20 September 2012
EMA/CHMP/655681/2012
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

**Avastin**

**(bevacizumab)**

**Procedure No.: EMEA/H/C/000582/II/0046**

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# 1. Background information on the procedure

## *1.1. Requested Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration Ltd. submitted to the European Medicines Agency on 12 August 2011 an application for a variation.

This application concerns the following medicinal product:

| Medicinal product: | International non-proprietary name: | Presentations: |
|---|---|---|
| Avastin | bevacizumab | See Annex A |

The following variation was requested:

| **Variation requested** | | **Type** |
|---|---|---|
| C.I.6.a | Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | II |

The MAH proposed the update of section 4.1 of the SmPC in order to extend the indication of Avastin in combination with carboplatin and gemcitabine in patients with recurrent, platinum-sensitive, epithelial ovarian, primary peritoneal or fallopian tube carcinoma. Related changes were proposed to SmPC sections 4.2, 4.8 and 5.1. In addition, Annex II has been updated in order to revise the list of conditions. The Package Leaflet was proposed to be updated accordingly.

Furthermore, the MAH took this opportunity to bring the PI in line with the latest QRD template version 8.

The requested variation proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Rapporteur: Jens Ersbøll

## *1.2. Steps taken for the assessment*

| | |
|---|---|
| Submission date: | 12 August 2011 |
| Start of procedure: | 21 August 2011 |
| Rapporteur's preliminary assessment report circulated on: | 18 October 2011 |
| Co-Rapporteur's assessment report | 14 October 2011 |
| Rapporteur's updated assessment report circulated on: | 11 November 2011 |
| Request for supplementary information and extension of timetable adopted by the CHMP on: | 17 November 2011 |
| MAH's responses submitted to the CHMP on: | 16 February 2012 |
| Rapporteurs' Joint assessment report on the MAH's responses circulated on: | 30 March 2012 |
| 2nd Request for supplementary information and extension of timetable adopted by the CHMP on: | 19 April 2012 |

| | |
|---|---|
| MAH's responses submitted to the CHMP on: | 16 May 2012 |
| Rapporteurs' Joint preliminary assessment report on the MAH's responses circulated on: | 8 June 2012 |
| Rapporteurs' Joint final assessment report on the MAH's responses circulated on: | 19 June 2012 |
| 3rd Request for supplementary information and extension of timetable adopted by the CHMP on: | 21 June 2012 |
| MAH's responses submitted to the CHMP on: | 20 July 2012 |
| Rapporteurs' Joint preliminary assessment report on the MAH's responses circulated on: | 31 August 2012 |
| Rapporteurs' Joint final assessment report on the MAH's responses circulated on: | 13 September 2012 |
| CHMP opinion: | 20 September 2012 |

### *Information on Paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/146/2009 on the granting of a class waiver.

### *Information relating to orphan market exclusivity*

### Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

# 2. Scientific discussion

## *2.1. Introduction*

Ovarian cancer is one of the most common gynaecological tumours in Europe and the United States. The incidence of ovarian cancer varies by geographic region, with the highest rates observed in North America, Europe, and other developed countries. Ovarian cancer is the fifth leading cause of cancer death in women.

The most common group of ovarian cancers that arise in the epithelium are epithelial ovarian cancer (EOC), fallopian tube cancer (FTC) and/or primary peritoneal cancer (PPC). The recommendation of the International Federation of Gynaecology and Obstetrics (FIGO) is that treatment for PPC and FTC follows the guidance for EOC. Throughout this document the term ovarian cancer is used to refer to all three diseases.

The definitive diagnosis and staging of ovarian cancer is by surgery, and cytological or histological examination of tissue samples. The FIGO surgical staging system is used for epithelial ovarian cancer and primary peritoneal adenocarcinoma. Because the disease tends to be asymptomatic in early

stages, or associated with vague, non-specific symptoms, the majority of patients are diagnosed with advanced stage disease.

Despite the high sensitivity of ovarian cancer to initial treatment with platinum and taxane combination chemotherapy (following cytoreductive surgery), which is the standard of care in the front-line setting, the majority of women diagnosed with advanced-stage disease will have a recurrence of their cancer. Recurrent disease is classified as platinum resistant or platinum sensitive, depending on whether the disease recurred less than or greater than 6 months following previous platinum therapy, and this classification is highly prognostic and is important in determining optimal chemotherapeutic treatment options. This time between last platinum therapy and disease relapse is referred to as the platinum-free interval (PFI). Patients with PFI ≥ 6 months have a better prognosis; response rates to single-agent platinum have a range of 32%–57%. Platinum-resistant disease (PFI < 6 months) response rates range from 15% to 20%, and response duration is often measured in weeks. Platinum combinations have become the accepted standard for the treatment of platinum-sensitive, recurrent disease and currently available options include platinum plus gemcitabine, taxane, or liposomal doxorubicin.

Although patients with platinum-sensitive disease do benefit from currently available regimens, their chemotherapy-free interval and disease control period may be relatively short; moreover, these will progressively shorten with subsequent relapses, which are generally accompanied by symptomatic disease progression (PD) with significantly lower rates of response.

Bevacizumab (Avastin) is a recombinant humanised monoclonal antibody. It inhibits angiogenesis by neutralising all isoforms of human vascular endothelial growth factor (VEGF), and blocking their binding to VEGF receptors.

Avastin was approved in the European Union (EU) on 12 January 2005 for the first-line treatment of patients with metastatic cancer of the colon or rectum (mCRC), in combination with intravenous 5-fluorouracil/folinic acid or intravenous 5-fluorouracil/folinic acid/irinotecan. Following this, Avastin was approved for the treatment of locally recurrent and metastatic breast cancer, for non-small cell lung cancer (NSCLC) for renal cell cancer and for the first-line ovarian cancer.

This variation concerns an application for extension of the approved indications for Avastin. The indication initially claimed by the MAH was:

Avastin, in combination with carboplatin and gemcitabine is indicated for the treatment of patients with recurrent, platinum-sensitive, epithelial ovarian, fallopian tube, or primary peritoneal cancer.

The final indication approved by the CHMP is as follows:

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

Consequently, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated to reflect the change in the indication accordingly. The PL has been updated accordingly. In addition, Annex II has been updated in order to revise the list of conditions. Furthermore, the MAH took this opportunity to bring the PI in line with the latest QRD template version 8.

## *2.2 Non clinical aspects*

### 2.2.1 Ecotoxicity/environmental risk assessment

A justification for not providing an updated Environmental Risk assessment for this new indication HAS has been submitted by the MAH. This is in accordance with the Guideline on the Environmental Risk assessment for Human medicinal products (EMEA/CHMP/SWP/4447/00, 2006) which states that for certain pharmacologically active substances, among others proteins, such is possible, as these substances are unlikely to result in significant risk to the environment.

Bevacizumab is a monoclonal antibody that is a recombinant humanised immunoglobulin of isotype IgG1 and as a protein bevacizumab is exempted from providing an ERA.

The old ERA from 2006 and a recent publication on proteins and pharmaceuticals supporting the conclusion of no significant environmental risk have been included in the application and have not raised any concerns.

## *2.3 Clinical aspects*

### *2.3.1 Pharmacokinetic interactions studies*

The chemotherapies used in combination with bevacizumab in Study AVF4095g were carboplatin and gemcitabine. Pharmacokinetic drug-drug interaction (PK-DDI) between bevacizumab, carboplatin and gemcitabine was not assessed specifically in EOC, PPC, and FTC. Available PK-DDI results for the impact of bevacizumab on carboplatin and gemcitabine disposition presented are from studies AVF0757g and BO17704 in NSCLC and study BO17706 in pancreatic cancer.

In Study AVF0757g, the pharmacokinetics of carboplatin and paclitaxel was evaluated in combination with bevacizumab in patients with locally advanced or metastatic NSCLC. Carboplatin plasma concentration data were collected at Day 0 and Day 63 and were available for 6 patients in the control arm. In the bevacizumab treated arm, 9 patients had concentration data for carboplatin. On the basis of limited data, there did not appear to be a difference in the exposure when carboplatin was administered in combination with bevacizumab, suggesting a lack of PK-DDI with bevacizumab.

A PK-DDI substudy within study BO17704 evaluated the impact of bevacizumab (either 7.5 mg/kg or 15 mg/kg every 3 weeks) and cisplatin on gemcitabine pharmacokinetics in a subset of patients with locally advanced, metastatic, or recurrent NSCLC. Forty-one patients were enrolled in the substudy; however, data was available for parameter estimates on only a limited number of patients. $AUC_{0\text{-inf}}$ could be calculated only in 13 patients from the low-dose group and in 7 patients from the high-dose group. In addition, the end of infusion time point for gemcitabine was not collected; therefore, a relevant part of the AUC estimate was not calculated. $AUC_{0\text{-inf}}$ was used to assess the effect of bevacizumab on the exposure of gemcitabine in the presence of cisplatin. In general, $AUC_{0\text{-inf}}$ results showed that on Day 1, on average, gemcitabine exposure was lower than on Day 8. Gemcitabine exposure on Day 8 was slightly higher compared to Day 1. The difference in gemcitabine exposure was less pronounced between the two active treatment groups and placebo on Day 8 compared to Day 1. High inter- and intra- patient variability, as well as limited sampling, precludes conclusions for a PK-DDI interaction of bevacizumab on gemcitabine pharmacokinetics.

The population PK results from BO17704 and BO17706 were comparable to the pharmacokinetics of patients treated with single-agent bevacizumab and of patients treated with bevacizumab co-administered with chemotherapies, suggesting that anti-cancer agents, including carboplatin and gemcitabine, do not alter bevacizumab pharmacokinetics when co-administered with bevacizumab.

Overall, the cumulative PK-DDI data to date for bevacizumab given in combination with various chemotherapy agents across tumour types do not suggest a potential for a PK-DDI between bevacizumab and chemotherapy agents. In addition, the lack of PK-DDI of sufficient magnitude does not necessitate dose modifications for the chemotherapeutics and anti-cancer agents used in combination with bevacizumab.

## *2.4 Clinical Efficacy*

### *2.4.1. Dose-response study*

No dose-response study was performed in the proposed indication.

The dose of Bv of 15 mg/kg every 21 days (q3w), which is equivalent to a dose of 5 mg/kg/week, is the most commonly used dose of Bv that has been shown to be effective in clinical trials across multiple tumour types. In ovarian cancer, this dose was also studied in the two single-arm Phase II studies in ovarian cancer, which demonstrated strong activity of Bv as a single agent and was thus the dose chosen for the subsequent frontline Phase III trial GOG-0218 in combination with carboplatin and paclitaxel as well as for Study AVF4095g in the recurrent setting. The second front-line Study BO17707 (ICON7) used a lower Bv dose of 7.5 mg/kg q3w (equivalent to 2.5 mg/kg/week), which has been used in trials in other solid tumours although there were no clinical data in ovarian cancer with use of this lower dose. Thus, given the positive results in Phase II and III studies in patients with ovarian cancer with the 5-mg/kg/week dose, including the greater magnitude of benefit seen in Study GOG-0218 compared with Study BO17707 accompanied by an equivalent safety profile, the MAH supports the use of the 5-mg/kg/week dose in this disease.

The selection of the chemotherapy regimen in combination with Bv for Study AVF4095g was based on the results of Study AGO-OVAR, in which patients with platinum-sensitive recurrent disease received gemcitabine 1000 mg/m2 on Days 1 and 8 and carboplatin AUC (area under the curve) 4 mg/mL/min on Day 1 of each cycle. In that study, treatment cycles were repeated q3w for six cycles and for up to 10 cycles at the investigator's discretion. The results of Study AGO-OVAR showed an improvement in response rate and PFS with the combination of CG compared with single-agent carboplatin. Gemcitabine in combination with carboplatin was approved in the United States and Europe for use in recurrent ovarian cancer on the basis of these data prior to the design and initiation of Study AVF4095g.

### *2.4.2. Main study*

### *Study AVF4095g (OCEANS)*

Study AVF4095g was a randomized, double-blind, placebo-controlled, multicenter Phase III trial comparing treatment with carboplatin + gemcitabine (CG) plus concurrent and extended bevacizumab (Bv) versus carboplatin + gemcitabine plus concurrent and extended placebo (Pl) in women with recurrent platinum-sensitive EOC, FTC, or PPC.

### *Methods*

### *Study Participants*

*Main inclusion criteria*

-women 18 years of age or older

-histologically documented EOC, FTC, or PPC that had recurred ≥ 6 months after last platinum-based chemotherapy. This must have been the first recurrence of EOC, FTC, or PPC

-an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 at baseline

-one of the following histologic epithelial cell types: serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, transitional cell carcinoma, malignant Brenner tumour, or adenocarcinoma not otherwise specified

-measurable disease according to modified Response Evaluation Criteria for Solid Tumours (RECIST v 1.0) with at least one lesion that could be accurately measured in at least one dimension (longest dimension recorded: minimum 20 mm with conventional techniques or 10 mm with spiral computed tomography [CT] scan).

*Main exclusion criteria*

-prior chemotherapy in the recurrent setting

-prior therapy with bevacizumab or prior treatment with other VEGF inhibitors or VEGF receptor–targeted agent

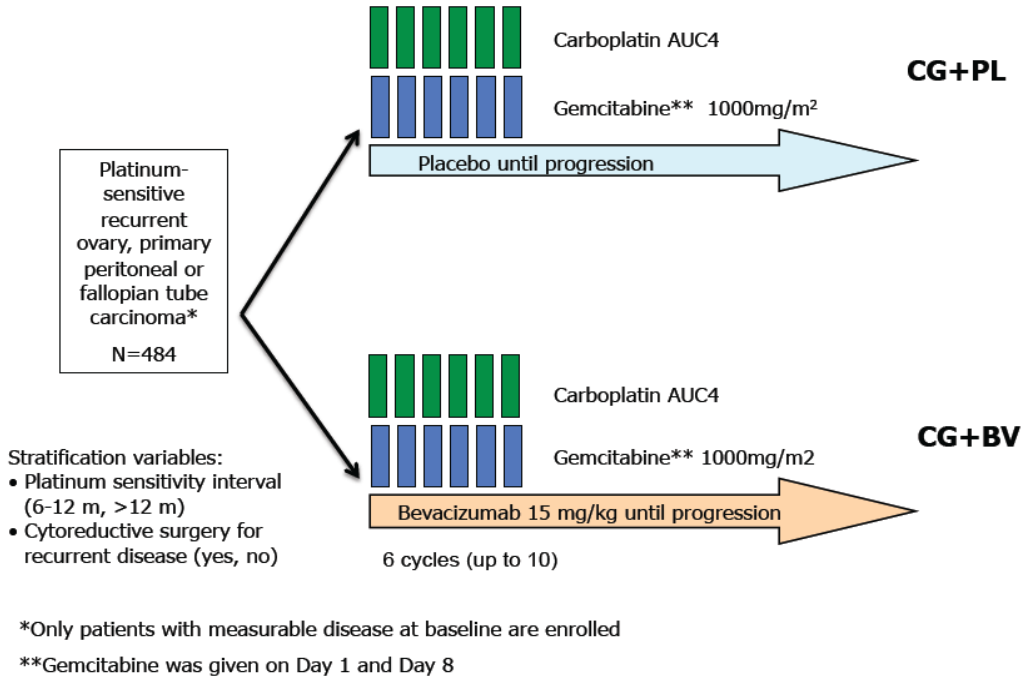
-malignancies other than ovarian cancer (except for tumours with a negligible risk for metastasis or death, such as adequately controlled basal-cell carcinoma or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix) within 5 years prior to randomization

-pregnant or nursing patients.

### *Treatments*

An overview of the design of Study AVF4095g is shown in Figure 1.

**Figure 1. Design of Study AVF4095g**




Patients were randomized to receive treatment with carboplatin (area under the curve [AUC] 4, Day 1, every 21 days [q3w]) and gemcitabine (1000 mg/m$^2$, Day 1, Day 8, q3w) plus concomitant and extended bevacizumab (15 mg/kg Day 1, q3w) or carboplatin and gemcitabine (CG) plus concomitant and extended placebo.

15 mg/kg of bevacizumab/placebo was administered by intravenous (IV) infusion on the first day of Cycle 1, every 3 weeks (21-day cycle). Patients received 6 (up to 10) cycles of CG concurrently with Bv or Pl. The patients then continued with single-agent Bv or Pl until PD or unacceptable toxicity.

Unblinding to study treatment was allowed at the time of documented PD, or after the final analysis of progression free survival (PFS). Patients who were randomised to treatment with bevacizumab and who were still receiving study drug at the time of study unblinding were offered the opportunity to enter an open-label bevacizumab phase. Bevacizumab was administered at the same dose and schedule in the open-label phase as in the blinded phase of the study. Open-label bevacizumab was continued until disease progression (PD), unacceptable toxicity, investigator decision, withdrawal of consent, or death, whichever occurred first.

Reduction in the dose of bevacizumab or placebo was not allowed in this study.

## *Objectives*

The primary objective of the study was to evaluate the efficacy (in terms of PFS) of combining bevacizumab with carboplatin and gemcitabine compared with carboplatin and gemcitabine with placebo in patients with platinum-sensitive, recurrent ovarian, primary peritoneal, or fallopian tube cancer.

Secondary objectives included evaluation of objective response rate (ORR), duration of response, overall survival (OS) and safety profile of bevacizumab in combination with CG.

Exploratory objectives were to evaluate the efficacy of bevacizumab as measured by PFS and objective response as determined by the Independent Review Committee (IRC), according to modified RECIST, to characterize cancer antigen 125 (CA-125) tumour marker levels and their relation to tumour response and treatment as measured by modified RECIST and to assess the effect of bevacizumab on ascites.

## *Outcomes/endpoints*

*Primary efficacy endpoint*

The primary efficacy endpoint of study AVF4095g was investigator-determined PFS defined as the time from randomization to PD based on investigator determination or death due to any cause.

*Secondary efficacy endpoints*

Objective response was defined as the occurrence of a complete response (CR) or partial response (PR), with use of modified RECIST, confirmed by a repeat assessment performed ≥ 4 weeks after the criteria for response were first met.

The duration of objective response was defined as the time from the initial CR or PR until documented PD or death.

OS was defined as the time from randomization until death by any cause in the ITT population.

## *Sample size*

The sample size was calculated on the basis of the following assumptions:

-80% power to reject the null hypothesis

-Two-sided test at $\alpha = 0.05$

-An HR of 0.73

-Median PFS in the control group of 8.6 months.

