over 3 hours on day 1 and cisplatin 50 mg/m^2 intravenous on day 2 (q3w); or
  Paclitaxel 175 mg/m^2 intravenous over 3 hours on day 1 and cisplatin 50 mg/m^2 intravenous on day 1 (q3w)

- Paclitaxel 135 mg/m^2 intravenous over 24 hours on day 1 and cisplatin 50 mg/m^2 intravenous on day 2 plus bevacizumab 15 mg/kg intravenous on day 2 (q3w); or
  Paclitaxel 175 mg/m^2 intravenous over 3 hours on day 1 and cisplatin 50 mg/m^2 intravenous on day 2 plus bevacizumab 15 mg/kg intravenous on day 2 (q3w); or
  Paclitaxel 175 mg/m^2 intravenous over 3 hours on day 1 and cisplatin 50 mg/m^2 intravenous on day 1 plus bevacizumab 15 mg/kg intravenous on day 1 (q3w)

- Paclitaxel 175 mg/m^2 intravenous over 3 hours on day 1 and topotecan 0.75 mg/m^2 intravenous over 30 minutes on days 1-3 (q3w)

- Paclitaxel 175 mg/m^2 intravenous over 3 hours on day 1 and topotecan 0.75 mg/m^2 intravenous

over 30 minutes on days 1-3 plus bevacizumab 15 mg/kg intravenous on day 1 (q3w)

Eligible patients had persistent, recurrent or metastatic squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which was not amenable to curative treatment with surgery and/or radiation therapy and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.

The median age was 46.0 years (range: 20-83) in the chemo alone group and 48.0 years (range: 22-85) in the chemo + bevacizumab group; with 9.3% of patients in the chemo alone group and 7.5% of patients in the chemo + bevacizumab group over the age of 65 years.

Of the 452 patients randomised at baseline, the majority of patients were white (80.0% in the chemo alone group and 75.3% in the chemo + bevacizumab group), had squamous cell carcinoma (67.1% in the chemo alone group and 69.6% in the chemo + bevacizumab group), had persistent/recurrent disease (83.6% in the chemo alone group and 82.8% in the chemo + bevacizumab group), had 1-2 metastatic sites (72.0% in the chemo alone group and 76.2% in the chemo + bevacizumab group), had lymph node involvement (50.2% in the chemo alone group and 56.4% in the chemo + bevacizumab group), and had a platinum free interval ≥ 6 months (72.5% in the chemo alone group and 64.4% in the chemo + bevacizumab group).

The primary efficacy endpoint was overall survival. Secondary efficacy endpoints included progression-free survival and objective response rate. Results from the primary analysis and the follow-up analysis are presented by bevacizumab treatment and by trial treatment in Table 25 and 26, respectively.

Table 25. Efficacy results from study GOG-0240 by bevacizumab treatment

	Chemotherapy (n = 225)	**Chemotherapy + bevacizumab (n = 227)**
Primary endpoint		
Overall survival - Primary analysis[6]		
Median (months)[1]	12.9	16.8
Hazard ratio [95% CI]	0.74 [0.58, 0.94] (p-value[5] = 0.0132)	
Overall survival - Follow-up analysis[7]		
Median (months)[1]	13.3	16.8
Hazard ratio [95% CI]	0.76 [0.62, 0.94] (p-value[5,8] = 0.0126)	
Secondary endpoints		
Progression-free survival - Primary analysis[6]		
Median PFS (months)[1]	6.0	8.3
Hazard ratio [95% CI]	0.66 [0.54, 0.81] (p-value[5] < 0.0001)	
Best overall response - Primary analysis[6]		
Responders (response rate[2])	76 (33.8%)	103 (45.4%)
95% CI for response rates[3]	[27.6%, 40.4%]	[38.8%, 52.1%]
Difference in response rates	11.60%	
95% CI for difference in response rates[4]	[2.4%, 20.8%]	
p-value (Chi-squared test)	0.0117	

1 Kaplan-Meier estimates.
2 Patients and percentage of patients with best overall response of confirmed CR or PR; percentage calculated on patients with measurable disease at baseline.
3 95% CI for one sample binomial using Pearson-Clopper method.
4 Approximate 95% CI for difference of two rates using Hauck-Anderson method.
5 log-rank test (stratified).