Based of these assumptions, a total of 317 PFS events would need to be observed at the time of the final PFS analysis. It was estimated that a total of 480 patients would be required to achieve this goal in an acceptable time frame based an enrolment rate of 20 patients per month, a ramp-up period of approximately 3 months, and an exponential drop-out rate of 0.019575. Complete enrolment was expected to occur after approximately 2.5 years, and full information for the primary endpoint was expected approximately 3.5 years after study initiation.

### *Randomisation*

Patients were randomized 1:1 to CG + Bv or CG + Pl and were stratified by platinum-sensitive disease (recurrence 6–12 months from last platinum-based treatment vs. recurrence > 12 months from last platinum-based treatment) and whether they had undergone cytoreductive surgery for recurrent disease (yes, no).

### *Blinding (masking)*

The study was double-blind.

### *Statistical methods*

All efficacy analyses were performed when approximately 317 PFS events were observed (full PFS information as specified by the protocol). An interim futility analysis was performed for the primary endpoint of investigator-determined PFS at approximately 50% of total information (i.e., approximately 160 events).

The primary efficacy analysis was the comparison of investigator-determined PFS between the two treatment arms (GC + Bv vs. GC + Pl) through the use of a two-sided stratified log-rank test. Results from an unstratified log-rank test are also provided. The overall Type I error rate for the two-sided test for the primary endpoint of PFS was controlled at $\alpha = 0.05$. Kaplan-Meier methodology was used to estimate the PFS curves and median times in the treatment arms. A Cox regression model was used to estimate the stratified and unstratified hazard ratio (HR).

Data for patients who did not have investigator-determined PD and who had not died at the time of the clinical cut-off were censored at the time of the last tumour assessment. If no tumour assessments were performed after the baseline visit, PFS was censored at the date of randomization plus 1 day. PFS data for patients receiving non–protocol-specified antineoplastic therapy (NPT) prior to documented PD were also censored at the time of the last tumour assessment prior to therapy initiation.

Exploratory and Sensitivity Analyses

The following exploratory and sensitivity analyses of PFS were performed:

- -Investigator-determined PFS analysis not censored for NPT.
- -IRC–determined analyses of PFS.
- -Discontinuation due to toxicity impact analyses on PFS.
- -Worst-case PFS analysis accounting for missing data: Two worst-case analyses were performed in which patients with two or more missing tumour assessments prior to the data cut-off were assumed to have progressed on the date of the first missed assessment.
- -IRC-determined and investigator-determined concordance analyses.
- -Impact of demographic and baseline characteristics on the primary endpoint of PFS.

In addition, an analysis of IRC-determined ORR and duration of OR was also performed.

The primary efficacy analysis population was the intent-to-treat (ITT) population, defined as all patients randomized to protocol treatment, irrespective of whether the assigned treatment was actually received. For all efficacy analyses, patients were grouped according to the treatment assigned at randomization.

The primary safety population consisted of all randomized patients who received at least one full or partial dose of any component of protocol treatment. For safety analyses, patients were grouped according to whether any full or partial dose of bevacizumab was received.

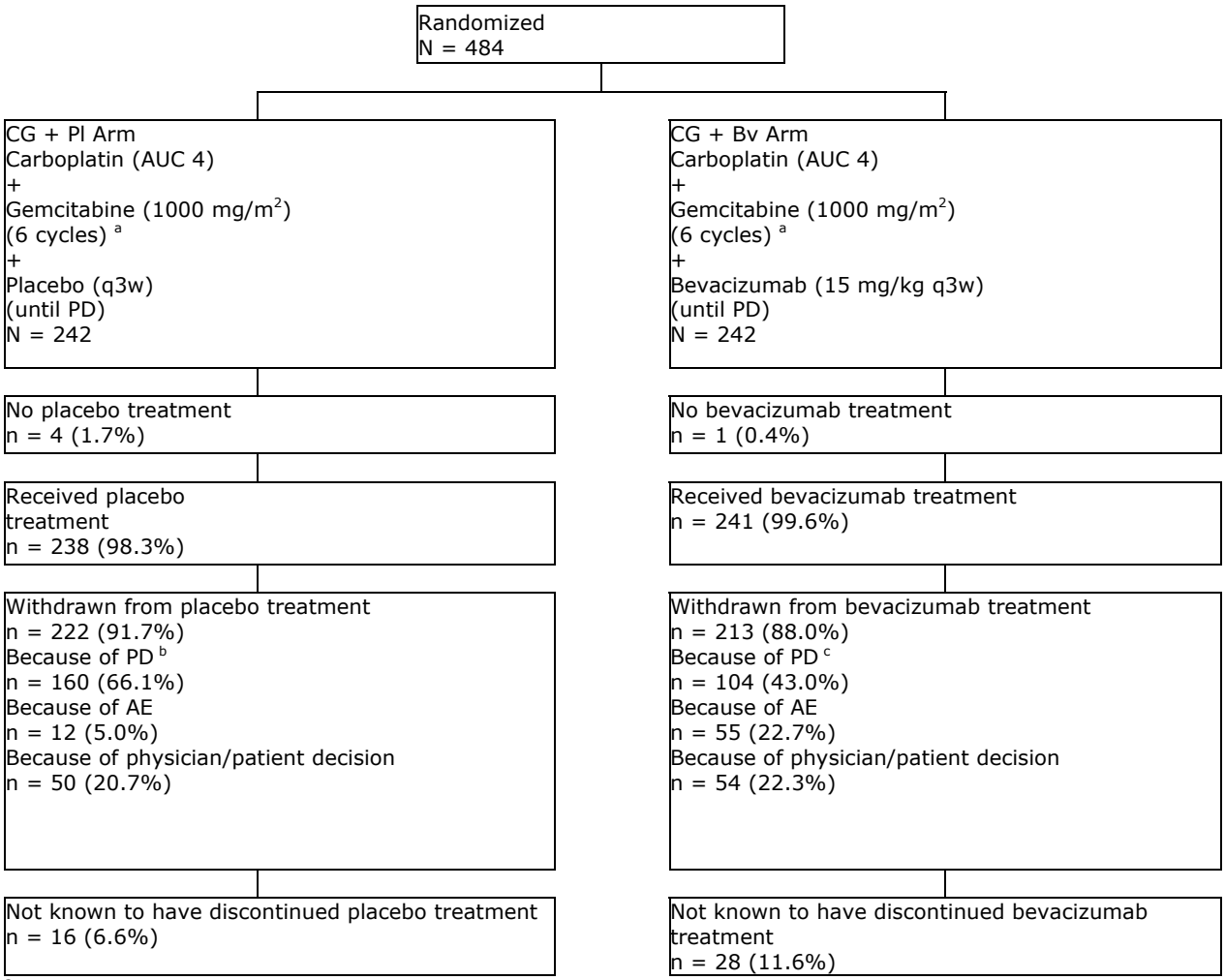
## *Results*

## *Participant flow*

The pivotal trial AVF4095g enrolled 484 patients over 33 months at 96 sites in the United States.

The disposition of patients is presented in Figure 2.

**Figure 2. Disposition of Patients and Reasons for Placebo or Bevacizumab Discontinuation (Study AVF4095g: All Randomized Patients)**




[a] Up to 10 cycles of carboplatin and gemcitabine were allowed.
[b] Includes 158 patients with PD per RECIST and 2 patients with clinical PD.
[c] Includes 100 patients with PD per RECIST and 4 patients with clinical PD.

## Recruitment

The first patient was enrolled in April 2007, and the last patient was enrolled in January 2010. Data cut-off date was 17 September 2010 for the PFS, ORR analysis and for the OS interim analysis.

## Conduct of the study

The protocol for Study AVF4095g was finalized on 21 November 2006 and was subsequently amended five times.

The first amendment (22 May 2007) was to allow the unblinding of protocol treatment at PD instead of at week 51.

The second amendment (8 April 2008) was mainly to change the primary endpoint of PFS to be investigator-determined (rather than IRC−determined) PFS, to update the exploratory objectives to include IRC-determined PFS, objective response, and duration of response, to increase the sample size from 200 patients to 450 patients to power the study as a Phase III trial, to exclude anti-neoplastic hormone therapy and to change the exclusion criteria regarding other malignancies.

The third amendment (15 October 2008) was mainly to add clarification that unblinding for clinical progression could not be based on CA125 levels alone. Clinical progression had to be supported with associated signs and symptoms.

The fourth amendment (11 August 2009) was to add a futility analysis for the primary endpoint and to increase the sample size to 480 patients as fewer patients progressed than expected. Consequently, the enrolment period was increased to 2.5 years.

The fifth amendment (22 December 2010) was to allow patients randomized to the bevacizumab-containing arm to continue to receive bevacizumab after unblinding if study results were positive.

## Baseline data

The baseline demographic and disease characteristics are presented in Tables 1 and 2.

**Table 1. Summary of Baseline Demographic Data (Study AVF4095g: Randomized Patients)**

| Parameter | CG + Pl<br>N = 242 | CG + Bv<br>N = 242 |
|---|---|---|
| Race | | |
| White | 222 (91.7%) | 218 (90.1%) |
| Asian | 6 (2.5%) | 9 (3.7%) |
| Black or African American | 7 (2.9%) | 8 (3.3%) |
| Other | 1 (0.4%) | 3 (1.2%) |
| Unknown | 6 (2.5%) | 4 (1.7%) |
| n | 242 | 242 |
| Age (years) | | |
| Mean (SD) | 61.6 (10.2) | 60.5 (9.8) |
| Median | 61.0 | 60.0 |
| Range | 28.0–86.0 | 38.0–87.0 |
| n | 242 | 242 |
| Age category (years) | | |
| < 40 | 2 (0.8%) | 2 (0.8%) |
| 40–64 | 147 (60.7%) | 155 (64.0%) |
| ≥ 65 | 93 (38.4%) | 85 (35.1%) |
| n | 242 | 242 |
| Weight in kg at baseline | | |
| Mean (SD) | 75.8 (19.1) | 75.5 (17.9) |
| Median | 73.5 | 71.5 |
| Range | 43.6–163.9 | 41.9–159.6 |

| | | |
|---|---|---|
| n | 242 | 242 |
| ECOG PS at baseline | | |
| 0 | 185 (76.4%) | 182 (75.2%) |
| 1 | 57 (23.6%) | 59 (24.4%) |
| 2 | 0 (0.0%) | 1 (0.4%) |
| n | 242 | 242 |

Bv = bevacizumab; CG = carboplatin + gemcitabine; ECOG = Eastern Cooperative Oncology Group; Pl = placebo; PS = performance status; SD = standard deviation.

**Table 2. Summary of Baseline Disease Characteristics (Study AVF4095g: Randomized Patients)**

| Parameter | No. (%) of Patients | |
|---|---|---|
| | CG + Pl N = 242 | CG + Bv N = 242 |
| Tumour type | | |
| Ovarian carcinoma | 207 (85.5) | 200 (82.6) |
| Fallopian tube carcinoma | 15 (6.2) | 14 (5.8) |
| Primary peritoneal carcinoma | 20 (8.3) | 28 (11.6) |
| n | 242 | 242 |
| Histology subtype | | |
| Serous | 202 (83.5) | 189 (78.1) |
| Endometrioid | 16 (6.6) | 13 (5.4) |
| Mucinous and clear cell | 7 (2.9) | 12 (5.0) |
| Other | 17 (7.0) | 28 (11.6) |
| n | 242 | 242 |
| Cytoreductive therapy for recurrent disease | | |
| Yes | 24 (9.9) | 30 (12.4) |
| No | 218 (90.1) | 212 (87.6) |
| n | 242 | 242 |
| Time to recurrence since last platinum-based therapy | | |
| 6–12 months | 102 (42.1) | 100 (41.3) |
| > 12 months | 140 (57.9) | 142 (58.7) |
| n | 242 | 242 |
| Baseline CA125 | | |
| ≤ 35 U/mL | 63 (27.4) | 57 (25.0) |
| > 35 U/mL | 167 (72.6) | 171 (75.0) |
| n | 230 | 228 |
| Baseline SLD category | | |
| ≤ median (59.0 mm) | 126 (52.1) | 118 (48.8) |
| > median | 116 (47.9) | 124 (51.2) |
| n | 242 | 242 |

SLD = sum of the longest diameter of lesions.

*Prior treatment for ovarian cancer*

Prior treatment for ovarian cancer is presented in Table 3.

**Table 3. Prior Treatment for Ovarian Cancer**

| | No. (%) of Patients | |
|---|---|---|
| | CG + Pl N = 242 | CG + Bv N = 242 |
| Any prior treatment | 242 (100) | 242 (100) |
| Surgery | 241 (99.6) | 241 (99.6) |
| Radiotherapy | 6 (2.5) | 3 (1.2) |
| Systemic therapy | 242 (100) | 242 (100) |
| Chemotherapy/platinum | 242 (100) | 242 (100) |
| Chemotherapy/nonplatinum | 241 (99.6) | 242 (100) |
| Hormonal | 10 (4.1) | 12 (5.0) |
| Biologic | 5 (2.1) | 5 (2.1) |
| Other | 8 (3.3) | 10 (4.1) |

*Non-Protocol Specified Therapy for Ovarian Cancer prior to PD*

Table 4 presents NPT for ovarian cancer received prior to documented progressive disease.

**Table 4. NPT for cancer prior to PD**

| | No. (%) of Patients | |
|---|---|---|
| | **CG + Pl N = 242** | **CG + Bv N = 242** |
| NPT started prior to PD | 12 (5.0) | 16 (6.6) |
| NPT for patients without PD | 18 (7.4) | 34 (14.0) |

*Cancer therapy received after PD*

Table 5 presents anti-cancer therapy administered after documented progression of disease.

**Table 5. Anti-neoplastic treatment given on or after INV determined PD**

| **Antineoplastic Treatment** | **No. (%) of Patients** | |
|---|---|---|
| | **CG + Pl N = 242** | **CG + Bv N = 242** |
| Any antineoplastic treatment | 177 (73.1) | 135 (55.8) |
| Chemotherapy | 166 (68.6) | 129 (53.3) |
| Biologics/small molecules | 66 (27.3) | 24 (9.9) |
| Radiation | 11 (4.5) | 12 (5.0) |
| Hormonal therapy | 14 (5.8) | 8 (3.3) |
| Surgery | 10 (4.1) | 3 (1.2) |
| Other | 7 (2.9) | 2 (0.8) |

## Numbers analysed

The patient populations analysed in this study were the ITT and the safety population (Table 6).

**Table 6. Overview of analysis populations**

| | No. of Patients | | |
|---|---|---|---|
| | CG + Pl | CG + Bv | All Patients |
| Intent to treat | 242 | 242 | 484 |
| Safety evaluable | 233 | 247 | 480 |

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

## Outcomes and estimation

### Primary endpoint

INV-determined PFS censored for NPT

The results of the primary stratified analysis of PFS that was censored for NPT are presented in Table 7.

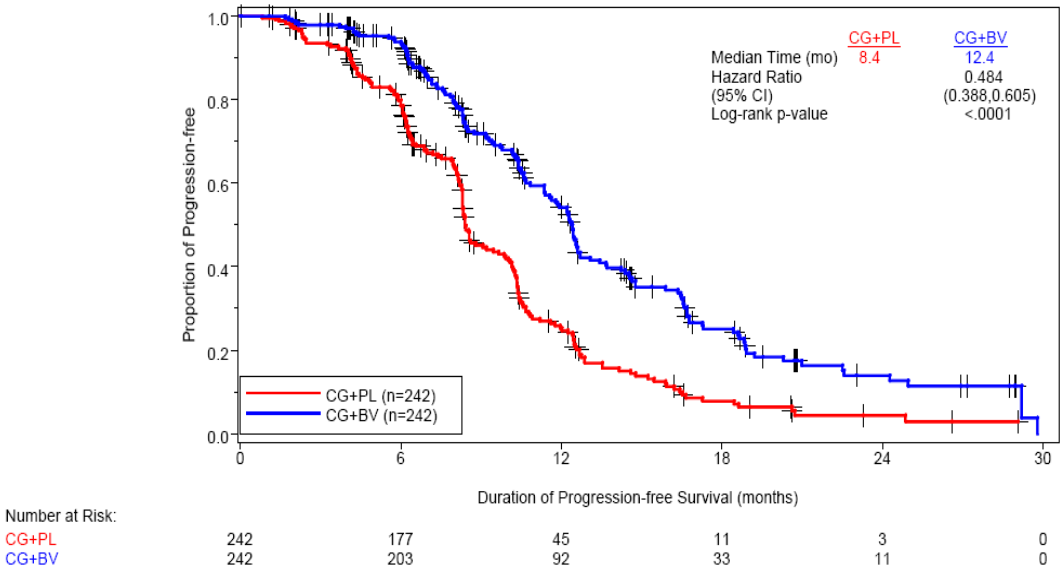
**Table 7. Investigator-Determined Progression-Free Survival Censored for Non–Protocol Specified Antineoplastic Therapy (Study AVF4095g: Randomized Patients)**

| **Progression Free Survival (Investigator Assessed)—Censored for NPT** | **CG + Pl N = 242** | **CG + Bv N = 242** |
|---|---|---|
| No. (%) of patients with an event | 187 (77.3) | 151 (62.4) |
| Disease progression (%) | 185 (76.4) | 146 (60.3) |
| Death (%) | 2 (0.8) | 5 (2.1) |
| Median, months (95% CI) | 8.4 (8.3; 9.7) | 12.4 (11.4; 12.7) |
| Hazard ratio, stratified [a] (95% CI) | 0.484 (0.388; 0.605) | |
| Log-rank p-value | < 0.0001 | |
| Hazard ratio, unstratified [a] (95% CI) | 0.492 (0.396; 0.613) | |
| Log-rank p-value | < 0.0001 | |

[a] Relative to CG + Pl.

Kaplan-Meier curve is presented in Figure 3.

**Figure 3. Kaplan Meier Estimate of Investigator-Determined Progression-Free Survival Censored for Non–Protocol-Specified Antineoplastic Therapy (Study AVF4095g: Randomized Patients)**




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

Sensitivity and exploratory analyses of PFS

An overview of the results of the sensitivity and exploratory analyses of PFS is presented in Table 8.

**Table 8. Overview of the Results of the Sensitivity Analyses of Progression-Free Survival (Study GOG-0218: Randomized Patients)**

| PFS Analysis | Median PFS months | | Hazard Ratio [a] (95% CI) |
|---|---|---|---|
| | CG + Pl N = 242 | CG + Bv N = 242 | |
| **Primary PFS Analysis** | | | |
| INV determined PFS, censored for NPT | 8.4 | 12.4 | 0.484 (0.388; 0605); p < 0.0001 |
| **Exploratory/Sensitivity PFS Analysis** | | | |
| INV determined PFS, not censored for NPT | 8.4 | 12.4 | 0.524 (0.425; 0.645); p < 0.0001 |
| IRC determined PFS, censored for NPT | 8.6 | 12.3 | 0.451 (0.351; 0.580); p < 0.0001 |
| IRC determined PFS, not censored for NPT | 8.6 | 12.3 | 0.480 (0.377; 0.613); p < 0.0001 |
| Discontinuation due to toxicity [b] | 8.4 | 12.5 | 0.466 (0.370; 0.586); p < 0.0001 |
| First worst-case analysis [c] | 8.4 | 10.7 | 0.669 (0.543; 0.824); p = 0.0001 |
| Second worst-case analysis [c] | 8.3 | 10.7 | 0.596 (0.486; 0.731); p < 0.0001 |

[a] Stratified analysis by time to recurrence since the last platinum therapy (6–12 months, > 12 months) and cytoreductive surgery for recurrent disease (yes, no).
[b] Investigator determined, censored for NPT. Data were censored for patients who discontinued study treatment prior to PD at the time of last tumour assessment prior to discontinuation.
[c] Accounting for missing data. Investigator determined, censored for NPT. Patients with two or more missing tumour assessments prior to the data cut-off were assumed to have progressed on the date of the first missed assessment. First worst-case analysis applied only to patients in the CG + Bv arm. Second worst-case analysis applied to all patients in both arms.

INV-determined PFS not censored for NPT

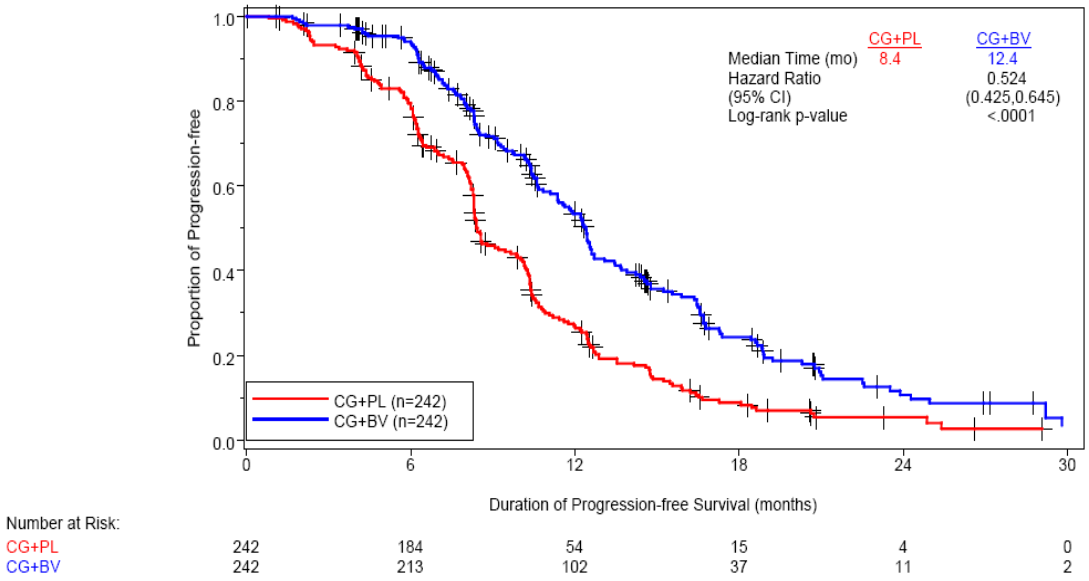
Results of the sensitivity analysis of INV determined PFS not censored for NPT are presented in Table 9 and the corresponding Kaplan-Meier curve is shown in Figure 4.

**Table 9. INV-determined PFS not censored for NPT (antineoplastic therapy): Randomized Patients)**

| Progression Free Survival (Investigator Assessed)—Not censored for NPT | CG + Pl N = 242 | CG + Bv N = 242 |
|---|---|---|
| No. (%) of patients with an event | 203 (83.9) | 174 (71.9) |
| Median, months (95% CI) | 8.4 (8.3; 9.9) | 12.4 (11.4; 12.7) |
| Hazard ratio, stratified a (95% CI) | 0.524 (0.425; 0.645) | |
| Log-rank p-value | < 0.0001 | |
| Hazard ratio, unstratified a (95% CI) | 0.526 (0.428; 0.647) | |
| Log-rank p-value | < 0.0001 | |

a Relative to CG + Pl.

**Figure 4. Kaplan Meier Estimate of INV-determined PFS not censored for NPT (antineoplastic therapy): Randomized Patients**




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

IRC-determined PFS censored for NPT

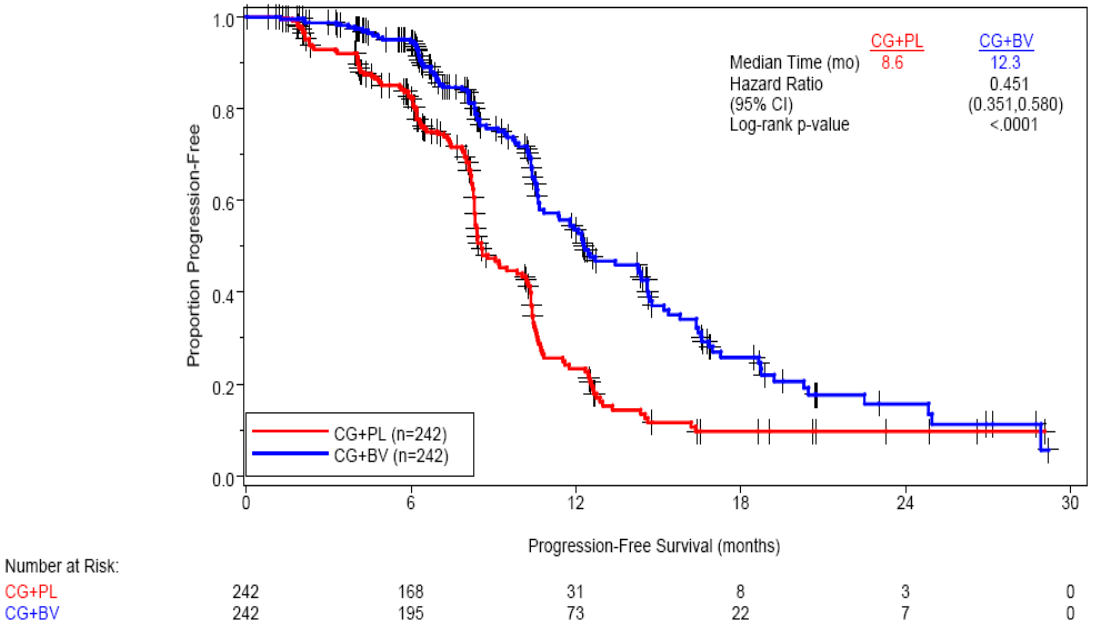
Results of the sensitivity analysis of IRC determined PFS censored for NPT are presented in Table 10 and the corresponding Kaplan-Meier curve is shown in Figure 5.

**Table 10. Independent Review Committee-Determined Progression-Free Survival: Censored for Non–Protocol-Specified Antineoplastic Therapy (Study AVF4095g: Randomized Patients)**

| PFS (IRC Determined), Censored for NPT | CG + Pl N = 242 | CG + Bv N = 242 |
|---|---|---|
| No. (%) of patients with an event | 148 (61.2) | 119 (49.2) |
| Median, months (95% CI) | 8.6 (8.3; 10.2) | 12.3 (10.7; 14.6) |
| Hazard ratio, stratified [a] (95% CI) | 0.451 (0.351; 0.580) | |
| Log-rank p-value | < 0.0001 | |
| Hazard ratio, unstratified [a] (95% CI) | 0.487 (0.381; 0.622) | |
| Log-rank p-value | < 0.0001 | |

[a] Relative to CG + Pl.

**Figure 5. Kaplan Meier Estimate of Independent Review Committee Determined Progression-Free Survival Censored for Non–Protocol-Specified Antineoplastic Therapy (Study AVF4095g: Randomized Patients)**




IRC-determined PFS not censored for NPT

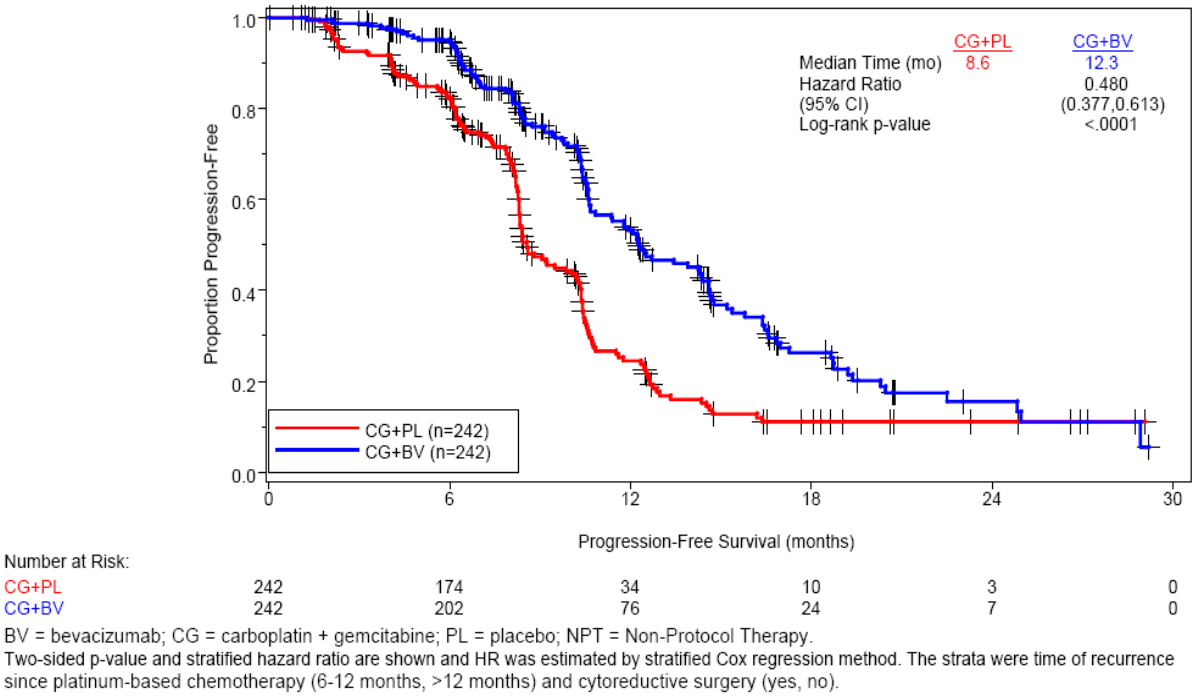
Results of the sensitivity analysis of IRC determined PFS not censored for NPT are presented in Table 11 and the corresponding Kaplan-Meier curve is shown in Figure 6.

**Table 11. Independent Review Committee-Determined Progression-Free Survival Not Censored for Non–Protocol-Specified Antineoplastic Therapy (Study AVF4095g: Randomized Patients)**

| PFS (IRC-Determined), Not Censored for NPT | CG + Pl N = 242 | CG + Bv N = 242 |
|---|---|---|
| No. (%) patients with an event | 153 (63.2) | 126 (52.1) |
| Median, months (95% CI) | 8.6 (8.3; 10.2) | 12.3 (10.7; 14.4) |
| Hazard ratio, stratified [a] (95% CI) | 0.480 (0.377; 0.613) | |
| Log-rank p-value | < 0.0001 | |
| Hazard ratio, unstratified [a] (95% CI) | 0.509 (0.401; 0.646) | |
| Log-rank p-value | < 0.0001 | |

[a] Relative to CG + Pl.

**Figure 6. Independent Review Committee–Determined Progression-Free Survival Not Censored for Non–Protocol-Specified Antineoplastic Therapy (Study AVF4095g: Randomized Patients)**




BV = bevacizumab; CG = carboplatin + gemcitabine; PL = placebo; NPT = Non-Protocol Therapy.
Two-sided p-value and stratified hazard ratio are shown and HR was estimated by stratified Cox regression method. The strata were time of recurrence since platinum-based chemotherapy (6-12 months, >12 months) and cytoreductive surgery (yes, no).

INV-determined PFS: Discontinuation due to toxicity

Results of the sensitivity analysis of impact of discontinuation due to toxicity on INV determined PFS are presented in Table 12.

**Table 12. Investigator-Determined Progression-Free Survival: Discontinuation Due to Toxicity (Study AVF4095g: Randomized Patients)**

| Progression Free Survival (Investigator Assessed), Discontinuation due to Toxicity | CG + Pl N = 242 | CG + Bv N = 242 |
|---|---|---|
| No. (%) patients with an event | 181 (74.8) | 135 (55.8) |
| Median, months (95% CI) | 8.4 (8.3; 9.9) | 12.5 (11.6; 13.7) |
| Hazard ratio, stratified [a] (95% CI) | 0.466 (0.370; 0.586) | |
| Log-rank p-value | < 0.0001 | |
| Hazard ratio, unstratified [a] (95% CI) | 0.473 (0.377; 0.593) | |
| Log-rank p-value | < 0.0001 | |

[a] Relative to CG + Pl.

INV-determined PFS: Worst-case analysis accounting for missing data

The results of the two "worst-case" sensitivity analyses of INV assessed PFS are presented in Table 13.

**Table 13. Investigator-Determined Progression-Free Survival: Worst-Case Analysis Accounting for Missing Data (Study AVF4095g: Randomized Patients)**

| PFS (Investigator Assessed), Worse Case Analyses | CG + Pl N = 242 | CG + Bv N = 242 |
|---|---|---|
| First worst-case analysis imputing PD in the Bv arm only | | |
| No. (%) of patients with an event | 187(77.3) | 185 (76.4) |
| Median, months (95% CI) | 8.4 (8.3; 9.7) | 10.7 (9.8; 12.2) |
| Hazard ratio, stratified [a] (95% CI) | 0.669 (0.543; 0.824) | |
| Log-rank p-value | 0.0001 | |
| Hazard ratio, unstratified [a] (95% CI) | 0.680 (0.553; 0.837) | |

| | | |
|---|---|---|
| Log-rank p-value | 0.0002 | |
| Second worst-case analysis imputing PD in the Bv and Pl arms | | |
| No. (%) of patients with an event | 207 (85.5) | 185 (76.4) |
| Median, months (95% CI | 8.3 (8.0; 8.4) | 10.7 (9.8; 12.2) |
| Hazard ratio, stratified [a] (95% CI) | 0.596 (0.486; 0.731) | |
| Log-rank p-value | < 0.0001 | |
| Hazard ratio, unstratified [a] (95% CI) | 0.608 (0.496; 0.744) | |
| Log-rank p-value | < 0.0001 | |

[a] Relative to CG + Pl.

Subgroup analyses (PFS)

The generalizability of the observed benefit of adding bevacizumab to CG therapy on the primary parameter of investigator-determined PFS was investigated by estimating the treatment effect in predefined subgroups. Subgroups and prognostic factors for assessing the treatment effect on PFS included the randomization stratification variables (time to recurrence since the last platinum-based therapy and occurrence of cytoreductive surgery for recurrent disease), age, race, baseline ECOG performance status, histopathological cell type, SLD of target lesions at baseline, prior biologic therapy, prior hormonal therapy, and prior myeloablative therapy.

Based on the results of all the subgroup analyses the HRs ranging from 0.41 - 0.68.

PFS subgroup analyses depending on recurrence since last platinum therapy are summarised in Table 14.

**Table 14. 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) | Avastin + C/G (n = 242) |
| **6- 12 months (n=202)** | | |
| **Median** | 8.1 | 10.6 |
| Hazard ratio (95% CI) | 0.35 (0.24 - 0.51) | |
| **> 12 months (n=282)** | | |
| **Median** | 10.2 | 12.5 |
| Hazard ratio (95% CI) | 0.57 (0.41 – 0.79) | |

**Secondary endpoints**

ORR (CR+PR): INV-determined

The results of the INV-determined ORR are presented in Table 15.

**Table 15. Objective Response Rate, Investigator-Determined (Study AVF4095g: Randomized Patients)**

| **ORR (Investigator Determined)** | **CG + Pl**<br>**N = 242** | **CG + Bv**<br>**N = 242** |
|---|---|---|
| No. (%) of patients with measureable disease | 242 (100) | 242 (100) |
| No. (%) of patients with an objective response (95% CI) | 139 (57.4) (51.2%; 63.7%) | 190 (78.5) (73.3%; 83.7%) |
| Difference in response rates (95% CI) | 21.1% (13.0%; 29.2%) | |
| p-value, stratified [a] | < 0.0001 | |
| p-value, unstratified [b] | < 0.0001 | |
| Complete response | 22 (9.1) | 42 (17.4) |
| Partial response | 117 (48.3) | 148 (61.2) |

[a] Cochran-Mantel-Haenszel test.
[b] $\chi^2$ test

Duration of ORR: INV-determined

The results of the INV-determined median duration of OR are presented in Table 16.

**Table 16. Duration of Objective Response: Investigator Determined (Study AVF4095g: Randomized Patients with an Objective Response)**

| **Duration of Objective Response (Investigator-Determined)** | **CG + Pl**<br>**N = 139** | **CG + Bv**<br>**N = 190** |
|---|---|---|
| No. of patients with an objective response | 139 | 190 |
| No. (%) of patients with an event | 105 (75.5) | 119 (62.6) |
| Median, months (95% CI) | 7.4 (6.31; 8.31) | 10.4 (9.36; 11.83) |
| Hazard ratio, stratified [a] (95% CI) | 0.534 (0.408; 0.698) | |
| Log-rank p-value [a] | < 0.0001 | |
| Hazard ratio, unstratified [a] (95% CI) | 0.537 (0.412; 0.700) | |
| Log-rank p-value [a] | < 0.0001 | |

[a] Descriptive purposes only.

Exploratory: IRC-determined ORR

The table 17 presents the results of the IRC analysis of ORR.