[6] Primary analysis was performed with a data cut-off date of 12 December 2012 and is considered the final analysis.
[7] Follow-up analysis was performed with a data cut-off date of 07 March 2014.
[8] p-value displayed for descriptive purpose only.

Table 26. Overall survival results from study GOG-0240 by trial treatment

Treatment comparison	Other factor	Overall survival - Primary analysis[1] Hazard ratio (95% CI)	Overall survival – Follow-up analysis[2] Hazard ratio (95% CI)
Bevacizumab vs. No bevacizumab	Cisplatin + Paclitaxel	0.72 (0.51, 1.02) (17.5 vs.14.3 months; p = 0.0609)	0.75 (0.55, 1.01) (17.5 vs.15.0 months; p = 0.0584)
	Topotecan + Paclitaxel	0.76 (0.55, 1.06) (14.9 vs. 11.9 months; p = 0.1061)	0.79 (0.59, 1.07) (16.2 vs. 12.0 months; p = 0.1342)
Topotecan +Paclitaxel vs. Cisplatin +Paclitaxel	Bevacizumab	1.15 (0.82, 1.61) (14.9 vs. 17.5 months; p = 0.4146)	1.15 (0.85, 1.56) (16.2 vs. 17.5 months; p = 0.3769)
	No bevacizumab	1.13 (0.81, 1.57) (11.9 vs.14.3 months; p = 0.4825)	1.08 (0.80, 1.45) (12.0 vs. 15.0 months; p = 0.6267)

[1] Primary analysis was performed with a data cut-off date of 12 December 2012 and is considered the final analysis.
[2] Follow-up analysis was performed with a data cut-off date of 07 March 2014; all p-values are displayed for descriptive purpose only.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies, in all subsets of the paediatric population, in breast carcinoma, adenocarcinoma of the colon and rectum, lung carcinoma (small cell and non-small cell carcinoma), kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney), ovarian carcinoma (excluding rhabdomyosarcoma and germ cell tumours), fallopian tube carcinoma (excluding rhabdomyosarcoma and germ cell tumours), peritoneal carcinoma (excluding blastomas and sarcomas) and cervix and corpus uteri carcinoma.

High-grade glioma

Anti-tumour activity was not observed in two earlier studies among a total of 30 children aged > 3 years old with relapsed or progressive high-grade glioma when treated with bevacizumab and irinotecan (CPT 11). There is insufficient information to determine the safety and efficacy of bevacizumab in children with newly diagnosed high-grade glioma.

- In a single-arm study (PBTC-022), 18 children with recurrent or progressive non-pontine high-grade glioma (including 8 with glioblastoma [WHO grade IV], 9 with anaplastic astrocytoma [grade III] and 1 with anaplastic oligodendroglioma [grade III]) were treated with bevacizumab (10 mg/kg) two weeks apart and then with bevacizumab in combination with CPT-11 (125-350 mg/m^2) once every two weeks until progression. There were no objective (partial or complete) radiological responses (MacDonald criteria). Toxicity and adverse reactions included arterial hypertension and fatigue as well as CNS ischaemia with acute neurological deficit.

- In a retrospective single institution series, 12 consecutive (2005 to 2008) children with relapsed or progressive high-grade glioma (3 with WHO grade IV, 9 with grade III) were treated with

bevacizumab (10 mg/kg) and irinotecan (125 mg/m^2) every 2 weeks. There were no complete responses and 2 partial responses (MacDonald criteria).

In a randomised 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 intravenously.

The study did not meet its primary endpoint of demonstrating a significant improvement of event free survival (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). These results were consistent with those from various sensitivity analyses and in clinically relevant subgroups. The results for all secondary endpoints (investigator assessed EFS, and ORR and OS) were consistent in showing no improvement associated with the addition of bevacizumab to the RT/T arm compared with the RT/T arm alone.

Addition of bevacizumab to RT/T did not demonstrate clinical benefit in study BO25041 in 60 evaluable children patients with newly diagnosed supratentorial or infratentorial cerebellar or peduncular high-grade glioma (HGG) (see section 4.2 for information on paediatric use).

Soft tissue sarcoma

In a randomised 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 EFS by 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; p-value = 0.72). The difference in ORR per independent central review was 18% (CI: 0.6%, 35.3%) between the two treatment arms in the few patients who had evaluable tumour at baseline and had a confirmed response prior to receiving any local therapy: 27/75 patients (36.0%, 95% CI: 25.2%, 47.9%) in the chemo arm and 34/63 patients (54.0%, 95% CI: 40.9%, 66.6%) in the BV + chemo arm. The final Overall Survival (OS) analyses showed no significant clinical benefit from addition of bevacizumab to chemotherapy in this patient population.

Addition of bevacizumab to standard of care did not demonstrate clinical benefit in clinical trial BO20924, in 71 evaluable children (from age 6 months to less than 18 years old) patients with metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma (see section 4.2 for information on paediatric use).

The incidence of adverse events, including grade ≥ 3 adverse events and serious adverse events, was similar between the two treatment arms. No adverse events leading to death occurred in either treatment arm; all deaths were attributed to disease progression. Bevacizumab addition to multimodal standard of care treatment seemed to be tolerated in this paediatric population.

5.2 Pharmacokinetic properties

The pharmacokinetic data for bevacizumab are available from ten 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. The pharmacokinetics of bevacizumab was linear at doses ranging from 1 to 10 mg/kg.

Distribution

The typical value for central volume (V_c) was 2.73 L and 3.28 L for female and male patients respectively, which is in the range that has been described for IgGs and other monoclonal antibodies.

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

Biotransformation

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

Elimination

The value for clearance is, on average, equal to 0.188 and 0.220 L/day for female and male patients, respectively. After correcting for body weight, male patients had a higher bevacizumab clearance (+ 17%) than females. According to the two-compartmental model, the elimination half-life is 18 days for a typical female patient and 20 days for a typical male patient.

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

Pharmacokinetics in special populations

The population pharmacokinetics were analysed in adult and paediatric patients to evaluate the effects of demographic characteristics. In adults the results showed no significant difference in the pharmacokinetics of bevacizumab in relation to age.

Renal impairment

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

Hepatic impairment

No trials 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.

Paediatric population

The pharmacokinetics of bevacizumab were evaluated in 152 children, adolescents and young adults (7 months to 21 years, 5.9 to 125 kg) across 4 clinical studies using a population pharmacokinetic model. The pharmacokinetic results show that the clearance and volume of distribution of bevacizumab were comparable between paediatric and young adult patients when normalised by body weight, with exposure trending lower as body weight decreased. Age was not associated with the pharmacokinetics of bevacizumab when body weight was taken into account.

The pharmacokinetics of bevacizumab was well characterised by the paediatric population PK model for 70 patients in Study BO20924 (1.4 to 17.6 years; 11.6 to 77.5 kg) and 59 patients in Study BO25041 (1 to 17 years; 11.2 to 82.3 kg). In Study BO20924, bevacizumab exposure was generally lower compared to a typical adult patient at the same dose. In Study BO25041, bevacizumab exposure was similar compared to a typical adult at the same dose. In both studies, bevacizumab exposure trended lower as body weight decreased.

5.3 Preclinical safety data

In studies of up to 26 weeks duration in cynomolgus monkeys, physeal dysplasia was observed in young animals with open growth plates, at bevacizumab average serum concentrations below the expected human therapeutic average serum concentrations. In rabbits, bevacizumab was shown to inhibit wound healing at doses below the proposed clinical dose. Effects on wound healing were shown to be fully reversible.

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

No specific studies in animals have been conducted to evaluate the effect on fertility. An adverse effect on female fertility can however be expected as repeat dose toxicity studies in animals have shown inhibition of the maturation of ovarian follicles and a decrease/absence of corpora lutea and associated decrease in ovarian and uterus weight as well as a decrease in the number of menstrual cycles.