**Table 17. Independent Review Committee–Determined Objective Response Rate (Study AVF4095g: Randomized Patients)**

| **Objective Response Rate (IRC Determined)** | **CG + Pl (N = 242)** | **CG + Bv N = 242** |
|---|---|---|
| No. (%) of patients with measureable disease | 242 (100) | 242 (100) |
| No. (%) of patients with an objective response (95% CI) | 130 (53.7) (47.4%; 60.0%) | 181 (74.8) (69.3%; 80.3%) |
| Difference in response rates (95% CI) | 21.1% (12.7%; 29.4%) | |
| p-value, stratified [a] | < 0.0001 | |
| p-value, unstratified [b] | < 0.0001 | |
| Complete response | 3 (1.2%) | 2 (0.8%) |
| Partial response | 127 (52.5%) | 179 (74.0%) |

[a] Cochran-Mantel-Haenszel test.
[b] $\chi^2$ test

Overall survival

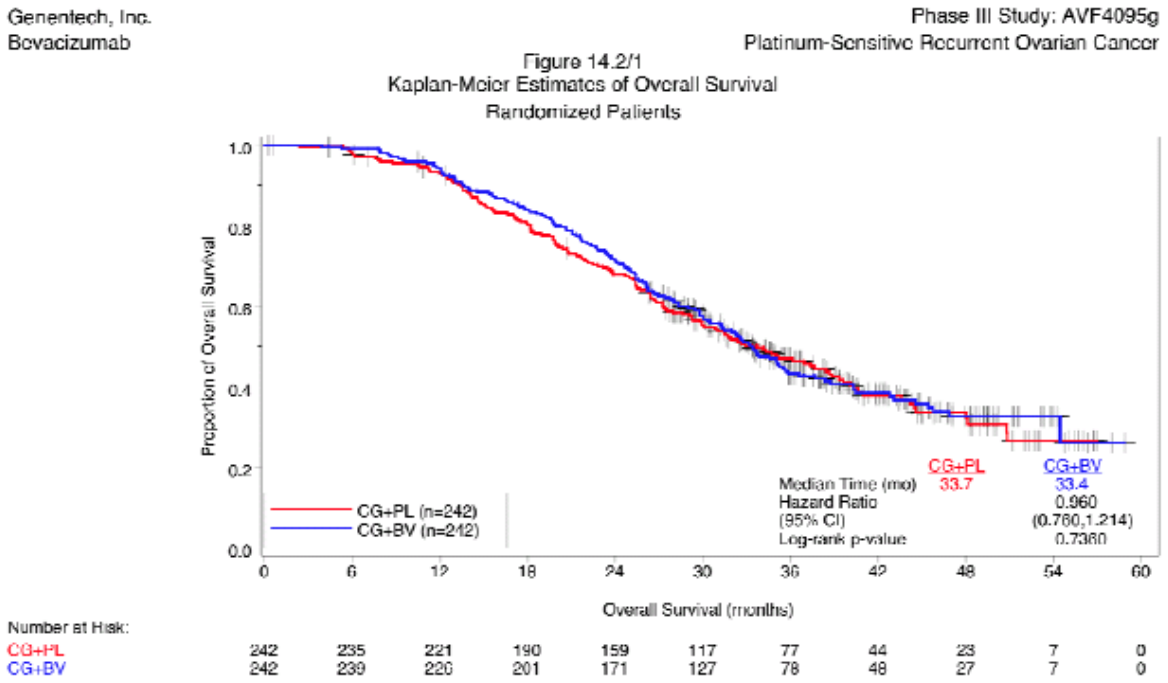
The results of the first interim analysis (cut-off date 17 September 2010), the second (cut-off date 29 August 2011) and the third updated OS analyses are presented in Table 18.

**Table 18. Summary of Overall Survival Analyses**

| | **1st Interim (17 September 2010)** | | **2nd Interim (29 August 2011)** | | **3rd Interim (30 March 2012)** | |
|---|---|---|---|---|---|---|
| | CG + PL | CG + BV | CG + PL | CG + BV | CG + PL | CG + BV |
| No. (%) events | 78 (32.2%) | 63 (26%) | 112 (46.3%) | 123 (50.8%) | 142 (58.7%) | 144 (59.5%) |
| Median OS (months) | 29.9 | 35.5 | 35.2 | 33.3 | 33.7 | 33.4 |
| Median follow up (months) | 23.5 | 23.7 | 33.7 | 35.4 | 41.9 | 42.3 |
| Hazard ratio (95% CI) | 0.751 (0.537, 1.052) | | 1.027 (0.792, 1.331) | | 0.960 (0.760, 1.214) | |
| Log-rank p-value | 0.0944 | | 0.8422 | | 0.736 | |

The corresponding Kaplan-Meier curve of the 3rd updated OS analysis is presented in Figure 7.

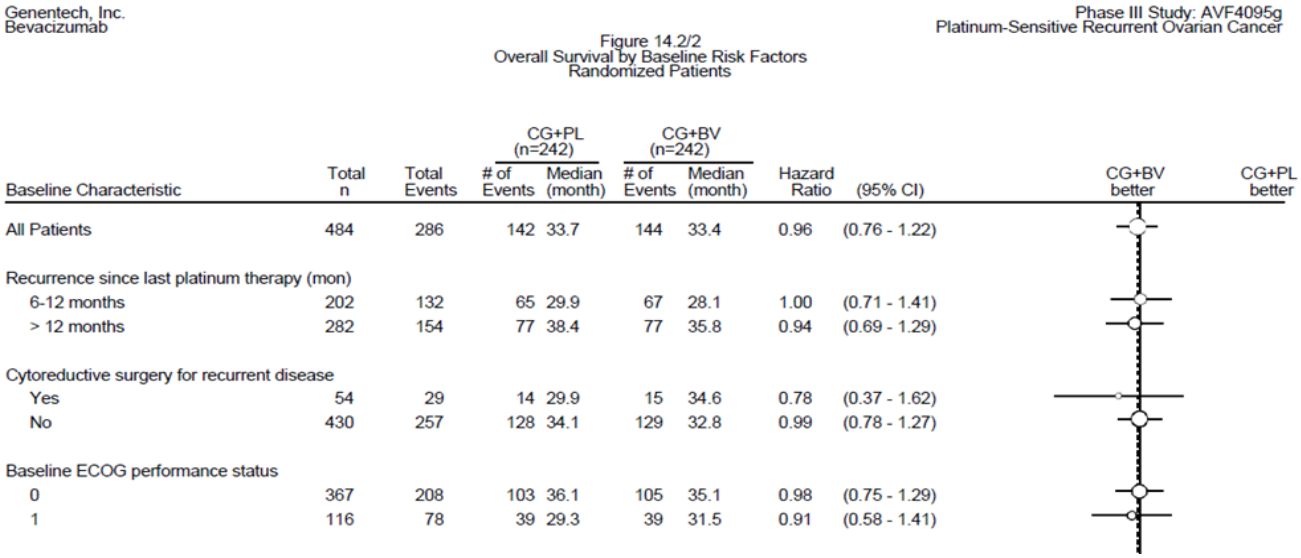
**Figure 7. Kaplan-Meier Estimate of Overall Survival (Study AVF4095g: Randomized Patients) -Updated analysis (cut-off date 30 March 2012)**

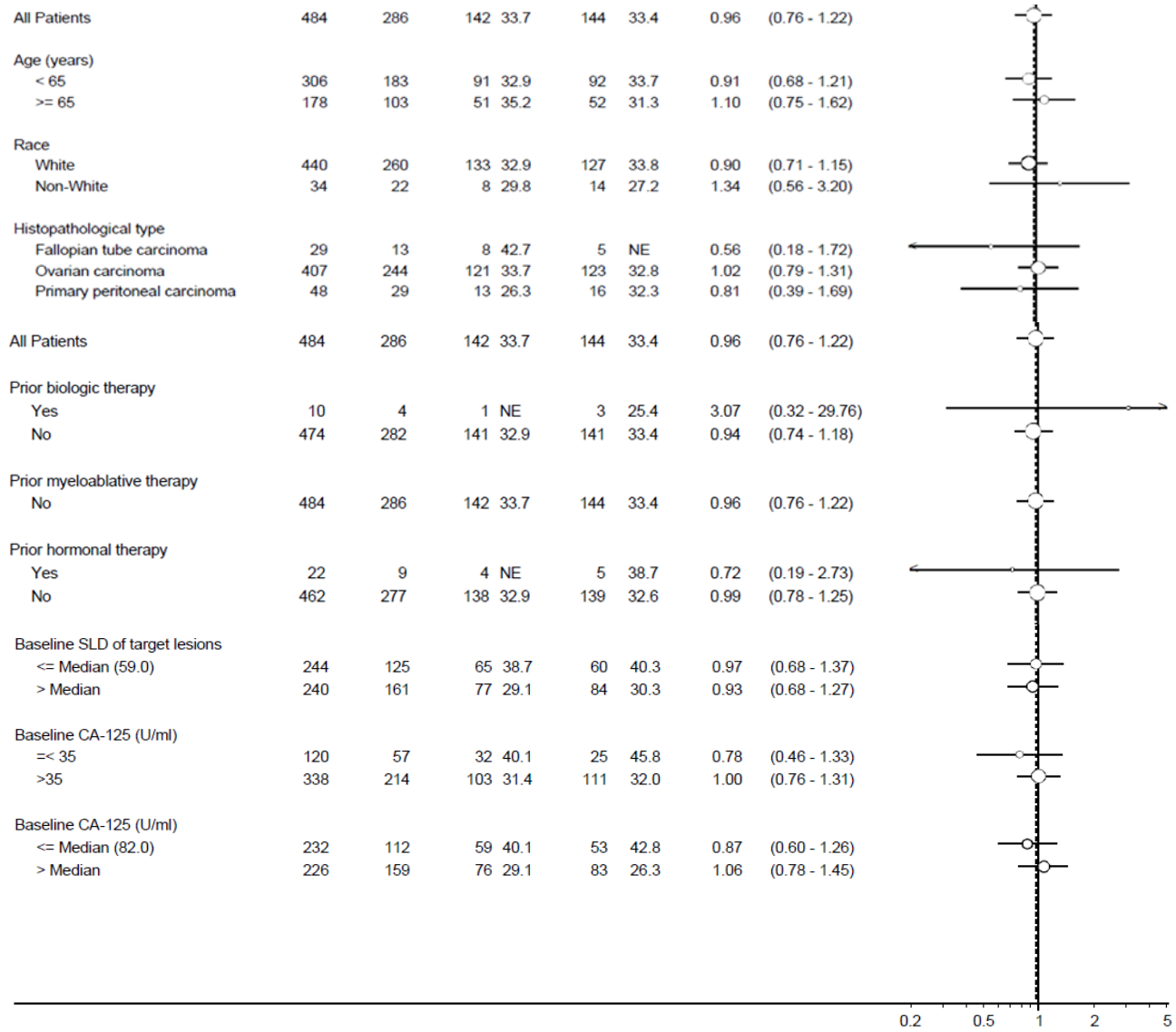



BV = bevacizumab; CG = carboplatin+gemcitabine; PL = placebo.

*Exploratory post-hoc OS subgroup analyses based on demographic and baseline characteristics*

**Figure 8. Overall Survival by Baseline Risk Factors: Randomised Patients**






BV=bevacizumab; CG=carboplatin+gemcitabine; NE=not estimatable; PL=placebo; SLD= sum of longest diameters. Median overall survival was estimated from Kaplan Meier method. Hazard ratio relative to placebo and 95%CI for the hazard ratio were estimated using Cox regression. The vertical dashed line indicates the hazard ratio for all patients. The diameter for a circle is proportional to the square root of the total number of events. Source:
Biostatistics(yingy)pgm(/onco/avf/avf4095g/os_update3/programs/g_blobogram_os) database (MAR30,2012) Generated 26JUNE2012 15:15

Subsequent therapies were widely used post-progression (Tables 19 and 20).

**Table 19. Number of Subsequent Anti-Cancer Therapies: Randomized Patients**

| Number of subsequent anti-cancer therapies | Number of Subsequent Anti-Cancer Therapies Randomized Patients CG+PL (n=242) | CG+BV (n=242) |
|---|---|---|
| 14 | 1 ( 0.4%) | 0 ( 0.0%) |
| 13 | 1 ( 0.4%) | 0 ( 0.0%) |
| 12 | 1 ( 0.4%) | 0 ( 0.0%) |
| 11 | 3 ( 1.2%) | 0 ( 0.0%) |
| 10 | 5 ( 2.1%) | 3 ( 1.2%) |
| 9 | 15 ( 6.2%) | 10 ( 4.1%) |
| 8 | 27 ( 11.2%) | 22 ( 9.1%) |
| 7 | 52 ( 21.5%) | 33 ( 13.6%) |
| 6 | 87 ( 36.0%) | 64 ( 26.4%) |
| 5 | 133 ( 55.0%) | 114 ( 47.1%) |
| 4 | 168 ( 69.4%) | 164 ( 67.8%) |
| 3 | 214 ( 88.4%) | 204 ( 84.3%) |
| 2 | 9 ( 3.7%) | 7 ( 2.9%) |
| 1 | 0 ( 0.0%) | 0 ( 0.0%) |

**Table 20. Summary of Subsequent Anti-Cancer Therapy: Randomized Subjects**

Summary of Subsequent Anti-Cancer Therapy

Randomized Subjects

| | CG+PL (n=242) | CG+BV (n=242) | All Patients (n=484) |
|---|---|---|---|
| Any non-protocol-specified anti-cancer therapies | 216 ( 89.3%) | 207 ( 85.5%) | 423 ( 87.4%) |
| Chemotherapy | 213 ( 98.6%) | 203 ( 98.1%) | 416 ( 98.3%) |
| Doxil Or Equivalent | 157 ( 72.7%) | 146 ( 70.5%) | 303 ( 71.6%) |
| Taxol Or Equivalent | 113 ( 52.3%) | 112 ( 54.1%) | 225 ( 53.2%) |
| Platinum Therapy | 84 ( 38.9%) | 95 ( 45.9%) | 179 ( 42.3%) |
| Experimental Chemo | 10 ( 4.6%) | 13 ( 6.3%) | 23 ( 5.4%) |
| Gemcitabine(Gemzar) + Platinum | 7 ( 3.2%) | 10 ( 4.8%) | 17 ( 4.0%) |
| Taxol + Platinum | 3 ( 1.4%) | 5 ( 2.4%) | 8 ( 1.9%) |
| Other Chemo | 136 ( 63.0%) | 116 ( 56.0%) | 252 ( 59.6%) |
| Biologics/Small Molecules | 92 ( 42.6%) | 55 ( 26.6%) | 147 ( 34.8%) |
| Bev/Avastin | 85 ( 39.4%) | 46 ( 22.2%) | 131 ( 31.0%) |
| Experimental Biologic | 10 ( 4.6%) | 6 ( 2.9%) | 16 ( 3.8%) |
| Other Or Experimental.. | | | |
| Small Molecule Inhibitors | 9 ( 4.2%) | 2 ( 1.0%) | 11 ( 2.6%) |
| Parp-Inhibitors | 8 ( 3.7%) | 3 ( 1.4%) | 11 ( 2.6%) |
| Amg-386 | 6 ( 2.8%) | 3 ( 1.4%) | 9 ( 2.1%) |
| Small Molecule Vegfr Inhibitors (I.E. Pazopanib, Sorafenib) | 3 ( 1.4%) | 1 ( 0.5%) | 4 ( 0.9%) |
| Hormonal Therapy | 26 ( 12.0%) | 21 ( 10.1%) | 47 ( 11.1%) |
| Radiation | 24 ( 11.1%) | 23 ( 11.1%) | 47 ( 11.1%) |
| Surgery | 20 ( 9.3%) | 15 ( 7.2%) | 35 ( 8.3%) |
| Other | 10 ( 4.6%) | 5 ( 2.4%) | 15 ( 3.5%) |

## Clinical studies in special populations

No studies in special populations were submitted.

## Analysis performed across trials (pooled analyses AND meta-analysis)

N/A

## Supportive studies

N/A

### *2.2.3 Discussion on clinical efficacy*

This application concerns the use of bevacizumab in patients with platinum-sensitive, recurrent ovarian cancer. It is based on a single pivotal trial, AVF4095g (OCEANS), a randomized, double-blind, placebo-controlled, multicenter Phase III trial comparing treatment with carboplatin + gemcitabine (CG) plus concurrent and extended bevacizumab (Bv) versus carboplatin + gemcitabine plus concurrent and extended placebo (Pl) in women with recurrent platinum-sensitive EOC, FTC, or PPC.

Design and conduct of clinical studies

The AGO-OVAR is the reference study for the carboplatin-gemcitabine backbone as used in the OCEANS trial and referenced to in most international guidelines, including ESMO Clinical Practice Guidelines. In the AGO-OVAR study patients in the experimental arm received gemcitabine 1,000 mg/m$^2$ on days 1 and 8 and carboplatin area under the curve (AUC) 4 mg/mL/min on day 1. Patients in the control arm received carboplatin AUC 5 on day 1, based on the Calvert formula (Phisterer J et al. JCO 2006; 24(29): 4699-4707.

In study AVF4095g, only patients with platinum-sensitive, recurrent disease who had not received prior therapy with bevacizumab or prior treatment with other VEGF inhibitors or VEGF receptor–targeted agent previously, and only those who experienced recurrence for the first time were eligible. The indication proposed by the MAH has been revised to reflect this target population and the section 5.1 of the SmPC has been updated to include the above inclusion criteria of study AVF4095g.

Platinum sensitivity is commonly defined as a patient who has had a relapse ≥ 6 months after initial platinum chemotherapy. There was no specific requirement for documented response to front-line therapy for patients to be considered eligible.

There were 9 weeks between tumour assessments. 9-week intervals have precedence in ovarian cancer and are considered convenient in relation to patient burden and the 6-10 cycles of chemotherapy given every 3 weeks. Due to the relatively long time to progression in ovarian cancer, the possible impact of a 9-week interval between tumour assessments on the estimate of PFS is considered minimal. Tumour assessments were performed by modified RECIST, which is considered acceptable. However, progression could also be determined clinically, but not based on CA-125 increase alone. Overall, 4 patients in the Bv arm and 2 patients in the Pl arm had clinical disease progression during the study.

CA125 rises and radiographic progressions are not always concordant in patients treated with bevacizumab. According to the protocol, an increase in CA-125 alone was not sufficient as basis for determining PD. In study AVF4095g 13% of patients in both treatment arms had a CA125 elevation without modified RECIST defined progression. As the proportion was similar across treatment arms, no influence on the PFS result is foreseen. This was confirmed in a sensitivity analysis in which CA125 progressions were also counted as events.