Bevacizumab has been shown to be embryotoxic and teratogenic when administered to rabbits. Observed effects included decreases in maternal and foetal body weights, an increased number of foetal resorptions and an increased incidence of specific gross and skeletal foetal malformations. Adverse foetal outcomes were observed at all tested doses, of which the lowest dose resulted in average serum concentrations approximately 3 times larger than in humans receiving 5 mg/kg every 2 weeks. Information on foetal malformations observed in the post-marketing setting are provided in sections 4.6 and 4.8.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trehalose dihydrate
Monobasic sodium phosphate monohydrate
Disodium phosphate
Polysorbate 20 (E 432)
Water for injections

6.2 Incompatibilities

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

A concentration dependent degradation profile of bevacizumab was observed when diluted with glucose solutions (5%).

6.3 Shelf life

Unopened vial

36 months

Diluted medicinal product

Chemical and physical in-use stability has been demonstrated for 30 days at 2ºC to 8ºC plus an additional 48 hours at temperature not exceeding 30°C in sodium chloride 9 mg/mL (0.9%) solution for injection. 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.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

4 mL solution in a vial (Type I glass) with a stopper (chlorobutyl rubber) containing 100 mg of bevacizumab.
16 mL solution in a vial (Type I glass) with a stopper (chlorobutyl rubber) containing 400 mg of bevacizumab.

Pack of 1 vial.

6.6 Special precautions for disposal and other handling

Do not shake the vial.

Alymsys should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared solution. A sterile needle and syringe should be used to prepare Alymsys.

The necessary amount of bevacizumab should be withdrawn and diluted to the required administration volume with sodium chloride 9 mg/mL (0.9%) solution for injection. The concentration of the final bevacizumab solution should be kept within the range of 1.4 mg/mL to 16.5 mg/mL. In the majority of the occasions the necessary amount of Alymsys can be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection to a total volume of 100 mL.

No incompatibilities between Alymsys and polyvinyl chloride or polyolefin bags or infusion sets have been observed.

Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration.

Alymsys is for single-use only, as the product contains no preservatives. Any unused medicinal product or waste material should be disposed in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Mabxience Research SL
C/ Manuel Pombo Angulo 28
28050 Madrid
Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1509/001 – 100 mg/4 ml
EU/1/20/1509/002 – 400 mg/16 ml

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 March 2021
Date of latest renewal: 19 January 2026

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

GH GENHELIX S.A.
Parque Tecnológico de León
Edifício GENHELIX
C/Julia Morros, s/n
Armunia, 24009 León, Spain

mAbxience S.A.U.
Calle Jose Zabala 1040
Garin, B1619JNA
Buenos Aires, Argentina

Name and address of the manufacturer responsible for batch release

GH GENHELIX S.A.
Parque Tecnológico de León
Edifício GENHELIX
C/Julia Morros, s/n
Armunia, 24009 León, Spain

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Alymsys 25 mg/mL concentrate for solution for infusion
bevacizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of concentrate contains 100 mg bevacizumab.

3. LIST OF EXCIPIENTS

Trehalose dihydrate, monobasic sodium phosphate monohydrate, disodium phosphate, polysorbate 20, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial of 4 mL
100 mg/4 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mabxience Research SL
C/ Manuel Pombo Angulo 28
28050 Madrid
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1509/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Alymsys 25 mg/mL sterile concentrate
bevacizumab
IV after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg/4 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Alymsys 25 mg/mL concentrate for solution for infusion
bevacizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of concentrate contains 400 mg bevacizumab.

3. LIST OF EXCIPIENTS

Trehalose dihydrate, monobasic sodium phosphate monohydrate, disodium phosphate, polysorbate 20, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial of 16 mL
400 mg/16 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mabxience Research SL
C/ Manuel Pombo Angulo 28
28050 Madrid
Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1509/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Alymsys 25 mg/mL sterile concentrate
bevacizumab
IV after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

400 mg/16 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Alymsys 25 mg/mL concentrate for solution for infusion
bevacizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Alymsys is and what it is used for
2. What you need to know before you use Alymsys
3. How to use Alymsys
4. Possible side effects
5. How to store Alymsys
6. Contents of the pack and other information

1. What Alymsys is and what it is used for

Alymsys contains the active substance bevacizumab, which is a humanised monoclonal antibody (a type of protein that is normally made by the immune system to help defend the body from infection and cancer). Bevacizumab binds selectively to a protein called human vascular endothelial growth factor (VEGF), which is found on the lining of blood and lymph vessels in the body. The VEGF protein causes blood vessels to grow within tumours, these blood vessels provide the tumour with nutrients and oxygen. Once bevacizumab is bound to VEGF, tumour growth is prevented by blocking the growth of the blood vessels which provide the nutrients and oxygen to the tumour.