The date of PD was based on the date of initial documentation rather than the time of confirmed PD for both investigator and IRC assessments. No confirmation of PD was required. Unfortunately, scans were not taken until both investigator and IRC decided on progressive disease for a patient. In 49 patients (20.2%) in the Bv arm and 56 patients (23.1%) in the Pl arm, the investigator determined PD while the IRC did not. In these cases, the patients discontinued treatment, and no more scans were taken. However, the overall concordance for PD status between investigators and IRC was high and not indicative of a systematic bias in investigators' assessments.

The MAH has provided adequate information about the number of patients included in the analyses of PFS, the number of patients censored from the analyses and the reason for censoring of data.

Efficacy data and additional analyses

The major reason for withdrawing from treatment was development of PD: 66.1% (placebo arm) vs. 43.0% (bevacizumab arm).

The HR for the primary stratified PFS analysis (INV assessed and censored for NPT) was 0.48 (95% CI: 0.388, 0.605; $p < 0.0001$) in favour of the bevacizumab-containing arm, with a median PFS of 8.4 months in the placebo arm vs. 12.4 months in the bevacizumab arms. A similar result was obtained in the unstratified analysis (HR = 0.492; 95% CI: 0.396, 0.613). The Kaplan-Meier curves demonstrated an early separation after two months. In contrast, to what was observed in the front-line setting, the curves stay separate, also in the last parts of the curves. The primary PFS analysis was the final (70% of events were reported).

A sensitivity analysis not censoring for NPT showed a very similar result (HR = 0.524; 95% CI: 0.425, 0.645). Reassuringly, the MAH has also performed a "worst-case analysis" as requested in which all patients with NPT use were counted as events. In this very conservative analysis, the HR of PFS was

0.529 (95% CI: 0.430, 0-652). It is therefore acknowledged that censoring for NPT was not a significant factor in the PFS analysis.

A number of pre-specified sensitivity analyses have also been performed that overall confirm the robustness of the primary PFS analysis. In these sensitivity analyses, the magnitude of the effect on PFS following treatment with bevacizumab compared to placebo in terms of HR ranged from 0.45 (IRC determined PFS: censored for NPT) to 0.67 (INV determined PFS: Worst Case Analysis Accounting for Missing Data: analysis imputing PD in the bevacizumab and placebo arms). The gain in PFS in favour of therapy with bevacizumab ranged from 2.3 months (INV determined PFS: Worst Case Analysis Accounting for Missing Data: analysis imputing PD in the bevacizumab arm only) to 4.1 months (INV determined PFS: Discontinuation Due to Toxicity).

The concordance rate between INV and IRC-based determination of progression was relatively high: 73.2% in the placebo arm vs. 75.2% in the bevacizumab arm. When comparing the dates of PD/death or censoring based as determined by INV and IRC, respectively, there was an absolute difference in PFS dates of ≤ 9 weeks (one tumour assessment interval) in the majority of patients (85%). Overall, the consistency between the IRC- and INV- based results indicates that investigators' assessments of PFS were not biased.

Consistent results were found in the pre-specified subgroup analysis according to prognostic factors/ stratification factors. A benefit in favour of the bevacizumab -containing arm was observed in all subgroups investigated.

ORR results (secondary endpoint) were also in favour of the bevacizumab-containg treatment arm. A statistical significantly higher ORR of 78.5% (INV-determined) was observed in patients treated with bevacizumab compared with 57.4% in the placebo arm resulting in an absolute difference of 21.1% ($p < 0.0001$) which is remarkable. The majority of responses were PRs. In responding patients the median duration of OR was also longer in the bevacizumab arm (10.4 months) compared to the placebo arm (7.4 months) (non-randomised subset). The overall result of the exploratory analysis of ORR based on IRC assessment is in accordance with the INV analysis; there was a statistically significant difference of 21.1% in ORR between the treatment arms in favour of treatment with bevacizumab. There was a large difference in the proportion of patients with CR assessed by the investigators and the IRC: according to the investigator assessment 9.1% and 17.4% of the patients in the placebo and bevacizumab arms, respectively, achieved CR. According to the IRC assessments the proportions were 1.2% and 0.8%. This discrepancy was caused by differences in the criteria used for assessments of the tumour size in the study protocol and IRF charter, respectively. It is acknowledged, however, that the overall results from the investigator-based and IRC-based analyses of ORR were comparable.

At the most recent OS analysis (3$^{rd}$ update, cut-off date: 30 March 2012) 59% of patients had died overall (142 (58.7%) in the placebo arm and 144 (59.5%) in the bevacizumab arm). The number of deaths was comparable between treatment arms. The median OS was 33.7 months in the placebo arm compared to 33.4 months in the bevacizumab arm. The HR for OS was 0.964 (95% CI: 0.764, 1.216) (unstratified analysis). The K-M curves were overlapping from 24 months and onwards.

The vast majority of deaths were attributed to disease progression in both treatment arms (only 0.4% of deaths in the placebo arm compared to 1.2% in the Bv arm were caused by adverse events) so there is no indication of significantly increased toxicity-related deaths in the Bv-containing arm.

The Applicant has also analysed the types of progressions as reported by Investigators. There was no indication that Bv should have promoted new lesions as a very similar pattern was observed across treatment arms in terms of types of first PD event (1/3 of patients had new lesions only in both treatment arms, 1/3 both new lesions and progression of exiting lesions, 1/3 progression of existing lesions only).

In summary, no difference was seen for OS between treatment arms in the updated 3rd interim OS analysis. The final OS analysis is awaited in Q4 2013 (73% of events projected) and the MAH should submit these results as an obligation.

The MAH has performed a number of additional analyses based on data from the 3rd interim OS analysis (date of data cut-off: 30 March 2012). No significant detriment was observed in the Bv arm compared to the Pl arm in any of the subgroups.

Based on the most recent OS analysis, it can be concluded that BV treatment does not have a detrimental effect on OS in the current setting. The median follow-up time is longer than the median OS estimate, and the KM curves stay separated at the time intervals when the degree of censoring is minimal.

Given the magnitude of the estimated improvement in PFS following therapy an OS benefit could have been expected. However, it is difficult to demonstrate transfer of PFS benefit into increased OS when post-progression survival is long also because long SPP (post-progression survival) allows for use of multiple lines of post-progression therapies. In the OCEAN study app. 85-89% of the patients received non-protocol specified anti-cancer therapies, of these app. 40% in the Pl arm and 22% in the Bv arm received Bv after progression. It is acknowledged that any effect on OS associated to the improvement in PFS of 4 months may be difficult to observe due to the relatively long post-progression survival, and also due to post-progression therapy that may have confounded the OS results. Indeed, a more positive OS trend in favour of Bv was actually observed in the front-line setting where fewer placebo-treated patients received bevacizumab as later therapy. It is the most likely explanation, but no definitive answer can be given to this question. Of note, 40% crossover from the Pl arm is not considered a high number, and since phase II studies have indicated effect of single agent Bv in ovarian cancer, a more convincing OS result would have been expected if the impact of Bv on OS was to be substantial. Nevertheless, the OS data are sufficiently mature and allow ruling out a significant detriment in terms of OS, which supports the clinical relevance of the observed difference in terms of PFS. This will be further confirmed with the final OS analysis although major changes are not expected, since the median follow-up time is longer than the median OS estimate, and the KM curves stay separated at the time intervals when the degree of censoring is minimal.

The discrepancy between PFS and OS results has been observed before in relation to bevacizumab therapy. Thus, a concern has been raised that PFS results might have been overestimated, analogous (but much less pronounced) to what was seen in glioblastoma. Although there seemed to be no ideal way to address this uncertainty, it has been suggested that longitudinal CA125 data might be informative despite reports of interference with bevacizumab.

CA-125 changes may not correspond to imaging responses in ovarian cancer patients receiving bevacizumab as reported by Azad et al. (Cancer 2008; 112: 1726-32) and Randall et al. Gynecol Oncol 2012; 124: 563-8). An interaction between bevacizumab and CA-125 has been described based on concordance rates of CA125 defined progressions and modified RECIST defined progressions in study AVF4095g.

The MAH has clarified the following points:

1) If PFS results had been overestimated, many patients would have discontinued therapy based on clinical signs or symptoms of disease progression which was not the case.

2) Depicting the requested longitudinal CA-125 levels for the entire study population would be challenging and difficult to interpret as criteria for defining tumour responses/progressions are based on relative CA-125 values. Therefore, alternative analyses have been provided which is considered acceptable.

3) In general, CA-125 levels correlate well with both responses and progressions as determined by modified RECIST in the pivotal study AVF4095g. Actually, CA-125 responses occurred at a higher rate than modified RECIST-based responses why the latter is considered a more conservative estimate.

4) Concordance rates between CA125-defined responses and modified RECIST defined responses were also high (80.8% in the placebo arm and 81.1% in the bevacizumab arm, respectively).

5) In addition, the time from randomization to CA-125 response and from randomization to modified RECIST-defined response was very similar in both treatment arms.

6) When PFS was estimated based on CA-125 levels, the observed PFS benefit was similar to what was found in the primary analysis.

7) Prior concerns related to the imaging of responses in glioblastoma do not apply to ovarian cancer due to different tumour characteristics and modalities of imaging.

In conclusion, the observed PFS benefit associated with bevacizumab as determined per modified RECIST in recurrent ovarian cancer is considered reliable, reflecting a true tumour response. The possible explanations for the apparent lack of improvement in OS despite a clear PFS benefit have been adequately addressed by the MAH and accepted as a reasonable interpretation of study data.

Material for biomarker analyses were not collected. Although specific biomarkers for Avastin may not have been identified at the time of the design of study AVF4095g, the potential for future analyses to be performed on such material should have been acknowledged. Although samples for exploratory biomarkers were collected in the two phase 3 front-line ovarian cancer studies, markers for recurrent disease may differ from those of interest in the front-line setting.

Finally, it is also worth discussing when to introduce bevacizumab in the treatment of ovarian cancer. Should it be given in the front-line or recurrent setting? Based on the presented results, it seems that either is possible which leaves the treating physicians/patients with some choices. Factors to be considered are the aggressiveness of the disease, the performance status of the patient, the toxicity profile and physician/patient preferences. Actually, the data seem to indicate that patients with the worst prognostic factors might actually gain the largest benefit from this treatment. It will eventually be a decision for the treating physician (in consultation with the patient) to decide if and when to introduce bevacizumab into the treatment of ovarian cancer.

**Conclusions on clinical efficacy**

The single pivotal study AVF4095 has demonstrated that bevacizumab in combination with carboplatin+gemcitabine for 6 cycles (up to 10 cycles) followed by bevacizumab as single-agent until PD resulted in a 52% reduction in the risk of progression or death and an absolute gain in median PFS of about 4 months in women with their first recurrence of platinum-sensitive ovarian cancer who had not previously been exposed to bevacizumab or other anti-angiogenesis inhibitors. This result is considered clinically relevant and unprecedented in the recurrent setting. A number of sensitivity analyses have confirmed the robustness of the result that was also confirmed in all subgroup analyses.

The result was supported by a marked increase in ORR. There was no significant difference in OS between treatment arms. At the latest 3$^{rd}$ OS updated analysis, where 59% of patients had died, there was no indication of a detrimental effect on OS. The extensive use of later lines of therapy may have confounded OS results.

## *2.3 Clinical Safety aspects*

The primary safety analysis (cut off date 17 September 201) was performed on the safety-evaluable population (N = 480), which was defined as all patients who received any partial or full dose of protocol treatment: carboplatin, gemcitabine, bevacizumab, or placebo.

In addition, post-marketing safety information up to 25 February 2011 (the cut off date used for the 8th Periodic Safety Update Report) is provided.

An adverse event (AE) was defined as any unfavourable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product or other protocol-imposed intervention, regardless of attribution. All AEs reported in the study were graded by the investigator for severity according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE), Version 3.0.

Patients were evaluated for all AEs and serious adverse events (SAEs) at each study visit for the duration of their participation in the study and up to 30 days after discontinuation from study treatment. Patients who discontinued during the treatment phase of the study for any reason were evaluated for safety approximately 30 days (+ 10 days) after discontinuation of treatment. Patients continuing in the open-label Bv phase after the study was unblinded were also followed with AE collection up to approximately 30 days (+ 10 days) after their last dose of bevacizumab.

After 30 days following the last protocol treatment, only SAEs that were attributed to prior protocol treatment were reported. Adverse events were followed to resolution, or until the investigator assessed them as stable or the patient was lost to follow-up; thus, information regarding AE resolution was not complete for all AEs.

### Patient exposure

The extent of exposure to bevacizumab/placebo and to chemotherapy in Study AVF4095g is summarized in tables 21 and 22.

**Table 21. Bevacizumab/Placebo Exposure, Safety-Evaluable Patients**

| | CG + Pl (n = 233) | CG + Bv (n = 247) |
|---|---|---|
| Total dose (mg) | | |
| n | 233 | 246 |
| Mean (SD) | 12,748.2 (7812.6) | 15,332.8 (10179.1) |
| Median | 11,190.0 | 13,220.0 |
| 25th and 75th percentiles | 7640.0, 16,353.0 | 7856.0, 20790.0 |
| Range | 750.0–41910.0 | 855.0–60375.0 |
| No. of cycles | | |
| n | 233 | 246 |
| 1–3 | 19 (8.2%) | 17 (6.9%) |
| 4–6 | 40 (17.2%) | 37 (15.0%) |
| 7–10 | 63 (27.0%) | 57 (23.2%) |
| 11–20 | 93 (39.9%) | 90 (36.6%) |
| 21–30 | 15 (6.4%) | 34 (13.8%) |
| 31–40 | 3 (1.3%) | 9 (3.7%) |
| 41–50 | 0 (0.0%) | 2 (0.8%) |
| Number of cycles | | |
| n | 233 | 246 |
| Mean (SD) | 11.2 (6.2) | 13.6 (8.5) |
| Median | 10.0 | 12.0 |
| 25th and 75th percentiles | 6.0, 14.0 | 8.0, 18.0 |
| Range | 1.0–36.0 | 1.0–43.0 |
| Estimated dose intensity (%) | | |
| n | 233 | 246 |
| Mean (SD) | 91.7 (8.4) | 91.4 (8.3) |
| Median | 92.3 | 92.3 |
| 25th and 75th percentiles | 86.7, 100.0 | 87.5, 100.0 |
| Range | 60.0–108.7 | 60.0–100.6 |
| Duration of Bv/Pl (weeks) | | |
| n | 233 | 246 |
| Mean (SD) | 33.9 (20.0) | 42.0 (27.4) |
| Median | 32.1 | 37.3 |
| 25th and 75th percentiles | 20.7, 43.6 | 23.0, 54.1 |
| Range | 0.1–123.1 | 0.1–141.1 |

Estimated dose intensity (%) is the actual dose received divided by the intended dose × 100. Duration of study drug treatment was calculated as the time from start of Bv/Pl to the date of last dose.

**Table 22. Chemotherapy Drug Exposure, Safety-Evaluable Patients**

| | CG + Pl (n = 233) | CG + Bv (n = 247) |
|---|---|---|
| Total carboplatin dose (mg) | | |
| n | 233 | 246 |
| Mean (SD) | 2475.8 (1033.2) | 2395.7 (1017.1) |
| Median | 2358.0 | 2298.6 |
| 25th and 75th percentiles | 1850.0, 3150.0 | 1776.0, 3077.2 |
| Range | 383.0–6552.0 | 260.0–5920.0 |
| No. of carboplatin cycles | | |
| n | 233 | 246 |
| 1–3 | 32 (13.7%) | 34 (13.8%) |
| 4–6 | 107 (45.9%) | 130 (52.8%) |
| 7–10 | 94 (40.3%) | 82 (33.3%) |
| No. of carboplatin cycles | | |
| n | 233 | 246 |
| Mean (SD) | 6.6 (2.4) | 6.3 (2.4) |
| Median | 6.0 | 6.0 |
| 25th and 75th percentiles | 6.0, 9.0 | 5.0, 8.0 |
| Range | 1.0–10.0 | 1.0–10.0 |
| Estimated carboplatin dose intensity (%) | | |
| n | 233 | 246 |
| Mean (SD) | 89.0 (11.3) | 88.5 (11.7) |
| Median | 88.9 | 89.4 |
| 25th and 75th percentiles | 82.5, 100.0 | 80.5, 100.0 |
| Range | 57.7–118.6 | 58.7–111.0 |
| Total gemcitabine dose (mg) | | |
| n | 233 | 247 |
| Mean (SD) | 20,743.1 (8600.9) | 20,317.0 (8802.6) |
| Median | 20,176.0 | 18,580.0 |
| 25th and 75th percentiles | 14,421.5, 26,280.0 | 15,090.0, 24,820.0 |
| Range | 1780.0–44,800.0 | 1600.0–46,850.0 |
| No. of gemcitabine cycles | | |
| n | 233 | 247 |
| 1–3 | 19 (8.2%) | 18 (7.3%) |
| 4–6 | 108 (46.4%) | 127 (51.4%) |
| 7–10 | 106 (45.5%) | 102 (41.3%) |
| No. of gemcitabine cycles | | |
| n | 233 | 247 |
| Mean (SD) | 7.0 (2.2) | 7.0 (2.3) |
| Median | 6.0 | 6.0 |
| 25th and 75th percentiles | 6.0, 9.0 | 6.0, 9.0 |
| Range | 1.0–10.0 | 1.0–10.0 |
| Estimated gemcitabine dose intensity (%) | | |
| n | 233 | 247 |
| Mean (SD) | 71.8 (16.9) | 70.7 (17.1) |
| Median | 74.2 | 74.0 |
| 25th and 75th percentiles | 60.0, 86.0 | 57.1, 85.7 |
| Range | 31.5–95.4 | 29.3–95.4 |

Estimated dose intensity (%) is the actual dose received divided by the intended dose × 100.

For carboplatin, the median number of cycles was 6 in both arms. The percentage of patients who received 7–10 cycles was higher in the placebo arm (40.3%) than in the bevacizumab arm (33.3%). The median dose intensity was comparable between two treatment arms.

For gemcitabine, patients received a median number of 6 cycles in both arms. A slightly higher percentage of patients received 7–10 cycles in the placebo arm (45.5%) compared with that in the bevacizumab arm (41.3%). The median dose intensity was similar across both treatment arms.