Alymsys is a medicine used for the treatment of adult patients with advanced cancer in the large bowel, i.e., in the colon or rectum. Alymsys will be administered in combination with chemotherapy treatment containing a fluoropyrimidine medicine.

Alymsys is also used for the treatment of adult patients with metastatic breast cancer. When used for patients with breast cancer, it will be administered with a chemotherapy medicinal product called paclitaxel or capecitabine.

Alymsys is also used for the treatment of adult patients with advanced non-small cell lung cancer. Alymsys will be administered together with a chemotherapy regimen containing platinum.

Alymsys is also used for the treatment of adult patients with advanced non-small cell lung cancer when cancer cells have specific mutations of a protein called epidermal growth factor receptor (EGFR). Alymsys will be administered in combination with erlotinib.

Alymsys is also used for treatment of adult patients with advanced kidney cancer. When used for patients with kidney cancer, it will be administered with another type of medicine called interferon.

Alymsys is also used for the treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer. When used for patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer, it will be administered in combination with carboplatin and paclitaxel.

When used for those adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer whose disease has come back at least 6 months after the last time they were treated

with a chemotherapy regimen containing a platinum agent, Alymsys will be administered in combination with carboplatin and gemcitabine or with carboplatin and paclitaxel.

When used for those adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer whose disease has come back before 6 months after the last time they were treated with a chemotherapy regimen containing a platinum agent, Alymsys will be administered in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin.

Alymsys is also used for the treatment of adult patients with persistent, recurrent or metastatic cervical cancer. Alymsys will be administered in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy.

2. What you need to know before you use Alymsys

Do not use Alymsys if:
- you are allergic to bevacizumab or any of the other ingredients of this medicine (listed in section 6).
- you are allergic to Chinese hamster ovary (CHO) cell products or to other recombinant human or humanised antibodies.
- you are pregnant.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Alymsys:

- Alymsys may increase the risk of developing holes in the gut wall. If you have conditions causing inflammation inside the abdomen (e.g. diverticulitis, stomach ulcers, colitis associated with chemotherapy), please discuss this with your doctor.

- Alymsys may increase the risk of developing an abnormal connection or passageway between two organs or vessels. The risk of developing connections between the vagina and any parts of the gut can increase if you have persistent, recurrent or metastatic cervical cancer.

- Alymsys can increase the risk of bleeding or increase the risk of problems with wound healing after surgery. If you are going to have an operation, if you have had major surgery within the last 28 days or if you still have an unhealed wound following surgery, you should not receive this medicine.

- Alymsys may increase the risk of developing serious infections of the skin or deeper layers under the skin, especially if you had holes in the gut wall or problems with wound healing.

- Alymsys can increase the incidence of high blood pressure. If you have high blood pressure which is not well controlled with blood pressure medicines, please consult your doctor as it is important to make sure that your blood pressure is under control before starting Alymsys treatment.

- If you have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.

- Alymsys increases the risk of having protein in your urine especially if you already have high blood pressure.

- The risk of developing blood clots in your arteries (a type of blood vessel) can increase if you are over 65 years old, if you have diabetes, or if you have had previous blood clots in your arteries. Please talk to your doctor since blood clots can lead to heart attack and stroke.

- Alymsys can also increase the risk of developing blood clots in your veins (a type of blood vessel).

- Alymsys may cause bleeding, especially tumour-related bleeding. Please consult your doctor if you or your family tend to suffer from bleeding problems or you are taking medicines to thin the blood for any reason.

- Alymsys may cause bleeding in and around your brain. Please discuss this with your doctor if you have metastatic cancer affecting your brain.

- Alymsys can increase the risk of bleeding in your lungs, including coughing or spitting blood. Please discuss with your doctor if you noticed this previously.

- Alymsys can increase the risk of developing a weak heart. It is important that your doctor knows if you have ever received anthracyclines (for example doxorubicin, a specific type of chemotherapy used to treat some cancers) or had radiotherapy to your chest, or if you have heart disease.