The number of study drug cycles was higher in the bevacizumab arm (median, 12 cycles; range, 1–43 cycles) than in the placebo arm (median, 10 cycles; range, 1–36 cycles). The median duration of

treatment for patients in the bevacizumab arm was correspondingly higher at 37.3 weeks, compared with 32.1 weeks for patients in the placebo arm.

## Adverse events

All patients in both treatment arms experienced one or more AE of any grade. For patients who received bevacizumab in Study AVF4095g, the most frequently reported AEs were fatigue (81.4%), nausea (71.7%), neutropenia (68.8%), thrombocytopenia (57.9%), epistaxis (54.3%), and anaemia (52.6%). The majority of these were Grade 1 events, with the exception of thrombocytopenia and neutropenia, of which the majority were Grade ≥ 3. The overall safety results of Study AVF4095g are shown in Table 23.

**Table 23. Overview of Safety in Study AVF4095g (Safety Population)**

| | **No. (%) of Patients** | |
|---|---|---|
| **Parameter** | **CG + Pl** (n = 233) | **CG + Bv** (n = 247) |
| Any adverse event | 233 (100.0) | 247 (100.0) |
| Grade 3–5 adverse event | 192 (82.4) | 221 (89.5) |
| Serious adverse event | 58 (24.9) | 86 (34.8) |
| Serious adverse event (Grade 3–5) | 47 (20.2) | 72 (29.1) |
| Adverse event leading to study drug (Bv/Pl) discontinuation | 11 (4.7) | 49 (19.8) |
| All deaths | 78 (33.5) | 63 (25.5) |
| Grade 5 adverse event | 1 (0.4) | 1 (0.4) |
| Adverse events of special interest | | |
| Adverse events of special Interest (any grade) | 198 (85.0) | 233 (94.3) |
| Grade 3–5 adverse events of special interest | 144 (61.8) | 182 (73.7) |
| Neutropenia (Grade ≥ 4) | 51 (21.9) | 51 (20.6) |
| Hypertension (Grade ≥ 3) | 1 (0.4) | 43 (17.4) |
| Proteinuria (Grade ≥ 3) | 2 (0.9) | 21 (8.5) |
| Bleeding (Non-CNS) (Grade ≥ 3) | 2 (0.9) | 14 (5.7) |
| Venous thromboembolic event (Grade ≥ 3) | 6 (2.6) | 10 (4.0) |
| Arterial thromboembolic event (any grade) | 2 (0.9) | 7 (2.8) |
| Febrile neutropenia (any grade) | 4 (1.7) | 4 (1.6) |
| Fistula/abscess (any grade) [a] | 1 (0.4) | 4 (1.6) |
| LV systolic dysfunction/CHF (Grade ≥ 3) | 2 (0.9) | 3 (1.2) |
| RPLS (any grade) | 0 (0.0) | 3 (1.2) [b] |
| Bleeding (CNS) (any grade) | 1 (0.4) | 2 (0.8) |
| Wound healing complication (Grade ≥ 3) | 0 (0.0) | 2 (0.8) |
| GI perforation (any grade) | 0 (0.0) | 0 (0.0) |

CHF = congestive heart failure; CNS = central nervous system; LV = left ventricular; GI = gastrointestinal; RPLS = reversible posterior leukoencephalopathy syndrome.
[a]Includes all fistula/abscess events: anal fistula; female genital tract fistula; pelvic abscess; perirectal abscess; rectal abscess (narratives provided only for GI-related events [anal fistula, perirectal abscess, and rectal abscess];
[b] Two were MRI–confirmed cases of RPLS .

AEs of all grades for which the incidence was at least 5% greater in the bevacizumab arm compared with the placebo arm are shown in Table 24. The events showing that the greatest difference in incidence between treatment arms was observed for hypertension (Pl 8.6% vs. Bv 40.5%), epistaxis (Pl 14.2% vs. Bv 54.3%), headache (Pl 30% vs. Bv 48.6%), and proteinuria (Pl 3.9% vs. Bv 16.6%).

**Table 24. Treatment-Emergent Adverse Events with ≥ 5% Higher Incidence in the Carboplatin + Gemcitabine plus Bevacizumab Arm versus the Carboplatin + Gemcitabine plus Placebo Arm, Safety-Evaluable Patients**

| | No. (%) of Patients | |
|---|---|---|
| MedDRA System Organ Class MedDRA Preferred Term | CG + Pl (n = 233) | CG + Bv (n = 247) |
| Any adverse events | 233 (100.0) | 247 (100.0) |
| Blood and lymphatic system disorders | | |
| Thrombocytopenia | 119 (51.1) | 143 (57.9) |
| Gastrointestinal disorders | | |
| Diarrhoea | 67 (28.8) | 92 (37.2) |
| Nausea | 153 (65.7) | 177 (71.7) |
| Stomatitis | 15 (6.4) | 37 (15.0) |
| Gingival bleeding | 1 (0.4) | 17 (6.9) |
| General disorders/administration site conditions | | |
| Fatigue | 175 (75.1) | 201 (81.4) |
| Mucosal inflammation | 22 (9.4) | 38 (15.4) |
| Infections and infestations | | |
| Sinusitis | 20 (8.6) | 36 (14.6) |
| Injury, poisoning, and procedural complications | | |
| Contusion | 21 (9.0) | 42 (17.0) |
| Musculoskeletal/connective tissue disorders | | |
| Arthralgia | 44 (18.9) | 68 (27.5) |
| Back pain | 30 (12.9) | 49 (19.8) |
| Nervous system disorders | | |
| Headache | 70 (30.0) | 120 (48.6) |
| Dizziness | 39 (16.7) | 55 (22.3) |
| Psychiatric disorders | | |
| Insomnia | 35 (15.0) | 50 (20.2) |
| Renal and urinary disorders | | |
| Proteinuria | 9 (3.9) | 41 (16.6) |
| Respiratory, thoracic, mediastinal disorders | | |
| Epistaxis | 33 (14.2) | 134 (54.3) |
| Dyspnoea | 56 (24.0) | 72 (29.1) |
| Cough | 42 (18.0) | 62 (25.1) |
| Oropharyngeal pain | 23 (9.9) | 40 (16.2) |
| Dysphonia | 8 (3.4) | 32 (13.0) |
| Rhinorrhoea | 8 (3.4) | 23 (9.3) |
| Sinus congestion | 4 (1.7) | 19 (7.7) |
| Vascular disorders | | |
| Hypertension | 20 (8.6) | 100 (40.5) |

Bv = bevacizumab; CG = carboplatin + gemcitabine; MedDRA Medical Dictionary for Regulatory Activities; Pl = placebo.
All reported events were included regardless of relationship to study drug. Maximum severity is selected for each event for each patient. Only those adverse events occurring within 30 days after last study drug and on or before the 17 September 2010 cut-off date were included in this analysis.

**Adverse events of NCI CTCAR Grades 3-5**

In the bevacizumab arm, 89.5% of patients experienced an AE of Grades 3–5 (NCI -CTCAE) severity in the bevacizumab arm comparing to 82.4% in the placebo arm. The grade 3 and grade 4 AEs in the CG + Pl arm (N=233) were 98 (42.1%) and 93 (39.9%), respectively. In the CG + Bv (n = 247) arm, the incidence of grade 3 and grade 4 AEs were 105 (42.5%) and 115 (46.6%), respectively. The most frequently reported AEs of Grade ≥ 3 were: neutropenia (51.1% Pl, 51.4 % Bv), thrombocytopenia (33.9% Pl, 40.1% Bv), anaemia (18.9% Pl, 15.8% Bv), and hypertension (0.4% Pl, 16.2% Bv).

Grade 3–5 AEs for which the incidence was ≥ 2% higher in the bevacizumab arm than in the placebo arm were thrombocytopenia, nausea, fatigue, headache, proteinuria, dyspnoea, epistaxis, and hypertension. One treatment-emergent death (grade 5 AE) was reported in each of the two treatment arms.

**Adverse events of special interest**

- Arterial thromboembolic events (ATE)

Arterial thromboembolic events of any grade were reported in a higher percentage of bevacizumab-treated patients (2.8%) than patients who received placebo (0.9%); the majority of these were Grade 3 events (Pl 0% vs. Bv 2.0%). In the placebo arm, two patients experienced a Grade 4 cerebrovascular accident and cerebral ischemia, respectively. In addition to the Grade 4 cerebral ischemia, the same patient (29634) also experienced a fatal myocardial infarction. The seven ATEs in the bevacizumab arm varied in nature: One bevacizumab-treated patient had a myocardial infarction (Grade 4), 2 patients experienced a transient ischemic attack (Grade 3), 1 patient had an arterial thrombus (Grade 3), 1 patient had an arterial occlusion (Grade 3), and 2 patients had arterial emboli (Grade 2 and Grade 3). Because of coding conventions, one event reported as "thrombosis/embolism (vascular access-related)" was categorized as an ATE, despite being venous in nature.

- Bleeding

A total of 3 patients experienced CNS bleeding of any grade: 1 patient in the placebo arm (Grade 1 cerebral haemorrhage and Grade 1 subarachnoid haemorrhage and 2 patients in the bevacizumab arm (fatal intracranial haemorrhage and Grade 4 hemorrhagic stroke.

The incidence of non-CNS bleeding events of any grade was higher in the bevacizumab arm (63.2%) compared with the Pl arm (27.0%); the majority of these were Grade 1 and 2 events (Pl 26.2% vs. Bv 57.5%), particularly Grade 1 epistaxis (Pl 13.3% vs. Bv 41.3%).

Grade 3 non-CNS bleeding was reported in a higher percentage of bevacizumab-treated patients (5.7%) compared with patients who received Pl (0.9%). The majority of these Grade 3 events were epistaxis (Pl 0.4% vs. Bv 4.9%). Other Grade 3 non-CNS bleeding events occurred in no more than 1 patient and included GI haemorrhage, haematuria, soft tissue haemorrhage, and upper GI haemorrhage. No Grade 4 or Grade 5 non-CNS bleeding events were reported.

- Gastrointestinal (GI) perforation

No patient in the study reported a treatment-emergent GI perforation within the 30-day safety reporting period. However, two patients, both in the bevacizumab arm, experienced GI perforations after the 30-day post-treatment AE reporting period:

- One patient received her last dose of bevacizumab on 14 April 2010 (Cycle 39). She was hospitalized with a Grade 4 event of intestinal perforation on 21 June 2010, 69 days after her last dose of bevacizumab. The AE resolved on 6 July 2010. The investigator assessed that the event was caused by bevacizumab or the disease under study. The patient had no history of inflammatory bowel disease or diverticulitis. She discontinued study treatment on 14 April 2010 because of PD.

- The second patient received her last dose of bevacizumab on 28 January 2010 (Cycle 34). She experienced a Grade 4 gastric ulcer perforation on 6 April 2010, 69 days after her last bevacizumab treatment; the AE resolved on 15 April 2010. The investigator assessed that the event was caused by bevacizumab or concurrent illness and concomitant medications. The patient had a history of irritable bowel syndrome and diverticulitis. She discontinued study treatment following an episode of small bowel obstruction on 5 March 2010.

- Fistula and Abscess

Fistulas/abscesses were reported in 1 patient in the Pl arm (Grade 1 anal fistula) and 4 patients in the bevacizumab arm (Grade 2 perirectal abscess; Grade 3 female genital tract fistula, Grade 3 pelvic abscess, and Grade 3 rectal abscess). No Grade 4 or Grade 5 fistulas/abscesses were reported.

- Hypertension

The overall incidence of all grade hypertension was 42.1% in the bevacizumab arm and 8.6 % in the placebo arm. The median time to onset of hypertension was 15.5 months in the bevacizumab arm (not reached for the placebo arm). During the AE reporting period, all grade hypertension was reported as resolved in 14 (70.0%) of the 20 patients in the placebo arm and in 57 (54.8%) of the 104 patients in the bevacizumab arm.

Hypertension Grade ≥ 3 was reported in a higher percentage of bevacizumab-treated patients (17.4%) than in patients who received placebo (0.4%). Two bevacizumab-treated patients experienced Grade 4 hypertension.

In patients with Grade ≥ 3 hypertension, the median time to onset of hypertension was not reached for both arms. Among the patients who developed Grade ≥ 3 hypertension, the AE resolved in the one patient in the Pl arm and in 24 (56%) of 43 patients in the bevacizumab arm. A total of 9 of 43 patients with Grade ≥ 3 hypertension discontinued bevacizumab.

- Left ventricular dysfunction/Congestive heart failure (CHF)

Overall, 6 bevacizumab-treated patients (2.4%) and two patients in the placebo arm (0.9%) experienced CHF events. In the bevacizumab arm, three of these were Grade ≤ 2 events, two were Grade 3, and one was a Grade 4 event (cardiomyopathy).

- Neutropenia and febrile neutropenia

Neutropenia events of any grade were also reported in similar proportions for the two treatment arms (Pl 76.0% and Bv 75.7%). In both arms, the majority of neutropenia events were Grade 3 (Pl 33.9% vs. Bv 36.8%) or Grade 4 (Pl 21.9% vs. Bv 20.6%).

Overall, 4 patients in each arm (Pl 1.7% vs. Bv 1.6%) experienced febrile neutropenia of any grade. In the bevacizumab arm, two of these events were Grade 3 and two were Grade 4. In the placebo arm, three events were Grade 3 and one was Grade 4.

- Proteinuria

In Study AVF4095g, proteinuria was closely screened for and followed with urinary protein-to-creatinine ratio (UPCR) measurements at each cycle.

The overall incidence of all grade proteinuria was 4.7% in the placebo arm versus 17.4% in the bevacizumab arm. The median time to onset of proteinuria of 21.2 months in the bevacisumab (not reached in the placebo arm). All grade proteinuria had resolved in 10 of the 11 patients in the placebo arm and in 29 (67%) of the 43 patients in the bevacizumab arm during the AE reporting period.

Proteinuria of Grade ≥ 3 was reported in a higher percentage of bevacizumab-treated patients (8.5%) than in patients who received placebo (0.4%). The majority of these events were Grade 3 (8.1%). One patient in each treatment arm developed nephrotic syndrome.

Among patients with Grade≥ 3 proteinuria, the median time to onset of was 26.5 months in the bevacizumab arm (not reached for the placebo arm). Among patients who had Grade ≥ 3 proteinuria, the resolution rate during the AE reporting period was 100% (2 of 2 patients) in the placebo arm and 86% (18 of 21 patients) in the bevacizumab arm. In addition, 6 of 21 patients with Grade ≥ 3 proteinuria discontinued bevacizumab treatment.

- Reversible posterior leukoencephalopathy syndrome (RPLS)

Three patients in the bevacizumab arm were reported to have developed RPLS. One patient developed RPLS during single-agent Bv treatment at Cycle 16) and 2 patients developed RPLS during concurrent

chemotherapy/Bv treatment in Cycles 4 and 5, respectively. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI).

- One patient experienced a Grade 3 event of RPLS on 25 April 2008. The event occurred during Cycle 16 and led to discontinuation of Bv treatment. A confirmatory MRI was not performed. The event, which resolved on 5 May 2009, was considered by the investigator to be related to Bv treatment. This patient had a history of hypertension. During the RPLS event, the patient had Grade 3 malignant and Grade 2 mental status changes.

- The second patient experienced a Grade 3 event of RPLS on 2 June 2008. The event occurred during Cycle 4, was confirmed by MRI, and led to discontinuation of Bv treatment. The event resolved on 8 June 2008 and was considered by the investigator to be related to Bv treatment. Although this patient had no history of hypertension, she had Grade 3 hypertension at the time of the RPLS event.

- The third patient experienced a Grade 4 event of RPLS on 25 March 2009. The event occurred during Cycle 5, was confirmed by MRI, and led to discontinuation of Bv treatment. The event was ongoing at the time of Bv discontinuation and was considered by the investigator to be related to Bv treatment. This patient had a history of hypertension. Prior to the RPLS event, she had two episodes of Grade 2 headache and worsening hypertension.

- Venous thromboembolic events (VTE)

Venous thromboembolic events of Grade ≥ 3 were reported in a higher percentage of Bv-treated patients (4.0%) than patients who received Pl (2.6%), and the majority of these were Grade 3 VTE events. Grade 3 VTEs consisted of deep venous thrombosis (Pl 0.4% vs. Bv 1.6%), jugular vein thrombosis (Pl 0% vs. Bv 0.4%), pulmonary embolism (Pl 0% vs. Bv 0.4%), thrombophlebitis (Pl 0.4% vs. Bv 0%), thrombophlebitis superficial (Pl 0% vs. Bv 0.4%), and thrombosis (Pl 0.4% vs. Bv 0.8%)

Five patients experienced Grade 4 VTEs. Three of these 5 patients were in the placebo arm and developed pulmonary embolism. One bevacizumab-treated patient developed a pulmonary embolism and vena cava thrombosis, and one bevacizumab-treated patient developed a pulmonary embolism. There were no Grade 5 VTE events.

- Wound healing complications

In the bevacizumab arm, one patient developed a Grade 3 wound healing complication, and one patient developed Grade 3 wound dehiscence; both cases resolved. No patients in the placebo arm experienced any wound healing complication events of Grade ≥ 3.

## Serious adverse events/deaths/other significant events

The overall incidence of SAEs (all grades) was higher in the bevacizumab arm (34.8%) than in the placebo arm (24.9%). However, there was no single serious adverse event with a 2% or more increased incidence in the bevacizumab arm compared to the placebo arm.

The most frequently reported SAEs (all grades) were GI disorders (Pl 6.9% vs. Bv 7.3%); blood and lymphatic system disorders (Pl 6.4% vs. Bv 5.7%); nervous system disorders (3.0% vs. 4.9%); respiratory, thoracic, and mediastinal disorders (Pl 3.4% vs. Bv 4.0%); infections and infestations (Pl 3.0% vs. Bv 4.0%) and vascular disorders (Pl 0.9% vs. Bv 5.3%).

By preferred term, the SAEs with a higher incidence in the bevacizumab arm compared with the placebo arm were anaemia (Pl 0.4% vs. Bv 2.4%), HTN (Pl 0.0% vs. Bv 1.6%), epistaxis (Pl 0.4% vs. Bv 2.0%), and RPLS (Pl 0.0% vs. Bv 1.2%).

Of the 144 patients with SAEs, 119 had Grade 3–5 events, and a greater proportion of these were patients in the bevacizumab arm (Pl 20.2% vs. Bv 29.1%).

As of the date of the data cut-off date for Study AVF4095g, 141 (29.4%) of the 480 patients who received any component of protocol treatment had died (Table 25). The majority of these deaths were due to PD.

**Table 25. Summary of Causes of Death**

| | **CG + Pl (n = 233)** | **CG + Bv (n = 247)** |
|---|---|---|
| No. of Deaths | 78 (33.5%) | 63 (25.5%) |
| Due to disease progression | 77 (33.0%) | 60 (24.3%) |
| Due to adverse event | 1 (0.4%) | 2 (0.8%) [a] |
| Cause unknown | 0 (0.0%) | 1 (0.4%) |

[a] One adverse event was not treatment emergent.

Two patients, 1 in each arm, had a treatment-emergent fatal (Grade 5) adverse event: the bevacizumab-treated patient died of an intracranial haemorrhage, and the placebo-treated patient died of a myocardial infarction. In addition, one patient in the bevacizumab arm died following an adverse event of sepsis that occurred 70 days after the last administration of bevacizumab and was not considered treatment emergent. One patient in the bevacizumab arm died of unknown causes 485 days after treatment.

## Laboratory findings

Safety laboratory evaluations, including physical examinations, BP, and laboratory measurements performed by central and local laboratories (including haematology, serum chemistry, and urinalysis) were performed for safety monitoring purposes. Other than at screening and at the time of treatment termination and with the exception of UPCR and CA125 levels at prespecified intervals, laboratory results were not collected on the patient's case report form. Abnormal laboratory values were reported as AEs only when determined to be clinically significant by the investigator or resulted in study withdrawal. Laboratory abnormality data were not reconciled with reported adverse events on a routine basis.

## Safety in special populations

Age

A summary of all AEs by age (< 65 vs. ≥ 65 years) has been provided. All patients in both treatment arms experienced at least one AE. The overall incidence of Grade ≥ 3 AEs was higher in the bevacizumab arm than in the placebo arm for each subpopulation (< 65 years: Pl 84% vs. Bv 90%; ≥ 65 years: Pl 79.8% vs. Bv 88.5%).

Within both age subgroups, there was a higher incidence of Grade ≥ 3 hypertension in bevacizumab-treated patients than in patients receiving Pl (< 65 years: 0.7% vs. 12.5%; ≥ 65 years: 0% vs. 22.9%). However, the increased incidence of hypertension in the bevacizumab arm was twofold higher in the subgroup of those ≥ 65 years of age. Other Grade 3–5 AEs that were higher in the bevacizumab arm compared with the placebo arm did not show a substantial differential increase in the subgroup of those ≥ 65 years of age vs. the subgroup < 65 years of age.

Race

A summary of all AEs by race (White vs. non-White) has been provided. The percentages of White and non-White patients who reported at least one Grade ≥ 3 AE were: Pl 81.4% vs. Bv 89.6%; and Pl 92.3% vs. Bv 85.0% respectively.

## Safety related to drug-drug interactions and other interactions

N/A

## Discontinuation due to adverse events

A higher percentage of patients in the bevacizumab arm (19.8%) than in the placebo arm (4.7%) experienced an AE of any grade that led to discontinuation of study drug. The incidence of AEs leading to bevacizumab discontinuation in this study was similar to what is observed in other bevacizumab clinical trials across indications (19%). The most common non-hematologic AEs that led to drug discontinuation in bevacizumab -treated patients were hypertension (9 patients; 3.6%), proteinuria (6 patients; 2.4%), RPLS (3 patients; 1.2%), and epistaxis (3 patients; 1.2%). Bevacizumab was discontinued because of neutropenia in 4 patients (1.6%) and thrombocytopenia in 4 patients (1.6%).

The majority of study drug discontinuations in both arms occurred during the chemotherapy treatment phase (concurrent with Pl or Bv) of the study (Table 25). Eight of eleven patients in the placebo arm and 36 of 49 patients in the bevacizumab arm discontinued study drug between Cycles 1 and 10. In addition, 3 patients in the placebo arm and 13 patients in the bevacizumab arm discontinued during the single agent bevacizumab or placebo treatment–extension phase after completion of their chemotherapy. Through all phases of treatment, the most common AEs associated with discontinuation of bevacizumab were Grade 3 hypertension, persistent Grade 3 proteinuria, thrombocytopenia (Grades 1, 3, and 4) and neutropenia (Grades 2–4). The most common AEs associated with discontinuation of bevacizumab during the single-agent extension phase were Grade 3 hypertension and Grade 3 proteinuria.

The median number of placebo and bevacizumab cycles was 10 and 12, respectively.

### *Post marketing experience*

Bevacizumab in combination with intravenous 5-fluorouracil–based chemotherapy for the first-line treatment of patients with metastatic carcinoma of the colon or rectum was approved in the United States on 26 February 2004 and in the European Union on 12 January 2005. Subsequently, bevacizumab was approved in the European Union, for the first-line treatment of metastatic breast cancer in combination with paclitaxel or capecitabine; unresectable, advanced, metastatic, or recurrent non-squamous non–small cell lung cancer in combination with platinum-based chemotherapy; advanced and/or metastatic renal cell cancer in combination with interferon alfa-2a; and in metastatic cancer of the colon or rectum in combination with fluoropyrimidine-based chemotherapy.

The post–marketing experience with bevacizumab is summarised below on the basis of safety data contained in eight previously scheduled PSURs. The total number of patients exposed to Bv in the post-marketing setting or in clinical trials over the 7-year period covered by the PSURs is estimated to be approximately 1,080,098.

During the 7-year period from 26 February 2004 to 25 February 2011, a total of 42,455 AEs, of which 35,007 were serious, were reported in 23,148 patients (2.1%). In 2678 cases (0.2%), the outcome was fatal.

The most frequently reported SAEs in patients treated with bevacizumab during the reporting period 26 February 2009–25 February 2011 were GI disorders (18.9%); respiratory, thoracic, and mediastinal disorders (11.2%); general disorders and administration site conditions (10.0%); and vascular disorders (8.1%) (Table 26).

**Table 26. Summary of Adverse Events by System Organ Class in Patients Receiving Bevacizumab: Post-Marketing Data**

| System Organ Class | No. of Patients with ≥ 1 AE/SOC | No. (%) of Adverse Events | | | |
|---|---|---|---|---|---|
| | | Serious | | Total | |
| Infections and Infestations | 642 | 646 | 8.3 | 733 | 7.2 |
| Neoplasms benign, malignant, and unspecified (including cysts and polyps) | 307 | 295 | 3.8 | 316 | 3.1 |
| Blood and lymphatic system disorders | 461 | 485 | 6.2 | 549 | 5.4 |
| Immune system disorders | 58 | 46 | 0.6 | 59 | 0.6 |
| Endocrine disorders | 8 | 7 | 0.1 | 9 | 0.1 |
| Metabolism and nutrition disorders | 261 | 244 | 3.1 | 320 | 3.1 |
| Psychiatric disorders | 86 | 69 | 0.9 | 97 | 1.0 |
| Nervous system disorders | 661 | 593 | 7.6 | 813 | 8.0 |
| Eye disorders | 217 | 211 | 2.7 | 286 | 2.8 |
| Ear and labyrinth disorders | 18 | 11 | 0.1 | 20 | 0.2 |
| Cardiac disorders | 277 | 297 | 3.8 | 317 | 3.1 |
| Vascular disorders | 703 | 631 | 8.1 | 754 | 7.4 |
| Respiratory, thoracic, and mediastinal disorders | 722 | 708 | 9.1 | 888 | 8.7 |
| Gastrointestinal disorders | 1258 | 1475 | 18.9 | 1861 | 18.3 |
| Hepatobiliary disorders | 105 | 113 | 1.5 | 128 | 1.3 |
| Skin and subcutaneous tissue disorders | 284 | 121 | 1.6 | 345 | 3.4 |
| Musculoskeletal and connective tissue disorders | 173 | 140 | 1.8 | 207 | 2.0 |
| Renal and urinary disorders | 238 | 201 | 2.6 | 267 | 2.6 |
| Pregnancy, puerperium, and perinatal conditions | 0 | 0 | 0 | 0 | 0 |
| Reproductive system and breast disorders | 46 | 35 | 0.4 | 48 | 0.5 |
| Congenital, familial, and genetic disorders | 5 | 4 | 0.1 | 5 | 0.0 |
| General disorders and administration site conditions | 1038 | 875 | 11.2 | 1217 | 11.9 |
| Investigations | 462 | 400 | 5.1 | 670 | 6.6 |
| Injury, poisoning, and procedural complications | 215 | 151 | 1.9 | 230 | 2.3 |
| Surgical and medical procedures | 45 | 24 | 0.3 | 47 | 0.5 |
| Social circumstances | 3 | 3 | 0.0 | 3 | 0.0 |
| Total | | 7785 | 100.0 | 10189 | 100.0 |

AE = adverse event; SOC = system organ class.

Data covering the period from 26 February 2009 to 25 February 2011.

## 2.3.1 Discussion on clinical safety

All patients in both treatment arms experienced one or more AE of any grade. For patients who received bevacizumab in this study, the most frequently reported AEs were fatigue (81.4%), nausea (71.7%), neutropenia (68.8%), thrombocytopenia (57.9%), epistaxis (54.3%), and anaemia (52.6%). The majority of these were Grade 1 events, with the exception of thrombocytopenia and neutropenia, the majority of which were Grade ≥ 3. Many of the most common AEs were observed with ≥ 5% higher incidence between the treatment arms.

The incidence of Grade ≥ 3 AEs was greater in the bevacizumab arm (89.5%) compared to the placebo arm (82.4%). Grade 3–5 AEs for which the incidence was ≥ 2% higher in the bevacizumab arm than in the placebo arm were thrombocytopenia, nausea, fatigue, headache, proteinuria, dyspnoea, epistaxis,

and hypertension. The difference in the incidence of Grade 3–5 AEs between the treatment arms was primarily due to a higher incidence of certain events in bevacizumab-treated patients, which included Grade 3 hypertension, Grade 3 proteinuria, and Grade 4 thrombocytopenia. In the younger (<65 years) and older age group (≥ 65 years), the overall incidence of Grade ≥ 3 AEs in bevacizumab - treated patients was generally similar.

Generally, hypertension was observed with a higher frequency (42.1%) for Bv-treated patients than earlier reported across indications (up to 34%). With regard to age, the incidence of hypertension of grade ≥ 3 among Bv-treated patients was twofold higher in the subgroup of patients ≥ 65 years of age than in the younger age group. The SmPC has been updated accordingly. The frequencies of grade ≥3 proteinuria (8.1%) and grade 3 bleeding (6.5%) were also somewhat higher than previously reported for bevacizumab (frequencies up to 7% and 5%, respectively). This has been adequately reflected in the amended SmPC.

On the basis of previous clinical trials with bevacizumab, some AEs are identified as being of special interest (AESI). A higher proportion of patients in the bevacizumab arm reported at least one AESI of any Grade (Pl 85.0% vs. Bv 94.3%), including at least one Grade 3-5 AESI (Pl 61.8% vs. bevacizumab 73.7%). Overall, AESI of Grade 3–5 for which there was a ≥ 2% higher incidence in the bevacizumab arm compared with the placebo arm were hypertension, proteinuria, and non-CNS bleeding.

One of the phase II ovarian cancer studies, denoted AVF2949g, was prematurely terminated due to a high incidence of GI perforations; five patients out of 44 (11.4%) developed GI perforations, of which one patient died. There were no GI perforations in the other ovarian cancer phase II study (GOG170D). The patients included in study AVF2949g had advanced ovarian cancer resistant to several prior treatments and this alarmingly high incidence of GI perforations cannot be directly transferred to a population of patients with first recurrence.

With regard to SAEs and GI disorders, however, 10 patients were reported by Preferred Term to have small intestinal obstruction; 4 of these were observed in the Bv arm.

In the pivotal trials (GOG-0218 and BO17707) in support of the frontline ovarian cancer indication, the incidence rates of gastrointestinal (GI) perforations were higher in all bevacizumab-containing treatment arms compared to the control arms across both studies. Only patients in the bevacizumab-containing treatment arms had events of GI perforations leading to death.

In the pivotal study AVF4095g no patient reported a treatment-emergent GI perforation within the 30-day safety reporting period. However, two patients, both in the bevacizumab arm, experienced GI perforations after the 30-day post treatment AE reporting period. Considering the wide indication there is a risk that the incidence of GI-perforations will be higher in clinical practice than what has been observed in the pivotal study. A cumulative analysis of GIP by Grade will be presented in the next PSUR (see RMP).

More SAEs were recorded in the Bv arm (34.8%) vs. 24.9% in the placebo arm. The majority of these events were not life-threatening (grade 3). The largest difference was observed for the MedDRA SOC of Vascular Disorders (overall incidence of 5.3% in the Bv arm vs. 0.9% in the placebo arm), however, there was no single SAE with more than a 2% increased incidence in the Bv arm compared to the placebo arm. The SAEs with > 1% higher incidence in the Bv arm compared to the placebo arm were anaemia, hypertension, epistaxis and RPLS.

During the study, 141 patients (29.4%) died, mainly due to disease progression. Fewer patients in the bevacizumab arm died (25.5%) as compared with the Pl arm (33.5%), due to the lower number of deaths classified as PD. One patient in each arm experienced a treatment emergent Grade 5 AE.

A higher percentage of patients in the bevacizumab arm (19.8%) than in the placebo arm (4.7%) experienced an AE of any grade that led to discontinuation of study drug. The observed frequency is in line with what is seen in other clinical trials with bevacizumab, across indications. The majority of study drug discontinuations in both arms occurred during the chemotherapy treatment phase (concurrent with Pl or Bv) of the study. Through all phases of treatment, the most common AEs associated with discontinuation of bevacizumab were Grade 3 hypertension, persistent Grade 3 proteinuria, thrombocytopenia (Grades 1, 3, and 4) and neutropenia (Grades 2–4).

**Conclusions on clinical safety**

In conclusion, the addition of bevacizumab to carboplatin/gemcitabine for up to 10 cycles and continued as single agent resulted overall in a well-known pattern of safety findings in patients with recurrent ovarian cancer, although the incidences of some events like hypertension, proteinuria and low-grade haemorrhages were slightly higher in this patient population. The SmPC has been updated accordingly. The safety profile was overall in line with the extensive experience with bevacizumab across multiple oncology indications. No unexpected safety signals were seen in this study.

## *2.4 Risk management plan*

The MAH submitted an updated Risk Management Plan within this variation procedure

**Table 27. Summary of the risk management plan**

| Safety Concern | Proposed PhV activities (planned and ongoing) | Proposed risk minimisation activities (planned and ongoing) |
|---|---|---|
| **Important identified risks** | | |
| **Bleeding/ Haemorrhage** | - prospective data collection in study BO17920 on the use of aspirin and other anti-platelet prophylactic antiaggregation therapy (completed).<br><br>- evaluation of the effect of anticoagulation in study E1505 | Routine.<br>EU SmPC section 4.4:<br>Haemorrhage<br>Patients treated with Avastin have an increased risk of haemorrhage, especially tumour-associated haemorrhage. Avastin should be discontinued permanently in patients who experience Grade 3 or 4 bleeding during Avastin therapy. Patients with untreated CNS metastases were routinely excluded from clinical trials with Avastin, 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 studies. Patients should be monitored for signs and symptoms of CNS bleeding, and Avastin treatment discontinued in case of intracranial bleeding. There is no information on the safety profile of Avastin in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting Avastin treatment, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating 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 |

| Safety Concern | Proposed PhV activities (planned and ongoing) | Proposed risk minimisation activities (planned and ongoing) |
|---|---|---|
| | | bleeding when treated with a full dose of warfarin and Avastin concomitantly.<br>Labelled in section 4.8 of the EU SmPC. |
| **Pulmonary haemorrhage** | - routine PhV | Routine.<br>EU SmPC section 4.4:<br>Pulmonary Haemorrhage/Haemoptysis<br>Patients with non-small cell lung cancer treated with Avastin 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 Avastin.<br>Labelled in section 4.8 of the EU SmPC |
| **Venous thromboembolic events** | - routine PhV | Routine.<br>EU SmPC section 4.4: Patients may be at risk of developing venous thromboembolic events, including pulmonary embolism under Avastin treatment. Avastin should be discontinued in patients with life-threatening (Grade 4) pulmonary embolism, patients with ≤Grade 3 need to be closely monitored.<br>Labelled in section 4.8 of the EU SmPC. |
| **Arterial thromboembolic events** | prospective data collection on the use of aspirin and other anti-platelets as well as history of arterial disease and risk factors for ATE<br><br>- guided questionnaire<br><br>- NSABP C08 | EU SmPC section 4.4:<br>In five randomised clinical trials, the incidence of arterial thromboembolic events including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs) was higher in patients receiving Avastin in combination with chemotherapy compared to those who received chemotherapy alone. Patients, receiving Avastin plus chemotherapy, with a history of arterial thromboembolism or age greater than 65 years have an increased risk of developing arterial thromboembolic events during therapy. Caution should be taken when treating these patients with Avastin. Therapy should be permanently discontinued in patients who develop arterial thromboembolic events.<br>Labelled in section 4.8 of the EU SmPC. |
| **Hypertension** | - prospective data collection for evaluation of incidence and reversibility<br><br>- NSABP C08 | Routine.<br>EU SmPC section 4.4:<br>An increased incidence of hypertension was observed in Avastin-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 Avastin treatment. There is no information on the effect of Avastin 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 |

| Safety Concern | Proposed PhV activities (planned and ongoing) | Proposed risk minimisation activities (planned and ongoing) |
|---|---|---|
| | | antihypertensive treatment appropriate for the individual situation of the affected patient. The use of diuretics to manage hypertension is not advised in patients who receive a cisplatin-based chemotherapy regimen. Avastin 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.<br>Labelled in section 4.8 of the EU SmPC. |
| **Proteinuria** | - prospective data collection for evaluation of incidence and reversibility<br><br>NSABP C08 | Routine.<br>EU SmPC section 4.4:<br>Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with Avastin. There is evidence suggesting that Grade 1 [US National Cancer Institute- Common Toxicity Criteria (NCI-CTC) version 2.0] proteinuria may be related to the dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Therapy should be permanently discontinued in patients who develop Grade 4 proteinuria (nephritic syndrome).<br>Labelled in section 4.8 of the EU SmPC. |
| **Congestive heart failure** | - in defined studies<br><br>- safety monitoring plan<br><br>- sequential regular LVEF monitoring<br><br>- consider inclusion of cardiology expert in DSMBs<br><br>- cardiac advisory board<br><br>- guided questionnaire | Routine.<br>EU SmPC section 4.4:<br>Events consistent with CHF were reported in clinical trials. The symptoms ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF, requiring treatment or hospitalisation. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF, such as pre-existing coronary heart disease or concomitant cardiotoxic therapy. Caution should be exercised when treating patients with clinically significant cardiovascular disease or pre-existing congestive heart failure with Avastin.<br>Labelled in section 4.8 of the EU SmPC. |
| **Wound healing complications** | - prospective data collection to evaluate incidence and risk factors<br><br>- evaluation of the safety of surgery in study MO18725<br><br>- monitoring by DSMB will be implemented in planned Roche-sponsored glioblastoma studies to assess safety on an ongoing basis.<br><br>- NSABP C08 | Routine.<br>EU SmPC section 4.4:<br>Avastin may adversely affect the wound healing process. 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.<br>Labelled in section 4.8 of the EU SmPC. |