- Alymsys may cause infections and a decreased number of your neutrophils (a type of blood cell important for your protection against bacteria).

- Alymsys can cause hypersensitivity (including anaphylactic shock) and/or infusion reactions (reactions related to your injection of the medicine). Please let your doctor, pharmacist or nurse know if you have previously experienced problems after injections, such as dizziness/feeling of fainting, breathlessness, swelling or skin rash.

- A rare neurological side effect named posterior reversible encephalopathy syndrome (PRES) has been associated with Alymsys treatment. If you have headache, vision changes, confusion or seizure with or without high blood pressure, please contact your doctor.

- Death of bone tissue (osteonecrosis) in bones other than the jaw has been reported in patients under 18 years old when treated with Alymsys. Pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth could be signs and symptoms of bone damage in the jaw (osteonecrosis). Tell your doctor and dentist immediately if you experience any of them.

Please consult your doctor, even if these above statements were only applicable to you in the past.
Before you are given Alymsys or while you are being treated with Alymsys:
- if you have or have had pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth tell your doctor and dentist immediately.
- if you need to undergo an invasive dental treatment or dental surgery, tell your dentist that you are being treated with Alymsys, in particular when you are also receiving or have received an injection of bisphosphonate into your blood.

You may be advised to have a dental check-up before you start treatment with Alymsys.

Alymsys has been developed and made to treat cancer by injecting it into the bloodstream. It has not been developed or made for injection into the eye. It is therefore not authorised to be used in this way.
When Alymsys is injected directly into the eye (unapproved use), the following side effects may occur:
- Infection or inflammation of the eye globe,
- Redness of the eye, small particles or spots in your vision (floaters), eye pain,
- Seeing flashes of light with floaters, progressing to a loss of some of your vision,
- Increased eye pressure,
- Bleeding in the eye.

Children and adolescents
Alymsys use is not recommended in children and adolescents under the age of 18 years because the safety and benefit have not been established in these patient populations.

Other medicines and Alymsys
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

Combinations of Alymsys with another medicine called sunitinib malate (prescribed for renal and gastrointestinal cancer) may cause severe side effects. Discuss with your doctor to make sure that you do not combine these medicines.

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

Please tell your doctor if you have recently received, or are receiving, radiotherapy.

Pregnancy, breast-feeding and fertility
You must not use this medicine if you are pregnant. Alymsys may cause damage to your unborn baby as it may stop the formation of new blood vessels. Your doctor should advise you about using contraception during treatment with Alymsys and for at least 6 months after the last dose of Alymsys.

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

You must not breast-feed your baby during treatment with Alymsys and for at least 6 months after the last dose of Alymsys, as this medicine may interfere with the growth and development of your baby.

Alymsys may impair female fertility. Please consult your doctor for more information.

Pre-menopausal women (women who have a menstrual cycle) may notice that their periods become irregular or are missed and may experience impaired fertility. If you are considering having children you should discuss this with your doctor before your treatment starts.

Driving and using machines
Alymsys has not been shown to reduce your ability to drive or to use any tools or machines. However, sleepiness and fainting have been reported with Alymsys use. If you experience symptoms that affect your vision or concentration, or your ability to react, do not drive and use machines until symptoms disappear.

Alymsys contains sodium and polysorbate 20
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

This medicine contains 1.6 mg of polysorbate 20 in each 100 mg/4 mL vial and 6.4 mg in each 400 mg/16 mL vial which is equivalent to 0.4 mg/mL. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How to use Alymsys

Dosage and frequency of administration
The dose of Alymsys needed depends on your body weight and the kind of cancer to be treated. The recommended dose is 5 mg, 7.5 mg, 10 mg or 15 mg per kilogram of your body weight. Your doctor will prescribe a dose of Alymsys that is right for you. You will be treated with Alymsys once every 2 or 3 weeks. The number of infusions that you receive will depend on how you are responding to

treatment; you should continue to receive this medicine until Alymsys fails to stop your tumour growing. Your doctor will discuss this with you.