| Safety Concern | Proposed PhV activities (planned and ongoing) | Proposed risk minimisation activities (planned and ongoing) |
|---|---|---|
| | | In addition, definition in glioblastoma study protocols of in- and exclusion criteria (e.g. time between surgical procedures or traumatic injury and initiation of bevacizumab therapy), and not permitted concomitant treatment (e.g. craniotomy, intratumoral interstitial therapy, radio surgery). |
| **Gastrointestinal perforations** | - routine PhV<br><br>- a cumulative analysis of GIP by Grade will be presented in the next PSUR | Routine.<br>EU SmPC section 4.4: Patients may be at an increased risk for the development of gastrointestinal perforation when treated with Avastin. 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. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.<br>Labelled in section 4.8 of the EU SmPC. |
| **Posterior Reversible Encephalopathy Syndrome(PRES)** | - routine PhV | Routine.<br>EU SmPC section 4.4:<br>There have been rare reports of Avastin-treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephalopathy Syndrome (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. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of Avastin. The safety of reinitiating Avastin therapy in patients previously experiencing PRES is not known.<br>Labelled in section 4.8 of the EU SmPC.<br>Updated wording has been included for the SmPC to provide information on PRES from study AVF4095g . |
| **Neutropenia** | - routine PhV | Routine.<br>EU SmPC section 4.4: Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus Avastin in comparison to chemotherapy alone. This has mainly been seen in combination with platinum- or taxane-based therapies in the treatment of NSCLC and mBC.<br>Labelled in sections 4.5 and 4.8 of the EU |

| Safety Concern | Proposed PhV activities (planned and ongoing) | Proposed risk minimisation activities (planned and ongoing) |
|---|---|---|
| | | SmPC. |
| **Fistula (other than gastrointestinal)** | - data collection in BO17920 (completed) | Routine.<br>EU SmPC section 4.4:<br>Patients may be at increased risk for the development of fistulae when treated with Avastin.<br>Permanently discontinue Avastin in patients with TE (tracheoesophageal) fistula or any grade 4 fistula.<br>Limited information is available on the continued use of Avastin in patients with other fistulae.<br>In cases of internal fistula not arising in the GI tract, discontinuation of Avastin should be considered.<br>Labelled in section 4.8 of the EU SmPC. |
| **Thrombotic microangiopathy** | - routine PhV | Routine.<br>Labelled in section 4.8 of the EU SmPC. |
| **Pulmonary hypertension** | - routine PhV | Routine.<br>Labelled in section 4.8 of the EU SmPC. |
| **Ovarian failure** | -routine PhV | Routine.<br>Wording has been added for SmPC sections 4.4, 4.6 and 4.8. |
| **Hypersensitivity reactions and Infusion Reactions** | -routine PhV | EU SmPC section 4.4<br>Patients may be at risk of developing infusion/hypersensitivity reaction. 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.<br>Labelled in section 4.8 of the EU SmPC |
| **Gall Bladder perforations** | - routine PhV | Routine.<br>EU SmPC section 4.4:<br>Labelled in section 4.8 of the EU SmPC. |
| **Peripheral sensory neuropathy** | - routine PhV | Routine.<br>Labelled in section 4.8 of the EU SmPC. |
| **Cardiac disorders (excl. CHF and ATE)** | - cardiac monitoring in BO17920 (completed).<br><br>- QTc study should results from cardiac monitoring in BO17920 indicate it is necessary. | Routine.<br>Supraventricular tachycardia is labelled in section 4.8 of the EU SmPC. |
| **Osteonecrosis of the Jaw** | -routine PhV and monitoring of cases using check list (see Annex 7b) | EU SmPC section 4.4<br>Cases of ONJ have been reported in cancer patients treated with Avastin, the majority of whom had received prior or concomitant treatment with IV bisphosphonates, for which ONJ is an identified risk. Caution should be exercised when Avastin and IV bisphosphonates are administered |

| Safety Concern | Proposed PhV activities (planned and ongoing) | Proposed risk minimisation activities (planned and ongoing) |
|---|---|---|
| | | simultaneously or sequentially.<br>Invasive dental procedures are also an identified risk factor. A dental examination and appropriate preventive dentistry should be considered prior to starting the treatment with Avastin. In patients who have previously received or are receiving IV bisphosphonates invasive dental procedures should be avoided, if possible.<br>Labelled in section 4.8 of the EU SmPC |
| **Important potential risks** | | |
| **Embryo-foetal development disturbance** | - routine PV | Routine.<br>Labelled in section 5.3 of the EU SmPC. |
| **Physical dysplasia** | - routine PhV<br><br>Study BO20924 | Routine.<br>Labelled in section 5.3 of the EU SmPC. |
| **Important missing information** | | |
| **Safety profile of the different treatment combinations in patients with non-squamous NSCLC** | - internal checklist | Routine.<br>EU SmPC text not applicable. |
| **Long-term use in paediatric patients** | Patients participating in study BO20924 will be followed within the context of this trial for a minimum follow-up for overall survival and long-term safety of 5.5 years to observe long-term survivors for the long-term consequences of cancer treatment incorporating bevacizumab as part of the cancer treatment. | Routine.<br>EU SmPC section 4.8:<br>*Paediatric population*<br>The safety of Avastin in children and adolescents has not been established. |
| **Patients with renal impairment** | - routine PhV | Routine.<br>EU SmPC section 4.2: safety and efficacy have not been studied in patients with renal impairment. |
| **Patients with hepatic impairment** | - routine PhV | Routine<br>EU SmPC section 4.2: safety and efficacy have not been studied in patients with hepatic impairment. |

The CHMP, having considered the data submitted, was of the opinion that routine pharmacovigilance was adequate to monitor the safety of the product.

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

In addition, the CHMP considered that the applicant should take minor points into consideration when an update of the Risk management Plan is submitted, as specified in a respective post-authorisation measure.

### *2.5 Changes to the Product Information*

The MAH proposed the following changes to the Product Information (PI), to which the CHMP agreed:

Update of sections 4.1, 4.2, 4.8 and 5.1 of the SmPC in order extend the indication of Avastin for the treatment of patients.

Changes were also made to the PI to bring it in line with the current Agency/QRD template which were reviewed by QRD and accepted by the CHMP.

# 3. Benefit-risk balance

Patients with ovarian cancer that recur after front-line treatment have a poor prognosis and further lines of therapy are considered palliative, although some patients may actually respond to several lines of therapy and have a relatively long survival. Patients who experience disease recurrence > 6 months after last platinum-based therapy are considered *platinum sensitive*. In general, these patients are offered re-treatment with a platinum-based therapy either combined with liposomal doxorubicin, paclitaxel or gemcitabine.

With the results of the single, pivotal, phase III, multicentre, randomised, blinded, placebo-controlled trial AVF4095g (OCEANS), the MAH is applying for an extension of the indication of bevacizumab to include bevacizumab in combination with carboplatin and gemcitabine in the treatment of women with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube carcinoma.

### *Benefits*

## Beneficial effects

The final primary analysis of PFS (INV assessed and censored for NPT) was submitted as part of the type II variation. This analysis showed a statistically significant improvement in median PFS of 4 months for patients in the Bv arm compared to patients in the Pl arm (median PFS for Pl arm 8.4 months vs. Bv arm 12.4 months) with a HR of 0.484 (95% CI, 0.388, 0.605; log-rank p < 0.0001). This translates into a 52% reduction in the risk of progression or death in patients treated with the Bv-containing regimen. The K-M curves demonstrated an early separation after 2 months.

The analysis of PFS based on IRC assessment supported the primary analysis with a HR of 0.451 (95% CI, 0.351, 0.580; log-rank p < 0.0001) and a gain in median PFS of 3.7 months in the Bv arm compared to the Pl arm (Pl 8.6 months vs. Bv 12.3 months). Additional exploratory and sensitivity analyses of investigator and IRC assessed PFS further supported the result of the primary analysis. Importantly, a sensitivity analysis not censoring for NPT showed a very similar result (HR = 0.524 (95% CI: 0.425, 0.645)). The applicant has also performed a "worst-case analysis" as requested in which all patients with NPT use were counted as events. In this very conservative analysis, the HR of PFS = 0.529 (95% CI: 0.430, 0-652).

Consistent PFS results were found in the pre-specified subgroup analysis according to prognostic factors/ stratification factors. A benefit in favour of the bevacizumab-containing arm was observed in all subgroups investigated.

ORR results were also in support of the Bv-containing treatment arm. A statistically significantly higher ORR of 78.5% (INV-determined) was observed in patients treated with bevacizumab compared with 57.4% in the Pl arm (absolute difference of 21.1% (p <0.0001)) which is remarkable in this setting. The majority of responses were PRs. Similarly, median duration of objective response by investigator

assessment was improved by 3 months in the Bv arm (Pl 7.4 months vs. Bv 10.4 months; HR, 0.53; 95% CI, 0.41, 0.70).

At the time of the 3rd OS interim analysis (data cut-off date: 30 March 2012) 59% of patients had died overall (142 (58.7%) in the Pl arm and 144 (59.5%) in the Bv arm). The median OS was 33.7 months in the placebo arm compared to 33.4 months in the bevacizumab arm. The HR for OS = 0.964 (95% CI: 0.764; 1.216) (unstratified analysis).

## Uncertainty in the knowledge about the beneficial effects

Exploratory OS analyses based on number of post-progression therapies and subgroup OS analyses based on demographic and baseline characteristics did not identify a clear OS benefit. Nevertheless, it was possible to rule out a significant detriment in OS for the Bv arm compared to the Pl arm in all of the subgroups analysed. It is acknowledged that it may be more difficult to demonstrate an OS benefit when the post-progression survival is relatively long as in this case (median OS of the Bv arm was 33 months) and that the extensive use of post-progression therapies including bevacizumab may have confounded the OS results. It is the most likely explanation supported by a number of exploratory post-hoc analyses, but no definitive explanation can be given.

Possible explanations for the apparent lack of improvement in OS despite a clear PFS benefit have been adequately addressed by the MAH and accepted as a reasonable interpretation of the study data.

Nevertheless, further follow-up is needed to provide further re-assurance on the benefit-risk of the product and the MAH is requested to provide this analysis by Q4 2013 for study AVF4095g (see Annex II of the PI).

### *Risks*

## Unfavourable effects

All patients experienced one or more AE of any grade, but the incidences of Grade 3-5 AEs and SAEs were higher in the Bv arm.

For patients who received bevacizumab in this study, the most frequently reported AEs were fatigue (81.4%), nausea (71.7%), neutropenia (68.8%), thrombocytopenia (57.9%), epistaxis (54.3%), and anaemia (52.6%). The majority of these were Grade 1 events, with the exception of thrombocytopenia and neutropenia, the majority of which were Grade ≥ 3. Many of the most common AEs were observed with ≥ 5% higher incidence between treatment arms. The adverse events showing the greatest difference and highest incidence in the Bv arm were hypertension, epistaxis, headache, and proteinuria. The most frequently reported AEs of Grade ≥ 3 were neutropenia, thrombocytopenia, anaemia, and hypertension. Grade 3–5 AEs for which the incidence was ≥ 2% higher in the Bv arm than in the Pl arm were thrombocytopenia, nausea, fatigue, headache, proteinuria, dyspnoea, epistaxis, and hypertension.

In the pivotal study AVF4095g no patient reported a treatment-emergent GI perforation within the 30-day safety reporting period. However, two patients, both in the bevacizumab arm, experienced GI perforations after the 30-day post treatment AE reporting period. Considering the wide indication there is a risk that the incidence of GI-perforations will be higher in clinical practice than what has been observed in the pivotal study. A cumulative analysis of GIP by Grade will be presented in the next PSUR (see RMP).

The overall incidence of serious adverse events (SAEs), all grades, was higher in the Bv arm (34.8%) than in the Pl arm (24.9%), primarily because of a higher incidence of serious vascular disorders in the Bv arm (5.3%) compared to the Pl arm (0.9%). The most common SAE reported in the study overall was thrombocytopenia experienced by eight patients each in the two treatment arms. By Preferred Terms (PT), the SAEs with a higher incidence in the Bv arm compared with the Pl arm were anaemia, hypertension, epistaxis, and RPLS. The proportion of patients who died of adverse events was similar across treatment arms (Pl: 0.4%, Bv: 1.2%).

On the basis of previous clinical trials, some AEs have been identified as being of special interest (AESI) to bevacizumab. Generally, the AESI profile was similar to previous experience with Bv across other indications. However, hypertension was observed with a higher frequency (42.1%) for Bv-treated patients than earlier reported across indications (up to 34%). With regard to age, the incidence of hypertension of grade ≥ 3 among Bv-treated patients was twofold higher in the subgroup of patients ≥ 65 years of age than in the younger age group. The frequencies of grade ≥3 proteinuria (8.1%) and grade 3 bleeding (6.5%) were also somewhat higher than previously reported for bevacizumab (frequencies up to 7% and 5%, respectively).

## Uncertainty in the knowledge about the unfavourable effects

See risk management plan.

### *Benefit-risk balance*

## Importance of favourable and unfavourable effects

Ovarian cancer is highly sensitive to antineoplastic chemotherapy, and responses are expected in the majority of women who receive standard platinum- and taxane combination chemotherapy (following surgery) in the front-line setting. Despite this, most women diagnosed with advanced ovarian cancer will have a recurrence of the disease. Second-line chemotherapy combinations are available, but there are well-known limitations to these regimens (lower response rate and shorter duration of responses). This is why there is an unmet medical need for a more efficacious treatment option.

In this context, a HR for PFS of 0.48 and an absolute gain of 4 months in median PFS in favour of the Bv-containing regimen is unprecedented in the recurrent setting. The primary PFS result was consistently supported by all sensitivity and exploratory analyses of PFS, and by results in clinically relevant patient subgroups based on ECOG performance status, age, histologic subtype, and stratification variables. The improvement in PFS achieved by adding Bv concurrently to chemotherapy and extending it as single agent therapy was also associated with a reduction or stabilisation of the tumour burden as 79% of the patients in the Bv arm experienced an objective response compared to 58% in the Pl arm. The majority of responses were PRs.

PFS is considered an acceptable endpoint for first recurrences, but a gain in PFS should preferably be accompanied by a positive trend in OS or at least no detrimental effects in OS in order to be regarded as a clinical benefit in itself. Although a positive trend in OS could have been expected, the extensive use of later lines of therapy may have confounded OS results. In the most recent OS analysis, there was no significant difference in OS between treatment arms and no indication of a detrimental effect on OS.

The safety profile of bevacizumab in the current setting is considered acceptable and overall in line with the experience with bevacizumab across multiple oncology indications. No unexpected safety signals were seen in study AVF4095g.

### Benefit-risk balance

Based on the important clinical benefit observed in terms of PFS, associated with improvement in ORR with relevant response duration, and a well-characterised safety profile that was overall acceptable, the benefit-risk balance is considered positive.

### Discussion on the benefit risk balance

The progression of ovarian cancer is characterized by a relentless increase in the number of burdensome symptoms including GI-disturbances, abdominal pain, dyspnoea and weight loss that can be related to tumour progression, the development of ascites and bowel obstruction/dysfunction. Delaying the emergence of these symptoms by stabilizing the disease for a longer period could be meaningful to patients with first recurrence of platinum-sensitive ovarian cancer. Importantly, the addition of bevacizumab offers clearly better responses than the available standard chemotherapy regimens. It is also acknowledged that a prolongation of PFS will delay the need for subsequent therapies which potentially could be beneficial to patients. In ovarian cancer, platinum agents are still considered the most active chemotherapies in the recurrent setting. Patients with a longer time interval between the last carboplatin dose and progression of disease have a higher chance of responding to platinum at rechallenged. Overall, it is thus considered reasonably well documented that the improvement in PFS as demonstrated in study AVF4095g is of clinical relevance to the patients. The majority of AEs following use of Bv are considered clinically manageable. The analyses of AEs do not indicate more events following early termination of Bv.

Study AVF4095 was set up without a programme for collection of specimen for analyses of candidate biomarkers with potential predictive properties for bevacizumab. This is considered a weakness of the study, since uncertainties in the characteristics of the target population who would benefit most from therapy with Bv still persist. However both studies GOG-0218 and BO17707 (first-line ovarian cancer) were set up with biomarker programmes, and verification of whether candidate markers identified in other tumour types may have predictive potential in ovarian cancer could be obtained from data collected in these studies. The results of these analyses will be available end of June 2012 (see Annex II of the Opinion).

# 4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation accepted** | | **Type** |
|---|---|---|
| C.I.6.a | Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | II |

Update of section 4.1 of the SmPC in order to extend the indication of Avastin in combination with carboplatin and gemcitabine in patients with ovarian cancer as a second line treatment. Related changes were proposed to SmPC sections 4.2, 4.8 and 5.1. In addition, Annex II has been updated in order to revise the list of conditions. The Package Leaflet was proposed to be updated accordingly.

Furthermore, the PI is being brought in line with the latest QRD template version 8.

The requested variation proposed amendments to the Update of Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.

This CHMP recommendation is subject to the following new condition:

## *Conditions and requirements of the marketing authorisation*

### *Obligation to complete post-authorisation measures*

The MAH shall complete, within the stated timeframe, the following measure:

| Description | Due date |
|---|---|
| The MAH shall submit results from the pre-specified final analysis for Overall Survival from study AVF4095g | 31/12/2013 |

## *Similarity with authorised orphan medicinal products*

The CHMP is of the opinion that Avastin is not similar to Yondelis within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.