Method and route of administration
Do not shake the vial. Alymsys is a concentrate for solution for infusion. Depending on the dose prescribed for you, some or all of the contents of the Alymsys vial will be diluted with sodium chloride solution before use. A doctor or nurse will give you this diluted Alymsys solution by intravenous infusion (a drip into 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 administration of Alymsys should be temporarily discontinued
- if you develop severe high blood pressure requiring treatment with blood pressure medicines,
- if you have problems with wound healing following surgery,
- if you undergo surgery.

The administration of Alymsys should be permanently discontinued if you develop
- severe high blood pressure which cannot be controlled by blood pressure medicines; or a sudden severe rise in blood pressure,
- presence of protein in your urine accompanied by swelling of your body,
- a hole in your gut wall,
- an abnormal tube-like connection or passage between the windpipe and the gullet, between internal organs and skin, between the vagina and any parts of the gut or between other tissues that are not normally connected (fistula), and are judged by your doctor to be severe,
- serious infections of the skin or deeper layers under the skin,
- a blood clot in your arteries,
- a blood clot in the blood vessels of your lungs,
- any severe bleeding.

If too much of Alymsys is given
- you may develop a severe migraine. If this happens you should talk to your doctor, pharmacist or nurse immediately.

If a dose of Alymsys is missed
- your doctor will decide when you should be given your next dose of Alymsys. You should discuss this with your doctor.

If you stop treatment with Alymsys
Stopping your treatment with Alymsys may stop the effect on tumour growth. Do not stop treatment with Alymsys unless you have discussed this with your doctor.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The side effects listed below were seen when Alymsys was given together with chemotherapy. This does not necessarily mean that these side effects were strictly caused by Alymsys.

Allergic reactions
If you have an allergic reaction, tell your doctor or a member of the medical staff straight away. The signs may include difficulty in breathing or chest pain. You could also experience redness or flushing of the skin or a rash, chills and shivering, feeling sick (nausea) or being sick (vomiting), swelling, lightheadedness, fast heartbeat and loss of consciousness.

You should seek help immediately if you suffer from any of the below mentioned side effects.

Severe side effects, which may be **very common** (may affect more than 1 in 10 people), include:
- high blood pressure,
- feeling of numbness or tingling in hands or feet,
- decreased number of cells in the blood, including white cells that help to fight against infections (this may be accompanied by fever), and cells that help the blood to clot,
- feeling weak and having no energy,
- tiredness,
- diarrhoea, nausea, vomiting and abdominal pain.

Severe side effects, which may be **common** (may affect up to 1 in 10 people), include:
- allergic reactions (the signs may include breathing difficulty, facial redness, rash, low blood pressure or high blood pressure, low oxygen in your blood, chest pain, or nausea/vomiting),
- perforation of the gut,
- bleeding, including bleeding in the lungs in patients with non-small cell lung cancer,
- blocking of the arteries by a blood clot,
- blocking of the veins by a blood clot,
- blocking of the blood vessels of the lungs by a blood clot,
- blocking of the veins of the legs by a blood clot,
- heart failure,
- problems with wound healing after surgery,
- redness, peeling, tenderness, pain, or blistering on the fingers or feet,
- decreased number of red cells in the blood,
- lack of energy,
- stomach and intestinal disorder,
- muscle and joint pain, muscular weakness,
- dry mouth in combination with thirst and/or reduced or darkened urine,
- inflammation of the moist lining of mouth and gut, lungs and air passages, reproductive, and urinary tracts,
- sores in the mouth and the tube from the mouth to the stomach, which may be painful and cause difficulty swallowing,
- pain, including headache, back pain and pain in the pelvis and anal regions,
- localised pus collection,
- infection, and in particular infection in the blood or bladder,
- reduced blood supply to the brain or stroke,
- sleepiness,
- nose bleed,
- increase in heart rate (pulse),
- blockage in the gut or bowel,
- abnormal urine test (protein in the urine),
- shortness of breath or low levels of oxygen in the blood,
- infections of the skin or deeper layers under the skin,
- fistula: abnormal tube-like connection between internal organs and skin or other tissues that are not normally connected, including connections between vagina and the gut in patients with cervical cancer.

Severe side effects, which may be **rare** (may affect up to 1 in 1,000 people), include:
- sudden, severe allergic reaction with breathing difficulty, swelling, lightheadedness, fast heartbeat, sweating and loss of consciousness (anaphylactic shock).

Severe side effects of **unknown** frequency (frequency cannot be estimated from the available data), include:
- serious infections of the skin or deeper layers under the skin, especially if you had holes in the gut wall or problems with wound healing,
- a negative effect on a woman’s ability to have children (see the paragraphs below the list of side

effects for further recommendations),
- a brain condition with symptoms including seizures (fits), headache, confusion, and changes in vision (Posterior Reversible Encephalopathy Syndrome or PRES),
- symptoms that suggest changes in normal brain function (headaches, vision changes, confusion, or seizures), and high blood pressure,
- an enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections),
- clogging of a very small blood vessel(s) in the kidney,
- abnormally high blood pressure in the blood vessels of the lungs which makes the right side of the heart work harder than normal,
- a hole in the cartilage wall separating the nostrils of the nose,
- a hole in the stomach or intestines,
- an open sore or hole in the lining of the stomach or small intestine (the signs may include abdominal pain, feeling bloated, black tarry stools or blood in your stools (faeces) or blood in your vomit),
- bleeding from the lower part of the large bowel,
- lesions in the gums with an exposed jaw bone that does not heal and may be associated with pain and inflammation of the surrounding tissue (see the paragraphs below the list of side effects for further recommendations),
- hole in the gall bladder (symptoms and signs may include abdominal pain, fever, and nausea/vomiting).

You should seek help as soon as possible if you suffer from any of the below mentioned side effects.

Very common (may affect more than 1 in 10 people) side effects, which were not severe, include:
- constipation,
- loss of appetite,
- fever,
- problems with the eyes (including increased production of tears),
- changes in speech,
- change in the sense of taste,
- runny nose,
- dry skin, flaking and inflammation of the skin, change in skin colour,
- loss of body weight,
- nose bleeds.

Common (may affect up to 1 in 10 people) side effects, which were not severe, include:
- voice changes and hoarseness.

Patients older than 65 years have an increased risk of experiencing the following side effects:
- blood clot in the arteries which can lead to a stroke or a heart attack,
- reduction in the number of white cells in the blood, and cells that help the blood clot,
- diarrhoea,
- sickness,
- headache,
- fatigue,
- high blood pressure.

Alymsys may also cause changes in laboratory tests carried out by your doctor. These include a decreased number of white cells in the blood, in particular neutrophils (one type of white blood cell which helps protect against infections) in the blood; presence of protein in the urine; decreased blood potassium, sodium or phosphorous (a mineral); increased blood sugar; increased blood alkaline phosphatase (an enzyme); increased serum creatinine (a protein measured by a blood test to see how well your kidneys are working); decreased haemoglobin (found in red blood cells, which carry oxygen), which may be severe.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Alymsys

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and on the vial label after the abbreviation EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C–8°C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.

Infusion solutions should be used immediately after dilution. 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 the infusion solutions have been prepared in a sterile environment. When dilution has taken place in a sterile environment, Alymsys is stable for a period of up to 30 days at 2°C to 8°C after dilution and a period of up to 48 hours at temperatures not exceeding 30°C.

Do not use Alymsys if you notice any particulate matter or discolouration prior to administration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Alymsys contains
- The active substance is bevacizumab. Each mL of concentrate contains 25 mg of bevacizumab, corresponding to 1.4 to 16.5 mg/mL when diluted as recommended.
  Each 4 mL vial contains 100 mg of bevacizumab, corresponding to 1.4 mg/mL when diluted as recommended.
  Each 16 mL vial contains 400 mg of bevacizumab, corresponding to 16.5 mg/mL when diluted as recommended
- The other ingredients are trehalose dihydrate, monobasic sodium phosphate monohydrate, disodium phosphate, polysorbate 20 (E 432) and water for injections (see section 2 “Alymsys contains sodium and polysorbate 20”).

What Alymsys looks like and contents of the pack
Alymsys is a concentrate for solution for infusion (sterile concentrate). The concentrate is a colourless to yellowish or brownish liquid with opalescence in a glass vial with a rubber stopper. Each vial contains 100 mg bevacizumab in 4 mL of solution or 400 mg bevacizumab in 16 mL of solution. Each pack of Alymsys contains one vial.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu