17 November 2011
EMA/CHMP/788079/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Avastin

bevacizumab

Procedure No.: EMEA/H/C/000582/II/0041

Note

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

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17 November 2011
EMA/CHMP/495806/2011
Committee for Medicinal Products for Human Use (CHMP)
Rev 1

Revised CHMP variation assessment report

Type II variation EMEA/H/C/000582/II/0041

Invented name/name:	Avastin
International non-proprietary name/common name:	bevacizumab

Indication summary (as last approved):	Treatment of metastatic carcinoma of the colon or rectum, metastatic breast cancer, non- small cell lung cancer and renal cell cancer
Marketing authorisation holder:	Roche Registration Ltd.

1. Scope of the variation and changes to the dossier

Scope of the variation:	Extension of indication to include the use of Avastin, in combination with carboplatin and paclitaxel for the front-line treatment of advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer. Consequently, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated to reflect the change in the indication. The Risk Management Plan and the Package Leaflet have been updated accordingly. Annex II has been updated as well in order to include the list of conditions. In addition, a minor change was made to the Labelling.
Rapporteur: Co-Rapporteurs:	Jens Ersbøll Eva Skovlund-Karsten Bruins Slot
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	Module 1, 2 and 5.
Product Information affected:	Summary of Product Characteristics, Annex II, Labelling and Package Leaflet (Attachment 1 - changes highlighted)

2. Steps taken for the assessment

Step	Step date
Submission date:	9 December 2010
Start of procedure:	19 December 2010
Rapporteur's assessment report circulated on:	15 February 2011
Co-Rapporteur's assessment report circulated on:	11 February 2011
Request for supplementary information and extension of timetable adopted by the CHMP on:	17 March 2011
MAH's responses submitted to the CHMP on:	20 May 2011
Rapporteur's and Co-Rapporteur's joint assessment report on the MAH's responses circulated on:	1 July 2011
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	21 July 2011
MAH's responses submitted to the CHMP on:	3 August 2011
Rapporteur's and Co-Rapporteur's joint assessment report on the MAH's responses circulated on:	7 September 2011
MAH's responses submitted to CHMP on:	15 September 2011
Rapporteur's and Co-Rapporteur's updated joint assessment report on the MAH's responses circulated on:	16 September 2011
CHMP opinion:	22 September 2011
Revised CHMP opinion, following a request for clarification from the European Commission dated 19 October 2011:	17 November 2011

3. Scientific discussion

Avastin, bevacizumab, is a recombinant humanised monoclonal antibody that inhibits angiogenesis by neutralising all isoforms of human vascular endothelial growth factor-A (VEGF-A), 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 colorectal cancer (mCRC), in combination with 5- fluorouracil/folinic acid or 5-fluorouracil/folinic acid/irinotecan. Afterwards, Avastin was approved for the treatment of locally recurrent and metastatic breast cancer (mBC), non-small cell lung cancer (NSCLC), metastatic renal cell cancer (RCC) and in combination with platinum containing regimens for mCRC.

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 paclitaxel is indicated for the front-line treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancer”.

The final indication approved by the CHMP is as follows:

“Avastin, in combination with carboplatin and paclitaxel is indicated for the front-line treatment of advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer”.

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, ''Batch'' has been replaced by ''lot'' in Annex IIIA. Finally, Annex II has been updated in order to include the new version number of the Risk Management Plan and the list of conditions.

Similarity

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

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.

3.1. Quality aspects

No new data related to pharmaceutical quality were submitted with this variation application, which is considered acceptable.

3.2. Non-clinical aspects

No new non-clinical data were submitted with this variation application, which is considered acceptable.

3.3. Clinical aspects

3.3.1. 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.

Since patients usually present with advanced disease, cure is difficult to achieve in the majority of cases, but prolongation of survival is possible and delay in first recurrence is considered clinically meaningful.

After initial surgical diagnosis, staging and cytoreductive surgery, the standard primary systemic chemotherapy for women with advanced ovarian cancer is a platinum and taxane combination usually carboplatin and paclitaxel. While there is a high response rate to this combination, the majority of women ultimately experience disease recurrence and die of their disease, which underlines the need to improve front line therapy.

Median progression free survival (PFS) for ovarian cancer patients with advanced disease including populations with mixed FIGO stages with no surgery restrictions or those with suboptimally debulked stage III/IV disease ranges between 11.2 and 18 months while the median overall survival (OS) lies between 25.8 and 38 months.

Intravenous (IV) paclitaxel plus carboplatin every three weeks is the standard of care globally (and the preferred comparator for front-line therapy studies). There is also reported evidence for improved outcomes with two modified regimens, weekly paclitaxel and intraperitoneal paclitaxel, and both are listed in treatment guidelines as options for standard of care.

The current application is mainly based on data from two international, randomised, phase III studies of bevacizumab in combination with paclitaxel and carboplatin chemotherapy for front line treatment of ovarian cancer, studies GOG-0218 and BO17707. An overview of the complete and ongoing studies of bevacizumab in ovarian cancer is presented in Table 1.

Table 1. Overview of Phase II and Phase III Studies of Bevacizumab in EOC, PPC and FTC

Study number/ status	Population	Design	Treatment	Sponsor/ Region	Primary endpoint
GOG-170D completed	62 patients with persistent or recurrent EOC/PPC after 1-2 regimes	Open label	Single agent bevacizumab 15 mg/kg q3w until progression or withdrawal	GOG/USA	PFS at 6 months and clinical response
AV2949g prematurely terminated	44 patients with platinum-resistant EOC/PPC who experienced PD during or within 3 months after topotecan, or liposomal doxorubicin	Open label	Single agent bevacizumab 15 mg/kg q3w until progression or withdrawal	Genentech/ USA	Objective RR
GOG-0218 Primary analysis completed Ongoing	1873 patients with FIGO stage III or greater EOC, PPC or FTC	Randomised, placebo-controlled, double blind	CPP CPB15 CPB15+	GOG/North America, Japan and South Korea	PFS
BO17707/ICON7 Primary analysis completed Ongoing	1528 patients with high risk FIGO stage I or IIA or FIGO stage IIB or greater EOC, PPC or FTC	Randomised controlled open-label	CP CPB7.5+	GCIG/ Europe, Australia, New Zealand, Canada	PFS
AVF4095g Ongoing	484 patients with EOC, PPC or FTC that has recurred No prior chemotherapy in the recurrent setting	Randomised, placebo-controlled, double blind	CGP CGB	Genentech/ USA	PFS

PFS: progression free survival, CR: clinical response, RR: response rate.
CPB15 = carboplatin (AUC6) + paclitaxel (175 mg/m^2) (6 cycles) + bevacizumab 15 mg/kg q3w (6 cycles) + placebo (16 cycles); CPB7.5+ = carboplatin (AUC 6) + paclitaxel (175 mg/m^2) (6 cycles) + bevacizumab 7.5 mg/kg q3w (18 cycles) CPB15+ = carboplatin (AUC 6 + paclitaxel (175 mg/m^2) (6 cycles) + bevacizumab 15 mg/kg q3w (21 cycles); CPP = carboplatin (AUC 6) + paclitaxel (175 mg/m^2) (5 cycles) + placebo (16 cycles). CG = [carboplatin (AUC 4) + gemcitabine (1000mg/m^{2}days 1 and 8)] q3w x 6 cycles. CGB = [carboplatin (AUC 4) + gemcitabine (1000mg/m^{2}days 1 and 8) + bevacizumab 15 mg/kg)] q3w x 6 cycles followed by bevacizumab until progression.
FIGO = International Federation of Gynecologic Oncology

GCIG: Gynecologic Cancer InterGroup, GOG: Gynecologic Oncology Group

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

3.3.2. Pharmacokinetics

A comprehensive population PK analysis was submitted with this application which was conducted using a first-order (FO) estimation method in NONMEM from eight clinical trials (Phase I, Phase II, and Phase III) in which several dosing regimens, patient populations, and concomitant anti-neoplastic regimens were used. Patients with mBC, NSCLC, CRC, and other solid tumours were included in this analysis. The analysis included a total of 491 patients who received IV doses of bevacizumab ranging

from 1 to 20 mg/kg at a dosing frequency of every 1 week, every 2 weeks, or every 3 weeks. Of the 491 patients included in the population PK model, 276 patients were female and 215 were male.

The population PK model also included covariates that account for inter-individual variability in the PK of bevacizumab, such as different chemotherapeutic agents used in combination with bevacizumab in these studies. This allowed for the assessment of the impact of co-administered chemotherapy evaluated to date on the PK of bevacizumab. Chemotherapy drugs in these studies were doxorubicin, carboplatin/paclitaxel, 5-FU/leucovorin, capecitabine, and bolus- irinotecan+5-fluorouracil+ leucovorin (IFL). The clearance (CL) of bevacizumab when bevacizumab was given in combination with bolus-IFL was not different than the CL with single-agent bevacizumab. In all other bevacizumab combinations, CL of bevacizumab was 17% slower. Because different combination therapies were given to patients with different tumour types, possible drug interactions (other than with the bolus-IFL regimen) were not distinguishable from tumour type effects on bevacizumab CL.

In addition, the MAH has submitted the results of a population PK analysis in patients with renal cell carcinoma. Using first-order conditional estimation (FOCE) in NONMEM to optimize the Reference Population PK Model, followed by a Bayesian feedback population PK analysis of bevacizumab PK data, the PK of bevacizumab in 102 patients with mRCC in Study BO17705 were compared with the previously investigated population pharmacokinetics of patients with mBC, NSCLC, CRC, and other solid tumours.

The observed bevacizumab trough levels in mRCC showed an increase in concentration from Week 3 to Week 11, consistent with a bevacizumab t1/2 of 20 days and a time to achieve steady state of approximately 14 weeks. In addition, the following evaluations were made for comparability of mRCC observations to bevacizumab observations described earlier by the Reference Population PK Model:

• The median simulated bevacizumab trough levels were in agreement with the median observed trough levels. A comparison of the 90% prediction interval indicates that 90.7% of the observed data were within this interval.

• Overall, median observed data in typical male and female patients for troughs and full concentration profiles were contained in the 95% confidence interval (CI) during the period with controlled dosing.

• There were no clinically relevant differences found in the individual PK parameter estimates for CL, central (Vc), and peripheral volume of distribution in the mRCC population on the basis of empirical Bayes estimates using a population PK approach.

Pharmacokinetic interaction studies

The MAH has not submitted any new drug-drug interactions studies. Instead available PK-DDI results for carboplatin and paclitaxel from Study AVF0757g have been presented. In Study AVF0757g, the PK of carboplatin and paclitaxel were evaluated in combination with bevacizumab in patients with locally advanced or metastatic NSCLC. Carboplatin and paclitaxel 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, 8 and 9 patients had concentration data for paclitaxel and carboplatin, respectively.

Based on these limited data, there did not appear to be a difference in the exposure of either carboplatin or paclitaxel when each was administered alone or in combination with bevacizumab, suggesting a lack of PK-DDI when these chemotherapy agents were administered in combination with bevacizumab. Patients in the control arm had slightly higher paclitaxel exposure at Day 63 compared to Day 0, however, 3 of 8 patients in the bevacizumab treated arm had lower paclitaxel exposure at Day 63 compared to Day 0.

3.3.3. Discussion on clinical pharmacology

Overall and across different solid tumours, population pharmacokinetic studies, although not including ovarian cancer patients, suggest that PK parameters were similar for bevacizumab across all doses and studies, whether administered as a single agent or in combination with chemotherapy, suggesting that the pharmacokinetics of bevacizumab are not markedly affected by administration of concomitant chemotherapy drugs evaluated to date.

Furthermore, cumulative PK-DDI data to date for bevacizumab given in combination with various chemotherapy agents across tumour types, including data in combination with carboplatin or paclitaxel mentioned above, 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.

3.3.4. Conclusions on clinical pharmacology

The pharmacokinetics of bevacizumab in ovarian cancer patients are expected to be consistent with the well-known PK profile for bevacizumab.

No further drug-drug interaction studies are considered necessary for the combination of bevacizumab with carboplatin and paclitaxel.

3.4. Clinical efficacy

3.4.1. Dose response studies

No dose-response studies were submitted (see discussion on clinical efficacy).

3.4.2. Main studies

- **Study GOG-0218**

Study GOG-0218 is a randomised, double-blind, placebo-controlled, multicentre Phase III comparative study in women with newly diagnosed, previously untreated, stage III or IV EOC, PPC, or FTC, designed to evaluate the efficacy and safety of bevacizumab in combination with carboplatin and paclitaxel in front-line therapy of ovarian cancer.

Methods

Study Participants

Main inclusion criteria

The target population for this study comprised patients with a histologic diagnosis of EOC, PPC or FTC; FIGO stage III with any gross (macroscopic or palpable) residual disease or FIGO stage IV defined surgically at the completion of initial abdominal surgery and with appropriate tissue available for histologic evaluation.

Patients with the following histologic epithelial cell types were eligible: Serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's tumour, or adenocarcinoma not otherwise specified (N.O.S.).

To be eligible for enrolment in the study, patients had to be age ≥ 18 years with adequate renal, hepatic, haematologic, and coagulation function, and to have a Gynaecology Oncology Group (GOG) performance status of 0 - 2 at baseline.

Main exclusion criteria

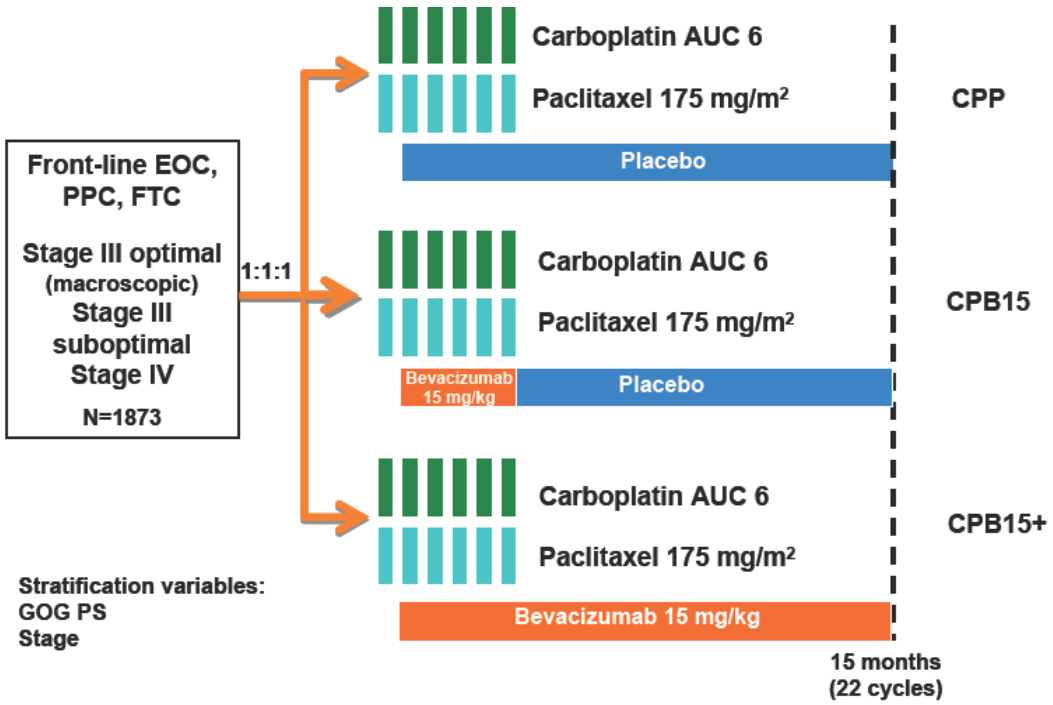
Patients who had received prior therapy with bevacizumab or prior systemic anti-cancer therapy for ovarian cancer (chemotherapy, monoclonal antibody therapy, tyrosine kinase inhibitor therapy, or hormonal therapy) or previous radiotherapy to the abdomen or pelvis were excluded from the study. Patients with malignancies other than ovarian cancer (with certain exceptions for cancers that had a very low likelihood of recurrence, as outlined in the study protocols) within 5 years prior to randomisation were also excluded.

Treatments

The study consisted of three arms (Figure 1):

- CPP arm: Placebo (5 cycles) in combination with carboplatin and paclitaxel chemotherapy (6 cycles), followed by placebo alone (16 cycles) for a total of up to 15 months (22 cycles) of therapy.
- CPB15 arm: Bevacizumab (5 cycles) in combination with carboplatin and paclitaxel chemotherapy (6 cycles), followed by placebo alone (16 cycles) for a total of up to 15 months (22 cycles) of therapy.
- CPB15+ arm: Bevacizumab (5 cycles) in combination with carboplatin and paclitaxel chemotherapy (6 cycles), followed by bevacizumab alone (16 cycles) for a total of up to 15 months (22 cycles) of therapy.

Figure 1. Design of Study GOG-0218



EOC = epithelial ovarian cancer; PPC = primary peritoneal cancer; FTC = fallopian tube cancer

Placebo/bevacizumab commenced with Cycle 2. The dose of carboplatin given was based on the Calvert formula, with target AUC 6. The dose of paclitaxel of 175 mg/m2 (over 3 hours) could be

substituted by docetaxel 75 mg/m2 (over one hour). If paclitaxel was discontinued for toxicity reasons, patients could receive treatment with docetaxel.

Objectives

The primary objectives were as follows:

- To determine if the addition of 5 concurrent cycles of bevacizumab to 6 cycles of standard therapy (carboplatin and paclitaxel [CPB15]) increases PFS when compared to 6 cycles of standard therapy alone (CPP) in women with newly diagnosed Stage III (with any gross residual disease) and Stage IV, epithelial ovarian, primary peritoneal, or fallopian tube cancer.
- To determine if the addition of 5 concurrent cycles of bevacizumab plus extended bevacizumab for 16 cycles beyond the 6 cycles of standard therapy (carboplatin and paclitaxel [CPB15+]) increases PFS when compared to 6 cycles of standard therapy (CPP) in women with newly diagnosed Stage III (with any gross residual disease) and Stage IV, epithelial ovarian, primary peritoneal, or fallopian tube cancer.
- The secondary objectives were as follows:
- In the event that both CPB15 and CPB15+ regimens were superior to the CPP regimen with respect to PFS, to determine whether the CPB15+ regimen prolonged PFS when compared to the CPB15 regimen.
- To determine whether the CPB15 or CPB15+ regimen increased the duration of OS when compared with the CPP regimen.
- To determine whether the CPB15 or CPB15+ regimen increased the ORR when compared with the CPP regimen.
- To evaluate the safety profile, as measured by the incidence of adverse events and adverse events of special interest, of standard chemotherapy (carboplatin and paclitaxel) with or without bevacizumab.
- To determine the impact on health-related quality of life (HRQoL) as measured by the Functional Assessment of Cancer Therapy–Ovarian Trial Outcome Index (FACT-O TOI) following treatment with the study regimens.
- To assess the relationship between angiogenic markers and clinical outcomes, including tumour response, PFS, and OS in patients randomised to standard cytotoxic chemotherapy with and without bevacizumab.
- To evaluate genetic signatures as predictors of OS in patients with advanced ovarian cancer.
- To determine whether specific genetic variations are predictive of development of hypertension in patients treated with bevacizumab.

Outcomes/endpoints

The primary endpoint was PFS defined as the time from randomisation to disease progression or death from any cause, based on investigator assessment. Tumour response and progression were evaluated in this study using RECIST (Response Evaluation Criteria in Solid Tumours, see statistical methods).

The secondary efficacy endpoints were OS and ORR. Overall survival was defined as the time from randomisation to death. All reported deaths were included in this analysis. OS for patients who had not died (or were not known to have died or were lost to follow-up) at the time of analysis was censored at the date the patient was last known to be alive.

Objective response was defined as the occurrence of a complete or partial best overall response (CR or PR; according to the RECIST) confirmed by repeat assessment performed by the investigator ≥ 4 weeks after the criteria for response were first met. Randomised patients who did not meet this criterion, including patients for whom post-baseline tumour assessments were not performed, were considered non-responders in the analysis of ORR.

The principal measure used in this study to assess the HRQoL was the self-administered FACT-O TOI for ovarian cancer patients. This HRQoL instrument had three subscales: physical well-being (PWB, 7 items), functional well-being (FWB, 7 items) and the ovarian cancer subscale (OCS, first 12 items indicated as "Additional Concerns" on the HRQoL case report form). The principal outcome measure was the TOI which consists of PWB + FWB + OCS. The minimum important difference for the TOI score is 5 points. A higher score means better HRQoL.

Sample size

Planned enrolment specified 1800 patients. The final analysis for the initial primary efficacy endpoint of PFS was to take place after the 375th event was observed among patients randomised to the CPP arm. If experimental regimen decreased the rate of progression or death by 23%, the study provided approximately 90% power to correctly identify that regimen as superior to standard therapy.

Randomisation

Patients were randomised in a 1:1:1 ratio to one of the three treatment arms: CPP, CPB15, or CPB15+. The two stratification factors for randomisation were the initial GOG performance status (0 vs. 1 or 2) and the disease stage (macroscopic optimally debulked FIGO Stage III, suboptimally debulked FIGO Stage III and FIGO Stage IV).

Blinding (masking)

The study was double-blind. To maintain the study blind, patients in the CPP received placebo throughout the study, and patients in the CPB15 arms received placebo following their bevacizumab treatment period.

Statistical methods

PFS was formally compared between each experimental arm and the control arm using a one-sided p-value from a stratified log-rank test. In the event that both the CPB15 and CPB15 + arms were statistically superior to the CPP arm with respect to PFS, a formal comparison of PFS between the two bevacizumab containing regimens was planned to be performed.

The overall type I error rate for the primary endpoint of PFS was controlled at a one-sided α=0.025. This was accomplished by hierarchically ordering the initial and late primary analyses. Specifically, the two hypotheses constituting the initial primary analysis were simultaneously tested at a one-sided α=0.025 level. Only if both hypotheses were rejected (i.e., both CPB15 and CPB15+were statistically superior to CPP), would the two experimental arms be formally compared. In this case, the late primary analysis would be tested at a one-sided α=0.025. Based on the SAP, a total one-sided $\alpha = 0.0135$ was allocated to each primary analysis of PFS comparing the experimental arm with the control arm. Based on this total one-sided α, the final p-value boundary for each comparison was 0.0116 which was calculated based on the following additional factors: (1) a one-sided $\alpha = 0.0043$ spent at the interim analysis that occurred in July 2009, (2) a non-binding futility boundary of HR = 1 at the interim analysis, and (3) the actual ratio of approximately 64% of interim total number of events to final total number of events as reported by the GOG in February 2010. A p-value ≤ 0.0116 was considered to have crossed the p-value boundary and was statistically significant.

Primary endpoint and sensitivity analysis

Based on the SAP, the primary analysis was Investigator (INV)-assessed PFS. Patients who progressed solely based on rising Cancer Antigen 125 (CA-125) levels were censored at the last tumour assessment for which the patient was known to be progression-free. Progression can be based upon serum CA-125, only during the period following completion of cytotoxic chemotherapy, if one of the three conditions is met: 1. Patients with elevated CA-125 pre-treatment and normalization of CA-125 must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart or 2. Patients with elevated CA-125 pre-treatment, which never normalizes must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart or 3. Patients with CA-125 in the normal range pre-treatment must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart.

Likewise, patients who received non-protocol- specified cancer therapy (NPT) for ovarian cancer prior to disease progression were censored at the last tumour assessment prior to the therapy initiation (SAP specified primary analysis). However, these censoring rules did not apply to the GOG protocol analysis: in this sensitivity analysis, CA-125 progressions were considered as events and patients were not censored for NPT given prior to disease progression.

Furthermore, PFS was assessed separately by an independent review of radiology studies. Two sensitivity analyses were performed for the independent review committee (IRC) assessed PFS.

Overall, the following sensitivity analyses of PFS were performed:

- A sensitivity analysis of PFS based on an IRC with censoring for NPT (+ censoring for CA-125 as IRC did not receive CA-125 measurements).
- An analysis of IRC-assessed PFS without NPT censoring.
- An analysis of INV-assessed PFS without NPT censoring.
- An analysis of INV-assessed PFS with neither NPT censoring nor CA-125 censoring (GOG protocol analysis). Because the CPB15 and CPB15+ arms had identical regimens until Cycle 7 (Week 19), PFS events that occurred prior to Cycle 7 were informative for both efficacy comparisons. Thus, in the formal PFS comparison of CPB15 versus CPP, PFS data from patients randomized to both experimental arms was combined. For this comparison, the PFS event times for patients randomized to CPB15+ were censored at the date of Cycle 7 treatment. An analogous use of PFS data from the CPB15 arm was made in the comparison of CPB15+ versus CPP. This pooling of PFS events was used for the Kaplan-Meier analysis as well as for the log-rank tests and the Cox model. Log-rank tests and Kaplan-Meier curves for a standard intent-to-treat (ITT) analysis (without the pooling of PFS events occurring prior to Cycle 7 in the active arms) were also reported.
- An analysis of the impact of discontinuation due to toxicity on INV-assessed PFS. In this analysis, PFS time for patients who discontinued study treatment due to toxicity prior to disease progression was censored at the time of the last tumour assessment prior to the discontinuation of study treatment.
- Worst-case INV-assessed PFS analyses accounting for missing scheduled assessments. Two sensitivity analyses were performed to evaluate the potential impact of missing scheduled tumour assessments on each initial primary analysis of PFS (comparison between an experimental arm and the control arm) using a PFS event imputation rule. Specifically, if a patient missed two or more assessments scheduled immediately prior to the date of the data cut-off, they were counted as having progressed on the date of the first of these missing assessments.

- A worst-case INV-assessed PFS analysis accounting for early discontinuation. A sensitivity analysis was performed to evaluate the potential impact of early discontinuation. In this analysis, progressive disease (PD) events were imputed for patients without documented disease progression who discontinued protocol treatment for reasons other than disease progression, or death or adverse event and who did not complete 22 cycles of study treatment. The date of progression for these patients was the date of the last tumour assessment.

The primary analysis efficacy population was the ITT population, defined as all patients randomised to study treatment, irrespective of whether the assigned treatment was actually received.

The primary safety population (safety-evaluable population) consisted of patients who had received at least Cycle 2 of study treatment or beyond.

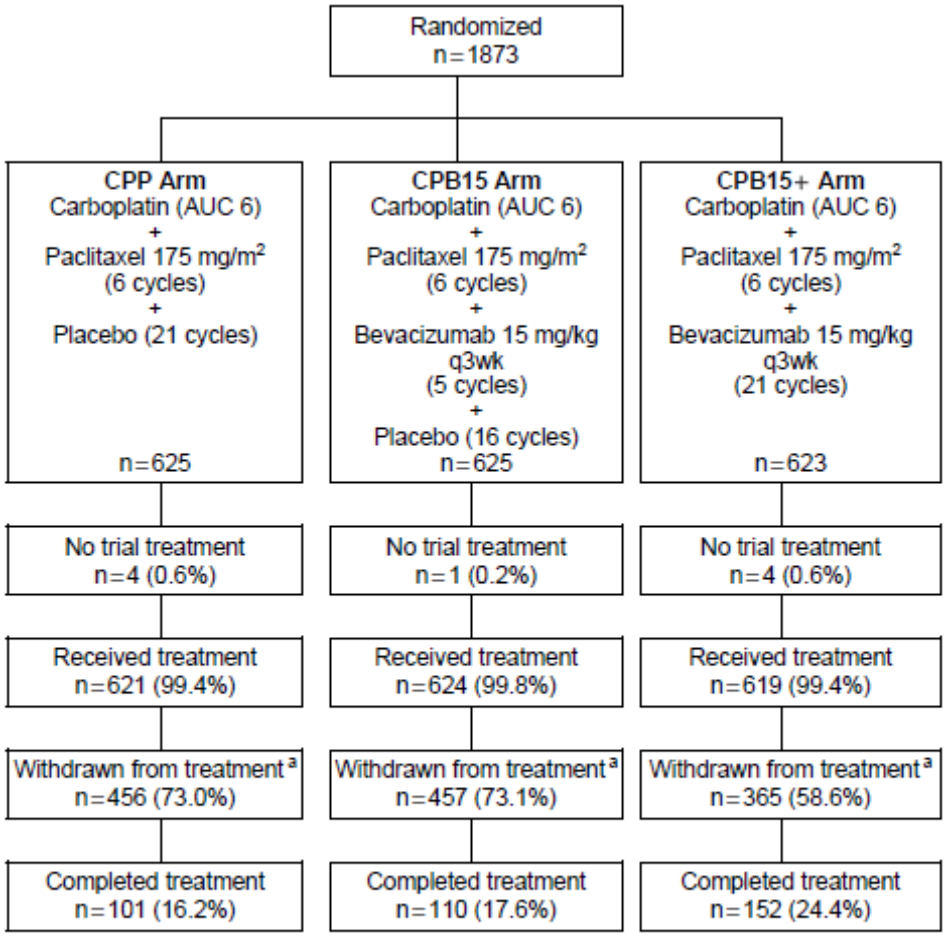
A separate exploratory-safety population consisted of patients who received at least one cycle of any study treatment.

Results

Participant flow

Patient disposition is presented in Figure 2.

Figure 2. Disposition of patients in GOG-0218 study



AUC=area under the concentration–time curve; q3wk=every 3 weeks.

[a] Disease progression or relapse during active treatment, adverse event, patient withdrawal or refusal for reasons other than toxicity, death on study, patient off treatment for other complicating disease, other.

Recruitment

The study period was from 14 October 2005 to 22 February 2010. A total of 1873 patients were enrolled at 336 centres in Canada, Japan, South Korea, and the United States.

Conduct of the study

The protocol for the study originally dated 14 June 2005 was amended eight times as follows:

- Administrative changes (Amendments 1 and 2).
- Revision of the entry criteria to include Stage III optimally debulked patients with macroscopic residual disease (Amendment 3).
- Change of the primary endpoint from OS to investigator-assessed PFS and decrease of the sample size from 2000 to 1800 patients (Amendment 4).
- Addition of an exploratory endpoint of PFS as determined by the IRC (Amendment 4).
- Expanded enrolment to include patients with FTC (Amendment 4).
- Allowance of unblinding at disease progression (Amendment 4).
- Addition of a translational research objective to assess whether specific genetic variations predict hypertension associated with bevacizumab (Amendment 5).
- Administrative changes (Amendment 6).
- Amendments 7 and 8 were instituted subsequent to the unblinding of the study data. These amendments consisted of instructions for patients who were continuing to receive open-label treatment (Amendment 7) and changes to clinical supplies (Amendment 8).

Overall, 60 patients (3.2%) in the three treatment arms had a protocol violation involving incorrect study drug administration. Additionally, 106 patients (5.7% overall; 27 patients in the CPP arm, 40 in the CPB15 arm, and 39 in the CPB15+ arm) had no macroscopic residual disease at study entry.

Baseline data

Baseline data

The baseline patient demographic characteristics are presented in Table 2. The disease characteristics are shown in Table 3.

Table 2. Patient demographic characteristics study GOG-0218

Characteristic	CPP (n = 625)	CPB15 (n = 625)	CPB15+ (n = 623)	All Patients (n = 1873)
Age (yr)				
n	625	625	623	1873
Mean (SD)	58.9 (10.8)	59.8 (10.3)	59.0 (10.6)	59.2 (10.6)
Median	60.0	60.0	59.0	60.0
Range	24–85	23–87	22–89	22–89
Age group (yr)				
n	625	625	623	1873
< 40	32 (5.1%)	14 (2.2%)	17 (2.7%)	63 (3.4%)
40–65	412 (65.9%)	429 (68.6%)	446 (71.6%)	1287 (68.7%)
> 65	181 (29.0%)	182 (29.1%)	160 (25.7%)	523 (27.9%)
Race				
n	625	623	621	1869

American Indian or Alaska native	2 (0.3%)	3 (0.5%)	2 (0.3%)	7 (0.4%)
Asian	41 (6.6%)	37 (5.9%)	39 (6.3%)	117 (6.3%)
Black or African-American	25 (4.0%)	29 (4.7%)	27 (4.3%)	81 (4.3%)
Native Hawaiian/other Pacific Islander	5 (0.8%)	2 (0.3%)	2 (0.3%)	9 (0.5%)
White	546 (87.4%)	542 (87.0%)	541 (87.1%)	1629 (87.2%)
Multiracial	1 (0.2%)	(0.0%)	(0.0%)	1 (< 0.1%)
Unknown	5 (0.8%)	10 (1.6%)	10 (1.6%)	25 (1.3%)
Baseline weight (kg)				
n	625	625	623	1873
Mean (SD)	70.48 (17.96)	71.11 (17.67)	70.88 (19.22)	70.82 (18.29)
Median	67.63	68.00	66.81	67.72
Range	34.0−157.0	36.8−151.8	38.0−173.6	34.0−173.6

CPB15 = carboplatin + paclitaxel and up to 5 cycles of bevacizumab 15 mg/kg and up to 16 cycles of placebo; CPB15+ = carboplatin + paclitaxel and up to 21 cycles of bevacizumab 15 mg/kg; CPP = carboplatin + paclitaxel and up to 21 cycles of placebo. Notes: The "n" row represents the number of patients with information. All percentages were based on n, the number of patients with information.

Table 3. Baseline disease characteristics study GOG-0218

	CPP (n = 625)	**CPB15 (n = 625)**	**CPB15+ (n = 623)**	**All Patients (n = 1873)**
Baseline performance status				
0	311 (49.8%)	314 (50.2%)	307 (49.3%)	932 (49.8%)
1	272 (43.5%)	270 (43.2%)	264 (42.4%)	806 (43.0%)
2	42 (6.7%)	41 (6.6%)	52 (8.3%)	135 (7.2%)
Primary site				
Ovary	515 (82.4%)	512 (81.9%)	531 (85.2%)	1558 (83.2%)
Fallopian tube	8 (1.3%)	17 (2.7%)	11 (1.8%)	36 (1.9%)
Peritoneum	102 (16.3%)	96 (15.4%)	81 (13.0%)	279 (14.9%)
Disease stage				
Stage III optimally debulked (macroscopic)	219 (35.0%)	204 (32.6%)	216 (34.7%)	639 (34.1%)
Stage III suboptimally debulked	253 (40.5%)	256 (41.0%)	242 (38.8%)	751 (40.1%)
Stage IV	153 (24.5%)	165 (26.4%)	165 (26.5%)	483 (25.8%)
Histologic type a				
Serous adenocarcinoma	530 (84.8%)	528 (84.5%)	533 (85.6%)	1591 (84.9%)
Clear cell carcinoma	20 (3.2%)	34 (5.4%)	25 (4.0%)	79 (4.2%)
Endometrioid adenocarcinoma	35 (5.6%)	30 (4.8%)	30 (4.8%)	95 (5.1%)
Mucinous adenocarcinoma	11 (1.8%)	10 (1.6%)	10 (1.6%)	31 (1.7%)
Mixed epithelial carcinoma	18 (2.9%)	9 (1.4%)	17 (2.7%)	44 (2.3%)
Adenocarcinoma, unspecified	17 (2.7%)	18 (2.9%)	20 (3.2%)	55 (2.9%)
Other	25 (4.0%)	24 (3.8%)	19 (3.0%)	68 (3.6%)
Size of residual disease				
0 cm or microscopic optimally debulked disease	27 (4.3%)	40 (6.4%)	39 (6.3%)	106 (5.7%)
> 0 cm and ≤ 1 cm	261 (41.8%)	247 (39.5%)	253 (40.6%)	761 (40.6%)
> 1 cm	337 (53.9%)	338 (54.1%)	331 (53.1%)	1006 (53.7%)
Ascites prior to initial staging surgery				
n	625	625	623	1873
Yes	454 (72.6%)	460 (73.6%)	445 (71.4%)	1359 (72.6%)
No	154 (24.6%)	141 (22.6%)	165 (26.5%)	460 (24.6%)
Unknown	17 (2.7%)	24 (3.8%)	13 (2.1%)	54 (2.9%)
Baseline disease measurability				
Yes	396 (63.4%)	393 (62.9%)	403 (64.7%)	1192 (63.6%)
No	229 (36.6%)	232 (37.1%)	220 (35.3%)	681 (36.4%)

Baseline CA-125				
Normal	35 (5.6%)	39 (6.2%)	31 (5.0%)	105 (5.6%)
Elevated b	590 (94.4%)	586 (93.8%)	592 (95.0%)	1768 (94.4%)

[a] Patients could be counted in more than one category for several variables. [b] Elevated indicates that CA-125 was greater than the ULN.

The percentage of patients who received NPT prior to disease progression was comparable across the treatment arms (CPP: 7.2%; CPB15: 8.2%; CPB15+: 6.9%).

More patients in the CPP (43.8%) and CPB15 (40.8%) arms received post-progression antineoplastic therapy than in the CPB15+ arm (33.4%).

The most common post-progression antineoplastic therapy was chemotherapy; commercially available Avastin was prescribed to 4.8% of patients in the CPP arm, 4.0% of patients in the CPB15 arm and 2.9% of patients in the CPB15+ arm.

Numbers analysed

Three analysis populations are summarised in Table 4.

Table 4. Analysis populations –Randomised patients

Analysis Population	CPP (n=625)	CPB15 (n=625)	CPB15+ (n=623)	All Patients (n=1873)
Randomized, ITT, and efficacy evaluable	625 (100.0%)	625 (100.0%)	623 (100.0%)	1873 (100.0%)
Safety evaluable	601 (96.2%)	607 (97.1%)	608 (97.6%)	1816 (97.0%)
Exploratory safety evaluable	621 (99.4%)	624 (99.8%)	619 (99.4%)	1864 (99.5%)

CPB15=carboplatin+paclitaxel and up to 5 cycles of bevacizumab 15 mg/kg and up to 16 cycles of placebo; CPB15+=carboplatin+paclitaxel and up to 21 cycles of bevacizumab 15 mg/kg; CPP=carboplatin+paclitaxel and up to 21 cycles of placebo; ITT=intent to treat.

Outcomes and estimation

Primary endpoint:

- Primary analysis - GOG protocol-specified analysis of PFS not censoring for CA-125 or NPT

An analysis of PFS (cut-of date 29 September 2009) comparing CPB15 versus CPP and CPB15+ versus CPP without pooling of CPB15 and CPB15+ events until cycle 7, not censoring for CA-125 (CA-125 PD to be acknowledged as PFS events) and not censoring for NPT is presented in Table 5.

Table 5. Analysis of Investigator-Assessed PFS without Pooling CPB15 and CPB15+ Events – Not Censored for CA-125 Not Censored for NPT (Study GOG-0218: Randomised Patients)

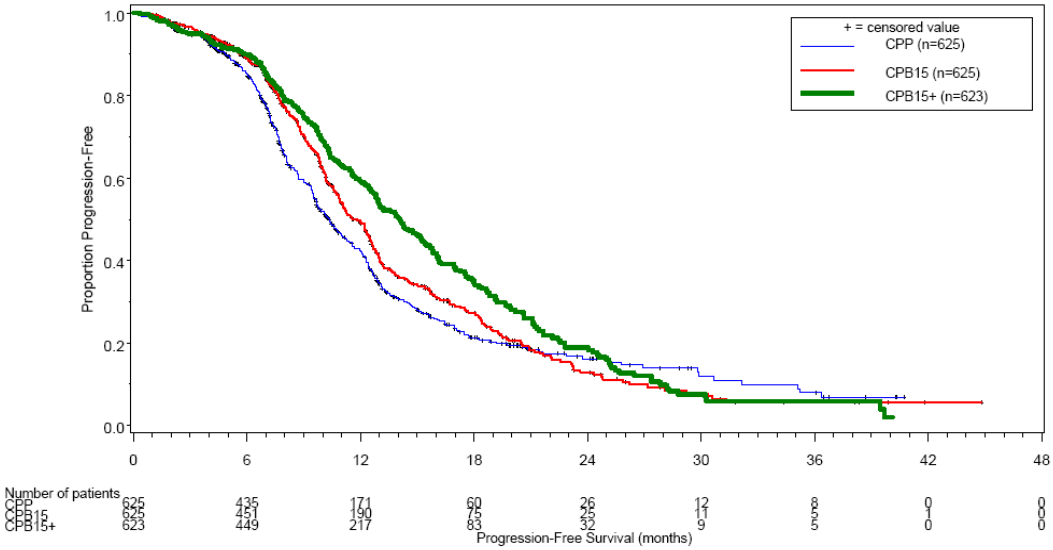
Sensitivity Analysis of INV-Assessed PFS [a]	**CPP (N = 625)**	**CPB15 (N = 625)**	**CPB15+ (N = 623)**
No. (%) patients with an event	375 (60.0%)	356 (57.0%)	317 (50.9%)
Median PFS (months) [b]	10.4	11.8	14.1
Hazard ratio (stratified) [c]		0.84	0.71
95% CI		[0.73; 0.98]	[0.61; 0.83]
One-sided log-rank p-value		0.0117	<0.0001
Hazard ratio (unstratified) [c]		0.86	0.72
95% CI		[0.75; 1.00]	[0.62; 0.84]
One-sided log-rank p-value		0.0243	<0.0001

CPP = carboplatin + paclitaxel up to 6 cycles + concurrent and extended placebo up to 21 cycles; CPB15 = carboplatin + paclitaxel up to 6 cycles + concurrent bevacizumab (15 mg/kg q3w) up to 5 cycles followed by placebo up to 16 cycles; CPB15+ = carboplatin + paclitaxel up to 6 cycles + concurrent and extended bevacizumab (15 mg/kg q3w) up to 21 cycles.

[a] Without pooling CPB15 and CPB15+ events - not censored for CA-125, not censored for NPT.
[b] Kaplan-Meier estimates.
[c] Relative to CPP.

Figure 3 shows the corresponding Kaplan-Meier plots for the GOG protocol-specified analysis of investigator-assessed PFS without pooling events prior to Cycle 7 in the CPB15 and CPB15+ arms.

Figure 3. Kaplan-Meier Estimate of Investigator-Assessed PFS Without Pooling CPB15 and CPB15+ Events - Not Censored for CA-125 Not Censored for NPT (Study GOG-0218: Randomised Patients)



BV = bevacizumab; CP = carboplatin + paclitaxel; CPP = CP + up to 21 cycles of placebo;
CPB15 = CP + up to 5 cycles of BV 15 mg/kg + up to 16 cycles of placebo; CPB15+ = CP + up to 21 cycles of BV 15 mg/kg;

- Updated GOG protocol pre-specified analyses of PFS not censoring for CA-125 or NPT

The results of the updated PFS analysis (cut-off date 25 February 2011) without censoring for CA-125 and NPT are presented in Table 6.

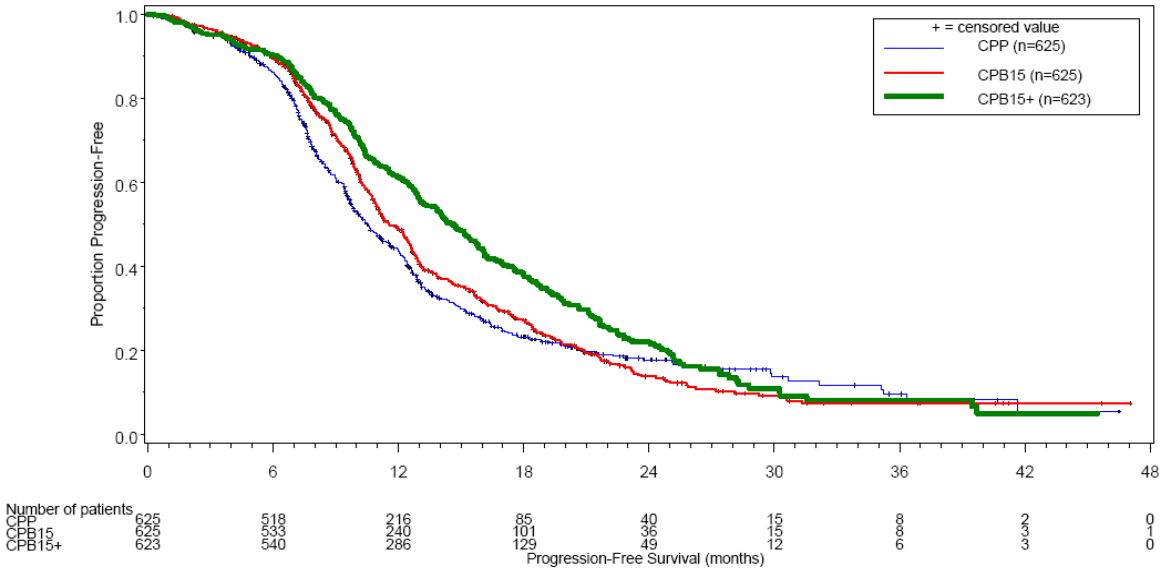
Table 6. Updated Analysis of Investigator-Assessed PFS – Not Censored for CA-125 Not Censored for NPT (Study GOG-0218: Randomised Patients)

	CPP (N=625)	CPB15 (N=625)	CPB15+ (N=623)
No. of patients	625	625	623
No. of patients with an event (%)	440 (70.4%)	435 (69.6%)	377 (60.5%)
Earliest contributing event:			
Disease progression	425 (96.6%)	416 (95.6%)	353 (93.6%)
Death	15 (3.4%)	19 (4.4%)	24 (6.4%)
No. of patients without an event (%)	185 (29.6%)	190 (30.4%)	246 (39.5%)
Progression free survival (months)			
Median	10.6	11.6	14.7
(95% CI)	(9.8, 11.4)	(10.9, 12.5)	(13.6, 15.7)
25^{th}-75^{th} percentile	7.4 – 17.0	8.5 – 18.4	9.3 – 22.1
Minimum-maximum	0.0+ - 46.5+	0.0+ - 50.1+	0.0+ - 45.5+
Stratified analysis			
Hazard ratio (relative to CPP)		0.890	0.702
(95% CI)		(0.779, 1.017)	(0.611, 0.806)
One-sided p-value			
Log-rank		0.0437	<.0001
Peto-Peto-Prentice		0.0010	<.0001
Unstratified analysis			
Hazard ratio (relative to CPP)		0.901	0.705
(95% CI)		(0.789, 1.029)	(0.614, 0.810)
One-sided p-value			
Log-rank		0.0626	<.0001

Peto-Peto-Prentice	0.0025	<.0001

Bv = bevacizumab; CP = carboplatin + paclitaxel; CPP = CP + up to 21 cycles of placebo; CPB15 = CP + up to 5 cycles of Bv 15 mg/kg + up to 16 cycles of placebo; CPB15+ = CP + up to 21 cycles of Bv 15 mg/kg; + = censored value; CI = confidence interval; NPT = Non-Protocol Cancer Therapy.
Summaries of progression-free survival (median, percentiles) were estimated from Kaplan-Meier curves. The 95% CI for median was computed using the method of Brookmeyer and Crowley. Stratified and unstratified hazard ratios were estimated using Cox regression. The strata were GOG performance status (0, 1 or 2) and Disease Stage (Stage III Optimal, Stage III Suboptimal, Stage IV).

Figure 4. Kaplan-Meier Estimate of Investigator-Assessed PFS – Not Censored for CA-125 Not Censored for NPT (Study GOG-0218: Updated Analysis)



BV = bevacizumab; CP = carboplatin + paclitaxel; CPP = CP + up to 21 cycles of placebo;
CPB15 = CP + up to 5 cycles of BV 15 mg/kg + up to 16 cycles of placebo; CPB15+ = CP + up to 21 cycles of BV 15 mg/kg;

- Sensitivity analyses of PFS

The results of the sensitivity analyses of investigator assessed PFS are presented in Table 7.

Table 7: Sensitivity analyses of investigator assessed PFS: Randomised patients

	CPP	CPB15	CPB15+
	(n = 625)	**(n = 1248) [a]**	**(n = 1248) [a]**
GOG protocol-specified investigator-assessed PFS (not censored for CA-125 or NPT)			
Patients with events	375 (60.0%)	405 (32.5%)	363 (29.1%)
Median (mo) [b]	10.4	11.5	13.9
Hazard ratio (stratified) [c]		0.864	0.726
95% CI		(0.750, 0.996)	(0.627, 0.840)
One-sided log-rank p-value [d]		0.0218	< 0.0001
Hazard ratio (unstratified) [c]		0.881	0.737
95% CI		(0.765, 1.015)	(0.637, 0.852)
One-sided log-rank p-value [d]		0.0398	< 0.0001
Investigator-assessed PFS (censored for CA-125, not censored for NPT)			
Patients with events	316 (50.6%)	346 (27.7%)	293 (23.5%)
Median (mo) [b]	12.0	12.9	17.5
Hazard ratio (stratified) [c]		0.862	0.666
95% CI		(0.739, 1.006)	(0.566, 0.783)
One-sided log-rank p-value d		0.0291	< 0.0001
Hazard ratio (unstratified) [c]		0.873	0.680
95% CI		(0.749, 1.018)	(0.580, 0.798)
One-sided log-rank p-value [d]		0.0412	< 0.0001
Investigator-assessed PFS (Missing assessments: first worst-case analysis, censored for CA-			

125 and NPT)			
Patients with events	227 (44.3%)	392 (31.4%)	357 (28.6%)
Median (mo) [b]	12.0	11.6	14.3
Hazard ratio (stratified) [c]		1.061	0.909
95% CI		(0.908, 1.240)	(0.776, 1.066)
One-sided log-rank p-value [d]		0.2265	0.1179
Hazard ratio (unstratified) [c]		1.081	0.1179
95% CI		(0.926, 1.262)	(0.785, 1.077)
One-sided log-rank p-value [d]		0.1608	0.1470
Investigator-assessed PFS (Missing assessments: second worst-case analysis, censored for CA-125 and NPT)			
Patients with events	335 (53.6%)	392 (31.4%)	357 (28.6%)
Median (mo) b	10.3	11.6	14.3
Hazard ratio (stratified) [c]		0.884	0.758
95% CI		(0.763, 1.025)	(0.651, 0.881)
One-sided log-rank p-value [d]		0.0511	0.0001
Hazard ratio (unstratified) [c]		0.900	0.766
95% CI		(0.777, 1.042)	(0.659, 0.890)
One-sided log-rank p-value [d]		0.0793	0.0002
Investigator-assessed PFS (off-treatment worst-case analysis, censored for CA-125 and NPT)			
Patients with events	324 (51.8%)	416 (33.3%)	350 (28.0%)
Median (mo) [b]	10.4	11.3	15.4
Hazard ratio (stratified) [c]		0.949	0.750
95% CI		(0.819, 1.100)	(0.644, 0.874)
One-sided log-rank p-value [d]		0.2445	0.0001
Hazard ratio (unstratified) [c]		0.961	0.762
95% CI		(0.830, 1.112)	(0.654, 0.887)
One-sided log-rank p-value [d]		0.2952	0.0002
Investigator-assessed PFS (toxicity-impact analysis, censored for CA-125 and NPT)			
Patients with events	260 (41.6%)	277 (22.2%)	216 (17.3%)
Median (mo) [b]	12.0	11.3	19.1
Hazard ratio (stratified) [c]		0.823	0.592
95% CI		(0.694, 0.977)	(0.493, 0.710)
One-sided log-rank p-value [d]		0.0131	□□0.0001
Hazard ratio (unstratified) [c]		0.842	0.606
95% CI		(0.710, 0.999)	(0.505, 0.726)
One-sided log-rank p-value [d]		0.0241	□□0.0001

[a] Events in the CPB15 and CPB15+ arms were pooled prior to Cycle 7 for PFS as specified in the Statistical Analysis Plan. [b] Kaplan−Meier estimates. [c] Relative to CPP. [d] Based on the total one-sided α, the final p-value boundary for statistical significance for each comparison was ≤ 0.0116.

The results of the IRC-assessed PFS analysis are presented in Table 8.

Table 8. Sensitivity Analyses of Independent Review Committee-Assessed PFS: Study GOG-0218 (Randomised Population)

Sensitivity Analysis of IRC-Assessed PFS	**CPP (N = 625)**	**CPB15 (N = 1248 [a])**	**CPB15+ (N = 1248 [a])**
IRC-Assessed PFS (Censored for NPT)			
Patients with events	203 (32.5%)	240 (19.2%)	177 (14.2%)
Median - months [b]	13.1	13.2	19.1
Hazard ratio (stratified) [c]		0.94	0.63
95% CI		[0.78; 1.14]	[0.51; 0.77]
One-sided log-rank p-value [d]		0.2663	<0.0001
Hazard ratio (unstratified) [c]		0.96	0.64
95% CI		[0.80; 1.16]	[0.53; 0.79]
One-sided log-rank p-value [d]		0.3493	<0.0001

IRC-Assessed PFS (Not Censored for NPT)			
Patients with events	229 (36.6%)	257 (20.6%)	189 (15.1%)
Median - months [b]	12.9	13.2	18.8
Hazard ratio (stratified) [c]		0.92	0.62
95% CI		[0.77; 1.10]	[0.51; 0.76]
One-sided log-rank p-value [d]		0.1765	<0.0001
Hazard ratio (unstratified) [c]		0.94	0.63
95% CI		[0.78; 1.12]	[0.52; 0.77]
One-sided log-rank p-value [d]		0.2365	<0.0001

CPP = carboplatin + paclitaxel up to 6 cycles + concurrent and extended placebo up to 21 cycles; CPB15 = carboplatin + paclitaxel up to 6 cycles + concurrent bevacizumab (15 mg/kg q3w) up to 5 cycles followed by placebo up to 16 cycles; CPB15+ = carboplatin + paclitaxel up to 6 cycles + concurrent and extended bevacizumab (15 mg/kg q3w) up to 21 cycles; INV = investigator-assessed; IRC = independent review committee-assessed; NPT = non protocol antineoplastic therapy.

[a] Events from the CPB15 and CPB15+ arms were pooled prior to Cycle 7 for PFS as specified in the SAP;

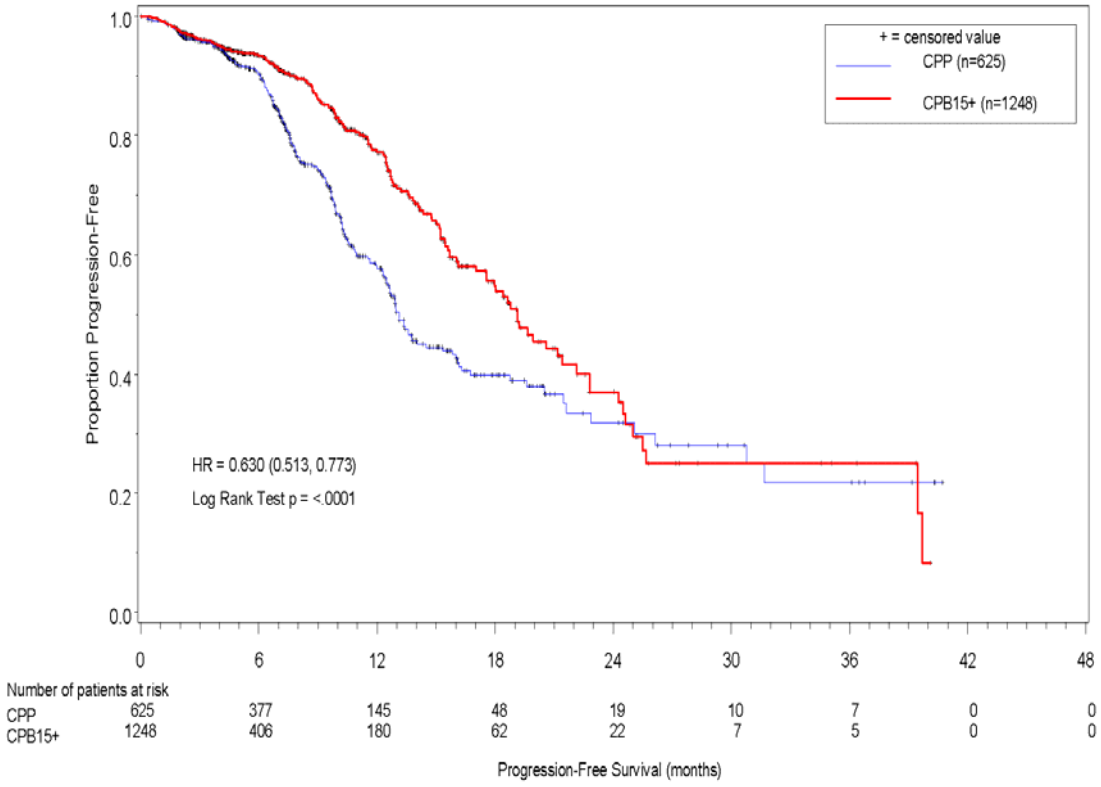
[b] Kaplan-Meier estimates; [c] Relative to CPP; [d] Based on the total one-sided α, the final p-value boundary for statistical significance for each comparison was ≤0.0116.

Note: CA-125 marker data were not sent to the IRC to determine progression status. Thus, the analysis is similar to the INV-assessed PFS analysis which was censored for both NPT and CA-125.

In the analysis which did not pool events from the CPB15 arm prior to Cycle 7, the stratified HR was 0.62 (95% CI 0.50; 0.77: p<0.0001) and the unstratified HR was 0.63 (95% CI 0.51; 0.78: p<0.0001).

The Kaplan – Meier curve of Independent Review Committee-Assessed PFS is presented in figure 5.

Figure 5. Kaplan Meier Curve of Independent Review Committee-Assessed PFS: Study GOG-0218 (CPB15+ vs. CPP – Pooled CPB15 Events) (Randomised Population)



- SAP specified INV-assessed PFS

The results of the initial primary analysis of PFS comparing the CPB15 arm versus the CPP arm and the CPB15+ arm versus the CPP arm are summarised in Table 9.

Table 9. Initial Primary PFS Comparison: CPB15 versus CPP and CPB15+ versus CPP, pooling of CPB15 and CPB15+ events until cycle7, Censoring for CA-125, Censoring for NPT: Randomised Patients

Progression-Free Survival	CPP (N = 625)	CPB15 (N = 1248[a])	CPB15+ (N = 1248[a])
Patients with events	277 (44.3%)	305 (24.4%)	248 (19.9%)
Median (months)	12.0	12.7	18.2
Hazard ratio (stratified)[b]		0.84	0.64
95% CI		[0.71; 0.99]	[0.54; 0.77]
One-sided log-rank p-value[c]		0.0204	<0.0001
Hazard ratio (unstratified)[b]		0.86	0.65
95% CI		[0.73; 1.02]	[0.55; 0.78]
One-sided log-rank p-value[c]		0.0383	<0.0001

[a] events from the CPB15 and CPB15+ arms were pooled prior to Cycle 7 for PFS as specified in the SAP; [b] relative to CPP; [c] based on the total one-sided α, the final p-value boundary for statistical significance for each comparison was ≤0.0116

In the analysis which did not pool events from the CPB15 arm prior to Cycle 7 the stratified HR was 0.62 (95% CI 0.52; 0.75: p<0.0001) and the unstratified HR was 0.63 (95% CI 0.53; 0.76: p<0.0001).

- Exploratory analyses

An analysis of the possible impact of bevacizumab on the pattern of relapse or the timing of disease progression in patients who discontinued treatment due to an adverse event has been submitted by the MAH.

The results are presented in Table 10.

Table 10. Time from Discontinuation of Chemotherapy/Bevacizumab to Progressive Disease or Death - Not Censored for CA-125 Not Censored for NPT (Study GOG-0218: Patients Who Discontinued Protocol Treatment due to Adverse Events)

	CPP (N=67)	CPB15 (N=81)	CPB15+ (N=88)
No. of patients	67	81	88
No. of patients with an event (%)	36 (53.7%)	47 (58.0%)	47 (53.4%)
Earliest contributing event:			
Disease progression	32 (88.9%)	39 (83.0%)	41 (87.2%)
Death	4 (11.1%)	8 (17.0%)	6 (12.8%)
No. of patients without an event (%)	31 (46.3%)	34 (42.0%)	41 (46.6%)
Duration of time to event (months)			
Median	8.3	8.3	8.3
(95% CI)	(6.1, 11.8)	(6.7, 9.9)	(5.3, 11.0)
25th-75th percentile	5.1 - 13.7	4.9 - 13.6	4.0 - 14.0
Minimum-maximum	0.0+ - 30.6	0.0+ - 34.0+	0.0+ - 24.7+
Stratified analysis			
Hazard ratio (relative to CPP)		1.389	1.108
(95% CI)		(0.874, 2.206)	(0.690, 1.779)
One-sided p-value			
Log-rank		0.0786	0.3322
Peto-Peto-Prentice		0.2030	0.3094
Unstratified analysis			
Hazard ratio (relative to CPP)		1.253	1.168
(95% CI)		(0.811, 1.936)	(0.753, 1.810)
One-sided p-value			
Log-rank		0.1531	0.2418
Peto-Peto-Prentice		0.2677	0.2321

Bv = bevacizumab; CP = carboplatin + paclitaxel; CPP = CP + up to 21 cycles of placebo; CPB15 = CP + up to 5 cycles of Bv 15 mg/kg + up to 16 cycles of placebo; CPB15+ = CP + up to 21 cycles of Bv 15 mg/kg; + = censored value; CI = confidence interval; NPT = Non-Protocol Cancer Therapy.
Summaries of progression-free survival (median, percentiles) were estimated from Kaplan-Meier curves. The 95% CI for median was computed using the method of Brookmeyer and Crowley. Stratified and unstratified hazard ratios were estimated using Cox regression. The strata were GOG performance status (0, 1 or 2) and Disease Stage (Stage III Optimal, Stage III Suboptimal, Stage IV).

Secondary endpoints

Overall survival

An overview of the results of the original and updated analyses of OS is shown in Table 11.

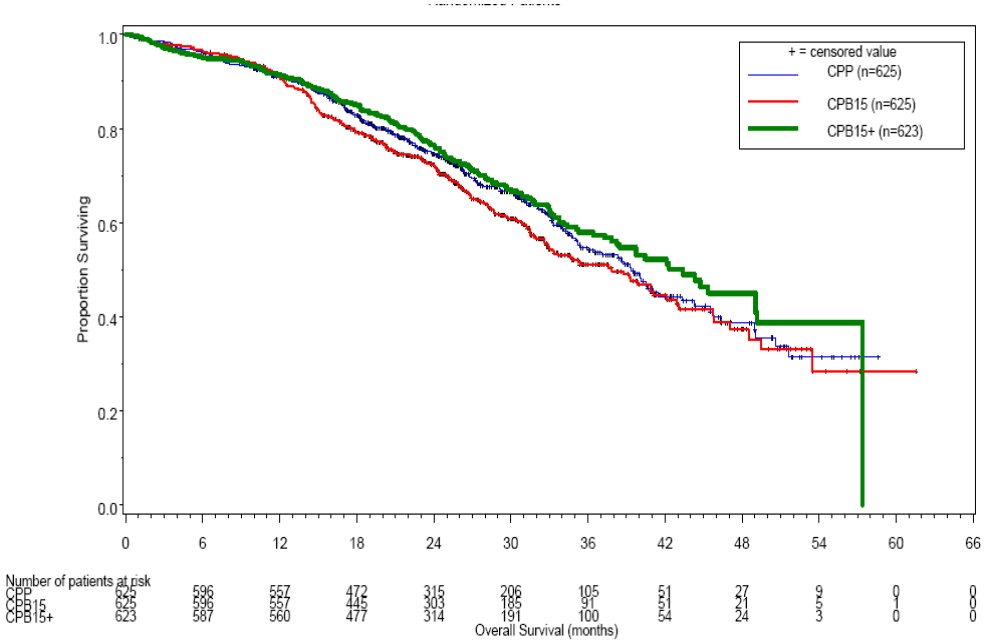
Table 11. Original and Updated Analyses of Overall Survival (Studies GOG-0218)

Overall Survival	**GOG-0218 Original (CSR) Analysis**			**GOG-0218 Updated Analysis**		
	CPP (N = 625)	**CPB15 (N = 625)**	**CPB15+ (N = 623)**	**CPP (N = 625)**	**CPB15 (N = 625)**	**CPB15+ (N = 623)**
No. (%) patients who died	157 (25.1%)	178 (14.3%)	156 (12.5%)	227 (36.3%)	245 (39.2%)	204 (32.7%)
Median survival time – months	39.4	38.8	39.8	39.4	37.9	43.4
[95% CI]	[34.0; 45.5]	[32.6; NE]	[35.1; NE]	[35.3; 43.3]	[32.9; 42.1]	[38.2; 49.1]
Stratified analysis						
Hazard ratio relative to CPP		1.09	0.90		1.14	0.90
[95% CI]		[0.87; 1.35]	[0.72; 1.13]		[0.95; 1.37]	[0.74; 1.08]
One-sided log-rank p-value		0.2256	0.1909		0.0809	0.1253
Unstratified analysis						
Hazard ratio relative to CPP		1.06	0.91		1.13	0.91
[95% CI]		[0.85; 1.32]	[0.72; 1.13]		[0.94; 1.35]	[0.75; 1.10]
One-sided log-rank p-value		0.2966	0.1934		0.0992	0.1590

CP = carboplatin + paclitaxel up to 6 cycles; CPB15 = CP + concurrent bevacizumab (15 mg/kg q3w) up to 5 cycles followed by placebo up to 16 cycles; CPB7.5+ = CP + bevacizumab (7.5 mg/kg q3w) up to 18 cycles; CPB15+ = CP + concurrent and extended bevacizumab (15 mg/kg q3w) up to 21 cycles; CPP = carboplatin + paclitaxel up to 6 cycles + concurrent and extended placebo up to 21 cycles; NE = not estimated;

The Kaplan−Meier estimate of OS (updated analysis) is presented in Figure 6.

Figure 6. Kaplan-Meier Estimate of Overall Survival (Study GOG-0218: Updated Analysis)



BV = bevacizumab; CP = carboplatin + paclitaxel; CPP = CP + up to 21 cycles of placebo;CPB15 = CP + up to 5 cycles of BV 15 mg/kg + up to 16 cycles of placebo; CPB15+ = CP + up to 21 cycles of BV 15 mg/kg; GOG = Gynecologic Oncology Group.

Objective Response Rate (ORR)

Table 12 displays the objective response rates in all treatment arms.

Table 12: Objective Response as Determined by the Investigators: Randomised Patients with Measurable Disease at Baseline

	CPP (N = 396)	CPB15 (N = 393)	CPB15+ (N = 403)
Patients with an objective response	251 (63.4%)	260 (66.2%)	266 (66.0%)
Patients without an objective response	145 (36.6%)	133 (33.8%)	137 (34.0)
95% CI for objective response rate	(58.6; 68.1]	(61.5; 70.8)	(61.4; 70.6)
Difference in objective response rates (relative to CPP) (95% CI)		2.8% (−3.9%, 9.4%)	2.6% (−4.0%, 9.2%)
Stratified analysis			
One-sided p-value		0.2341	0.2041
Unstratified analysis [c]:			
One-sided p-value		0.2074	0.2191
Best overall confirmed response			
Complete response	63 (15.9%)	68 (17.3%)	68 (16.95)
Partial response	188 (47.5%)	192 (48.9%)	198 (49.1%)
Stable disease	117 (29.5%)	108 (27.5%)	99 (24.6%)
Progressive disease	17 (4.3%)	10 (2.5%)	16 (4.0%)
Unable to evaluate	11 (2.8%)	15 (3.8%)	22 (5.5%)

Objective response was defined as a complete or partial best overall confirmed response per modified RECIST. The 95% CIs for response rate and for the difference in response rates were computed using the normal approximation to the binomial distribution. The p-value for the unstratified analysis was from the Pearson's $\chi 2$ test. The p-value for the stratified analysis was from the Cochran–Mantel–Haenszel test.

Compared to the investigator analysis, the ORR as determined by the IRC was higher in all three treatment arms (CPP: 68.8%; CPB15: 75.4%; CPB15+: 77.4%) as were the differences between the CPP arm versus the CPB15 (6.7%) and CPB15+ (8.6%) arms.

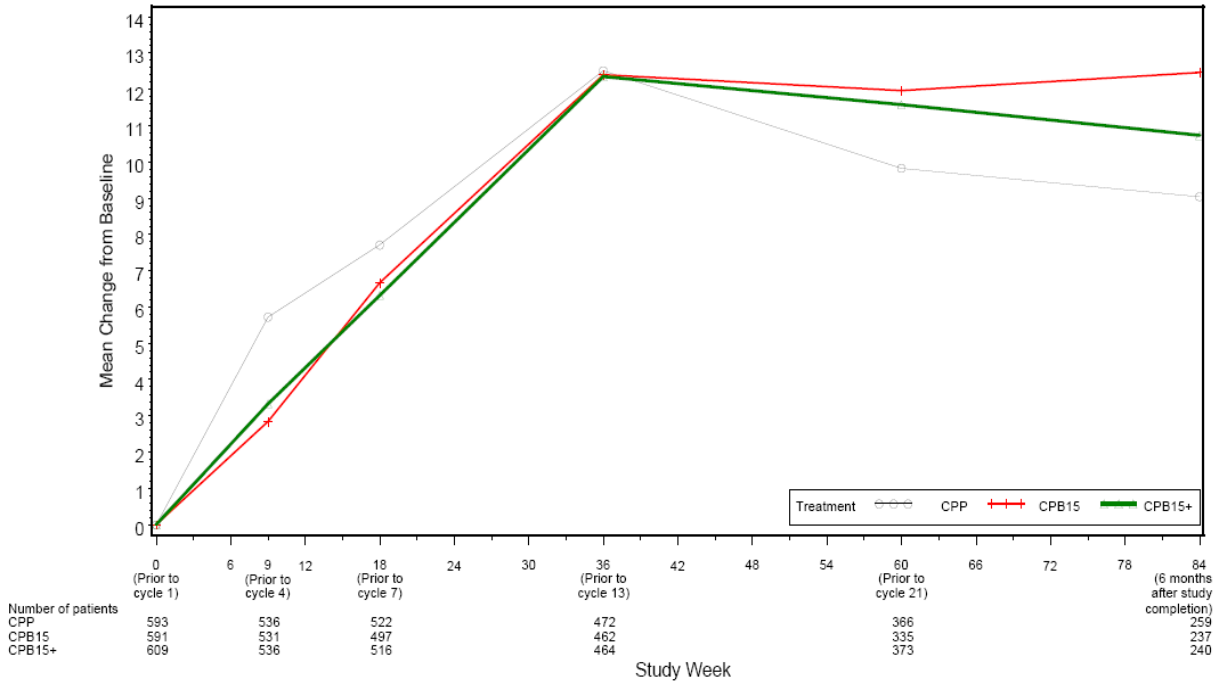
Health Related Quality of Life (HRQoL)

A mixed effect model for the TOI scores was built using all scores post-baseline as dependent variables, and treatment group, time and interaction between treatment group and time as fixed effects and baseline score and age as covariates. Three pre-specified interaction contrasts were tested and showed that:

- The contrast examining change in HRQoL in the second half of the chemotherapy phase (between Cycles 4 and 7) indicated a slightly stronger improvement in TOI scores over this period for patients in the CPB15 and CPB15+ arms compared to those for patients in the CPP arm, but this was not statistically significant (p=0.0864).
- The contrast examining change in HRQoL between the second half of the chemotherapy phase (Cycles 4 and 7) and the latter portion of the extended treatment phase (Cycles 13 and 21) indicated a statistically significant improvement in TOI scores over time for patients in the CPB15+ arm compared to those for patients in the CPP arm (p=0.0008). This change (2.6 points) did not exceed the minimally important difference of 5 points.
- The contrast examining change in TOI scores during the latter portion of the extended treatment phase (Cycles 13 and 21) found no statistically significant difference between the CPB15 and CPB15+ arms (p=0.8236).

Figure 7 displays the changes from baseline in TOI scores in each treatment arms.

Figure 7. Plot of Mean Change From Baseline in Overall FACT-O TOI Scores over Time (Randomised Patients)



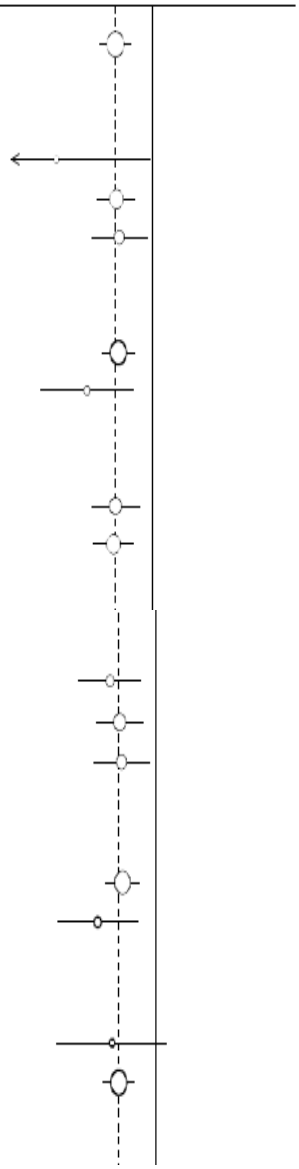
Subgroup analyses

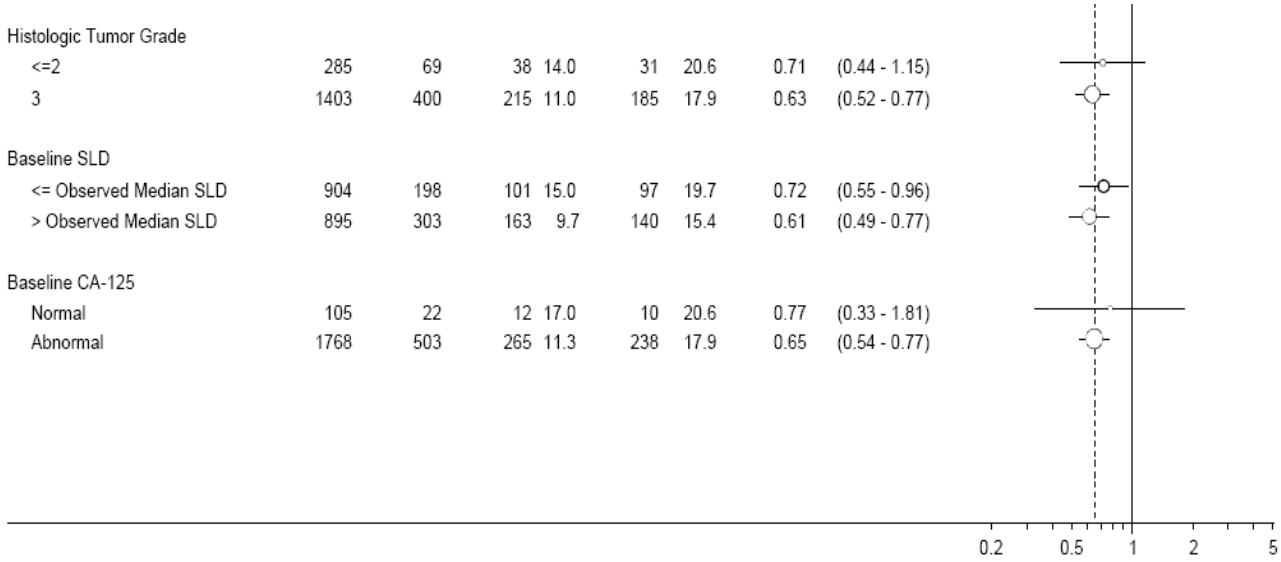
- *Subgroup analysis of INV-assessed PFS*

Table 13 presents the results of the subgroup analysis of PFS.

Table 13. PFS as Determined by the Investigators Using Baseline Risk Factors, CPB15+ versus CPP, Pooling CPB15 Events, Censoring for CA-125, Censoring for NPT: Randomised Patients

			CPP (n=625)		CPB15+ (n=1248)				
Baseline Characteristic	Total n	Total events	# of events	Median (month)	# of events	Median (month)	Hazard Ratio	(95% CI)	Hazard Ratio
All Patients	1873	525	277	12.0	248	18.2	0.65	(0.55 - 0.78)	
Age (yr)									
< 40	63	17	12	12.4	5	NE	0.34	(0.12 - 0.96)	
40-65	1287	343	176	12.3	167	18.2	0.66	(0.53 - 0.82)	
> 65	523	165	89	10.4	76	17.5	0.69	(0.50 - 0.93)	
Race									
White	1630	468	246	12.1	222	17.9	0.68	(0.57 - 0.81)	
Non-White	243	57	31	11.7	26	19.7	0.47	(0.28 - 0.80)	
Baseline GOG Performance Status									
0	932	218	118	13.4	100	19.7	0.65	(0.50 - 0.86)	
1 or 2	941	307	159	10.2	148	15.7	0.64	(0.51 - 0.80)	
Disease Stage									
Stage III Optimally Debulked	639	127	71	13.6	56	18.2	0.59	(0.42 - 0.84)	
Stage III Sub-optimally Debulked	751	237	131	11.7	106	18.6	0.66	(0.51 - 0.85)	
Stage IV	483	161	75	10.2	86	16.0	0.68	(0.50 - 0.92)	
Primary Site									
Ovary	1558	446	230	12.1	216	18.2	0.68	(0.57 - 0.82)	
Non-Ovary	315	79	47	9.7	32	16.7	0.52	(0.33 - 0.81)	
Histologic Cell Type									
Mucinous or Clear Cell	109	40	18	5.8	22	9.3	0.60	(0.32 - 1.13)	
All Others	1764	485	259	12.1	226	18.6	0.65	(0.54 - 0.78)	





BV = bevacizumab; CP = carboplatin + paclitaxel; CPP = CP + up to 21 cycles of placebo; CPB15 = CP + up to 5 cycles of BV 15 mg/kg + up to 16 cycles of placebo; CPB15+ = CP + up to 21 cycles of BV 15 mg/kg. NE = Non-Estimable; NPT = Non-Protocol Cancer Therapy. Median progression-free survival was estimated from Kaplan-Meier method. Hazard ratio relative to CPP 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 of a circle is proportional to the square root of the total number of events.

- *PFS subgroup analyses by disease stage and debulking status*

The PFS analysis for patients with optimally debulked stage III disease for study GOG-0218 (protocol-specified analysis without censoring for CA-125 or NPT) is provided in Table 14 below. The cut-off date for this analysis is 25 February 2010

Table 14. PFS Results by Disease Stage and Debulking Status from Study GOG-0218

Randomized patients stage III optimally debulked disease [1,2]			
	CPP (n = 219)	CPB15 (n = 204)	CPB15+ (n = 216)
Median **PFS (months)**	12.4	14.3	17.5
Hazard ratio (95% CI)[3]		0.81 (0.62, 1.05)	0.66 (0.50, 0.86)
Randomized patients with stage III suboptimally debulked disease[3]			
	CPP (n = 253)	CPB15 (n = 256)	CPB15+ (n = 242)
Median PFS (months)	10.1	10.9	13.9
Hazard ratio (95% CI)[3]		0.93 (0.77, 1.14)	0.78 (0.63, 0.96)
Randomized patients with stage IV disease			
	CPP (n = 153)	CPB15 (n = 165)	CPB15+ (n = 165)
Median PFS (months)	9.5	10.4	12.8
Hazard Ratio (95% CI)[3]		0.90 (0.70, 1.16)	0.64 (0.49, 0.82)

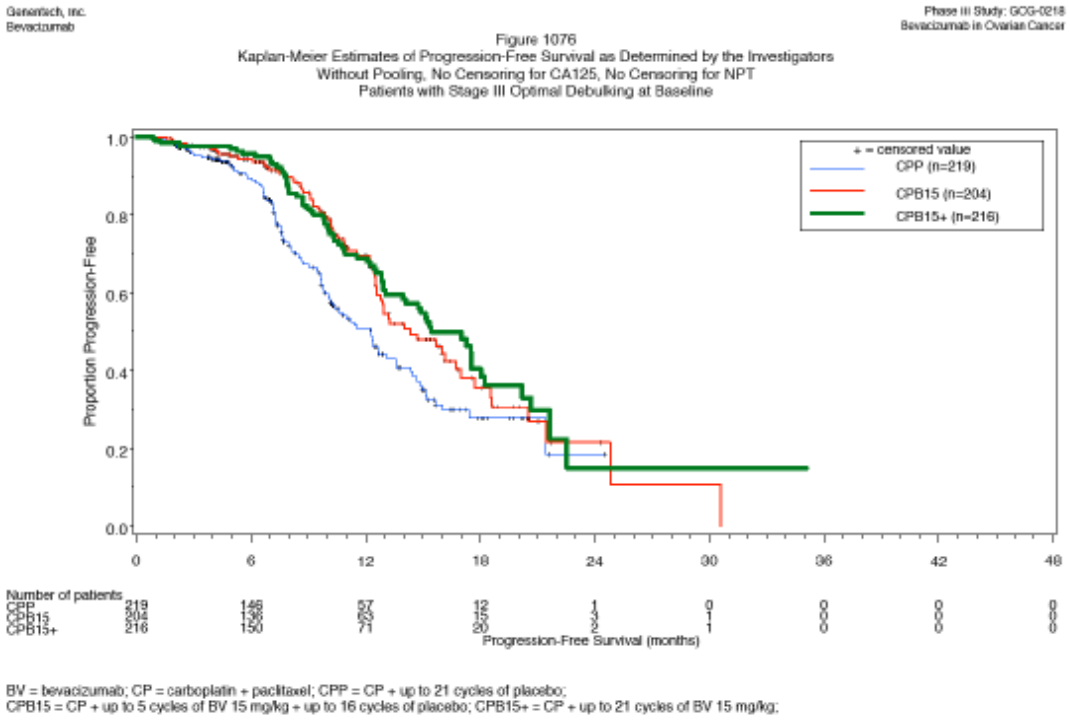
[1]With gross residual disease.

[2] 3.7% of the overall randomized patient population had Stage IIIB disease.

[3]Relative to the control arm.

The Kaplan – Meier curve is presented in Figure 8.

Figure 8. Kaplan-Meier Estimates of PFS for Patients with Optimally Debulked FIGO Stage III Ovarian Cancer Without Censoring for CA-125 or NPT (Study GOG-0218: Randomized Patients)



BV = bevacizumab; CP = carboplatin + paclitaxel; CPP = CP + up to 21 cycles of placebo;
CPB15 = CP + up to 5 cycles of BV 15 mg/kg + up to 16 cycles of placebo; CPB15+ = CP + up to 21 cycles of BV 15 mg/kg;

Subgroup analysis of OS

Overall, the subgroup analyses of OS were generally consistent (data not shown).

- **Study BO17707**

Study BO17707 is a multicentre, randomised, open-label, controlled phase III study designed to investigate the efficacy and safety of bevacizumab in combination with carboplatin and paclitaxel in front-line therapy of ovarian cancer.

METHODS

Study Participants

Main inclusion criteria

The target population for this study comprised patients with histologically confirmed EOC, FTC or PPC and high-risk early stage (FIGO Stage I + IIA: Grade 3 - poorly differentiated) or advanced stage (FIGO Stage IIB – IV: Grade 1 - well differentiated, Grade 2 - moderately differentiated, or Grade 3).

Enrolment was limited in any individual country or group to a maximum of 10% of FIGO Stage I + IIA patients. Patients with clear cell carcinoma (defined as either ≥ 50% clear cell elements present or reported as clear cell carcinoma by the local pathologist) of any stage were eligible due to the poorer prognosis associated with this subtype. Patients with previous early stage EOC or FTC treated with surgery alone were eligible at the time of diagnosis of abdominopelvic recurrence as long as no further interval cytoreductive therapy was planned prior to disease progression. Patients should have already

undergone surgical debulking, by a surgeon experienced in the management of ovarian cancer, with the aim of maximal surgical cytoreduction. Patients with Stage III and IV disease in whom initial surgical debulking was not appropriate were still eligible provided that the patient had a histological diagnosis and debulking surgery prior to disease progression was not foreseen. There must have been no planned surgical debulking prior to disease progression. To be eligible for enrolment, patients also had to be age ≥ 18 years with adequate renal, hepatic, haematologic, and coagulation function, and to have a ECOG performance status of 0 - 2 at baseline.

Main exclusion criteria

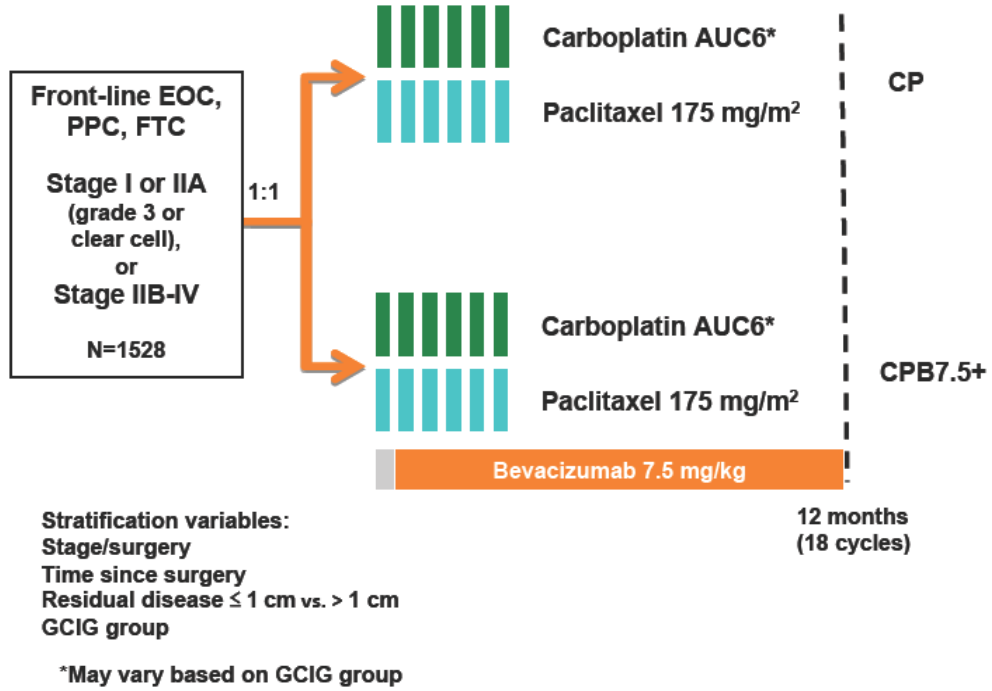
Patients who had received prior therapy with bevacizumab or prior systemic anti-cancer therapy for ovarian cancer (e.g., chemotherapy, monoclonal antibody therapy, tyrosine kinase inhibitor therapy, or hormonal therapy) or previous radiotherapy to the abdomen or pelvis were excluded from the study. Patients with malignancies other than ovarian cancer (with certain exceptions for cancers that had a very low likelihood of recurrence, as outlined in the study protocols) within 5 years prior to randomisation were also excluded.

Treatments

The study consisted of two arms (Figure 9):

- CP arm: Carboplatin and paclitaxel chemotherapy for 6 cycles.
- CPB7.5+ arm: Bevacizumab (7.5 mg/kg q3w) in combination with carboplatin and paclitaxel chemotherapy for 6 cycles, followed by therapy with bevacizumab alone for a total of up to 12 months (18 cycles) of treatment.

Figure 9. Design of Study BO17707



EOC = epithelial ovarian cancer; PPC = primary peritoneal cancer; FTC = fallopian tube cancer

Bevacizumab started with Cycle 2 if treatment was initiated within 4 weeks of surgery or with Cycle 1 if treatment was initiated more than 4 weeks after surgery.

Treatment in the CPB7.5+ arm continued for a total of 12 months of therapy, or until disease progression/unacceptable toxicity.

The recommended dose of carboplatin to be given was AUC6, however, the initial carboplatin dose (between AUC5 and AUC7.5) could be selected according to the standard practice of the individual GCIG groups. The dose of paclitaxel was 175 mg/m^2 administered over 3 hours. Patients who discontinued paclitaxel treatment could continue treatment with carboplatin (with or without bevacizumab according to randomisation). If carboplatin therapy was discontinued, patients could continue to receive paclitaxel and cisplatin could be substituted for carboplatin, at the discretion of the treating physician. Paclitaxel could not be substituted with docetaxel.

Following completion of 6 cycles of carboplatin and paclitaxel treatment, patients in the CP arm were followed up every 6 weeks for a further 36 weeks.

Outcomes/endpoints

The primary endpoint for this study was PFS defined as the time from randomisation to the time of first documented disease progression or death, whichever occurred first. Progression (based on RECIST) was only considered on radiological or clinical grounds, and progression based on CA-125 had to be confirmed by CT scan. If the scan was negative, the patient remained on study.

Secondary endpoints were OS (defined as the time from randomisation to death), ORR (Patients were classified as responders if their best overall response was either confirmed CR or PR patients without any assessments were regarded as non-responders), duration of tumour response, biological progression-free interval (PFIBIO) defined as time to CA-125 progression, and quality of life.

Sample size

The planned sample size was 1444 patients randomised at a steady rate over a period of 24 months with an additional 12 months follow-up after the last patient was randomised (36 months after the first patient was enrolled). Based on this sample size, the trial had 93% power (two-sided test, significance level of 5%) to show a 28% change in PFS from a median value of 18 months in the control arm to 23 months in the bevacizumab arm i.e. a HR of 0.78. It was expected that 788 PFS events would have occurred at this point. To achieve 90% power (two-sided test, significance level of 5%) required 684 events.

The trial was also powered to detect an improvement in OS. A total of 715 deaths needed to be observed in the two treatment arms in order to be able to demonstrate a 19% improvement in OS from a median value of 43 months in the control arm to 53 months in the bevacizumab arm i.e. a HR of 0.81 with 80% power at a significance level of 5% (two-sided test). Given a total sample size of 1444 patients and assuming linear recruitment over a period of 24 months, it was expected that 715 deaths would have occurred 36 months after the last patient was randomised, approximately 24 months after the final analysis of the PFS endpoint. To allow for non-compliance of the order of 5%, 1520 patients were to be enrolled, 760 in each treatment arm.

Randomisation

Patients were randomised to receive either chemotherapy (carboplatin and paclitaxel) alone (control arm) or chemotherapy plus bevacizumab (research arm) in a 1:1 ratio through a central randomisation process, using the following stratification factors:

- FIGO stage (category 1: stage I-III with residual disease ≤ 1 cm, category 2: Stage IIII with residual disease > 1 cm, category 3: FIGO stage IV and inoperable FIGO stage III).
- Intent to start chemotherapy ≤ 4 weeks following surgery versus intent to start chemotherapy > 4 weeks after surgery.

- GCIG group (only included for logistical reasons and not included in stratified analysis).

Blinding (masking)

The study was unblinded.

Statistical Methods

Primary efficacy endpoint

For the primary endpoint PFS, the log-rank test (non-stratified) at an α-level of 5% was used to test the difference between the CP arm and the CPB7.5+ arm. The following sensitivity analyses of PFS were performed:

- Time to censoring analysis. A Kaplan-Meier plot of the time to censoring in the different treatment arms was generated to investigate differences in follow-up time. In this analysis, patients who had an event were censored at the date of their event and patients without an event were regarded as having had an event at the censoring date.
- Missing assessments analysis. A sensitivity analysis was performed investigating the effect of missing assessments followed by an assessment of PD/recurrence. In this analysis the missing assessment was considered to be PD/recurrence.
- Worst case analysis was used to assess the effect of incomplete tumour assessment follow-up information (in this type of analysis, all patients with incomplete tumour assessment follow-up were considered as having an event). For the PFS endpoint, patients with incomplete tumour assessment follow-up were patients who had not progressed or died and who did not have a follow-up for progression within 3 months prior to clinical cut-off for the first year following randomisation and 6 months during years 2 and 3 after randomisation. There was no scheduled tumour assessment after year 3. These patients were counted as having an event at the last time they were known to be progression free by radiographical imaging.
- Before start of non-study anti-neoplastic treatment analysis. PFS before start of non-study anti-neoplastic treatment was defined as the time between randomisation and the date of first documented disease progression or death, whichever occurred first and only if it occurred before the start of non-study antineoplastic treatment (including surgery for ovarian cancer).

Multiple Cox regression analyses were performed in order to assess the robustness of the conclusions drawn from the primary analysis of PFS.

Secondary efficacy endpoints:

Overall survival: Kaplan-Meier curves and estimates are provided. The final analysis of OS would take place when 715 deaths had occurred.

Objective Response Rates: Summary tables with the number and proportion of responders and non-responders in each of the treatment groups, together with the two-sided 95% Pearson-Clopper confidence intervals for response rates were provided. The rates and the corresponding 95% Pearson-Clopper confidence intervals for each of the response categories (CR, PR, SD, PD, Missing) by treatment group were also presented. A Chi-square test with Schouten correction was used to test for treatment differences between the bevacizumab and the control arm.

Duration of Tumour Response: Kaplan-Meier curves and estimates were provided of the "Responders", "RECIST Responders" and "CA-125 Responders" but no formal hypothesis testing was performed as this analysis was based on a non-randomised subset of patients. Hazard ratios and confidence intervals

were displayed. RECIST Response outputs were produced for the sub-population of patients with measurable disease at baseline, which was considered the primary population for this analysis.

Quality of Life Analysis: Summary statistics for the assessment scores from the three QoL questionnaires EORTC-QLQ-C30, EORTC-QLQ-OV28 and EuroQol EQ-5D were presented for the two treatment groups at each scheduled visit, together with the change from baseline. Plots of mean values and standard error of the mean values by treatment group over time and the change from baseline were depicted for each scale or item from the three QoL questionnaires up to cycle 18, or on day 1 of cycle 1 of second-line therapy for those patients who progress.

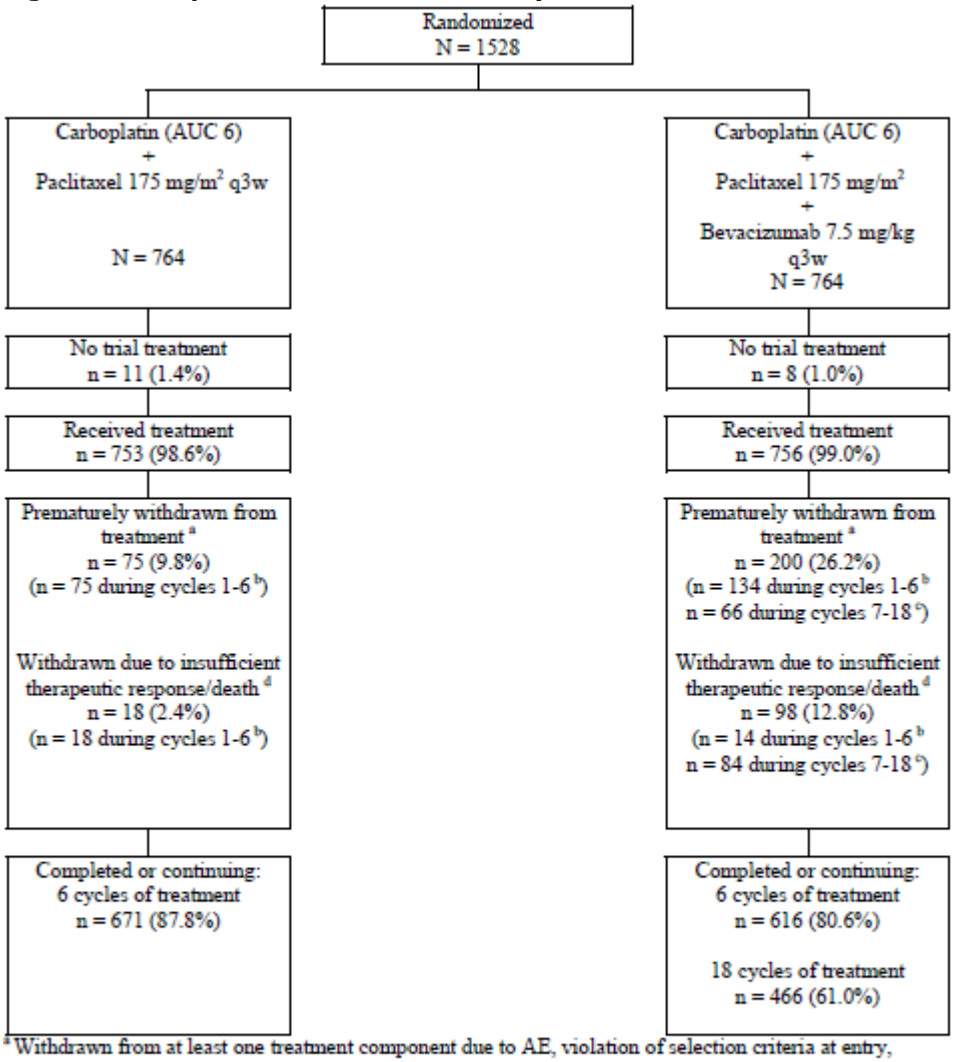
For the secondary efficacy parameters, all tests were performed at a two-sided 5% alpha level. No adjustment for the multiplicity of testing was performed.

Results

Participant flow

Overall 1528 patients were enrolled in the study and randomised into one of the two study arms; 764 patients were randomised to the CP arm and 764 patients were randomised to the CPB7.5+ arm. Disposition of study patients is illustrated in Figure 10.

Figure 10. Disposition of Patients: Study BO17707



[a] Withdrawn from at least one treatment component due to AE, violation of selection criteria at entry, withdrawal of consent, or administrative/other reasons
[b] Carboplatin and paclitaxel administered in the CP arm and carboplatin and paclitaxel with bevacizumab administered in the CPB7.5+ arm
[c] Bevacizumab administered alone in the CPB7.5+ arm only
[d] Two patients in the CP arm and one patient in the CPB7.5+ arm had death as the reason for withdrawal on the CRF.

Recruitment

The study period was from 18 December 2006 to 28 February 2010. A total of 1528 patients were enrolled at 263 centres in 8 European countries (Denmark, Finland, Germany, U.K., France, Norway, Sweden and Spain) and 3 non-European countries (Canada, Australia and New Zealand).

Conduct of the study

The protocol was finalized in June 2006 and amended four times. The major changes were the modification of the inclusion criteria to allow enrolment of inoperable stage III patients, for whom de-bulking surgery was not foreseen prior to disease progression, and the increase of the maximum time allowed between surgery and study treatment start from 6 to 8 weeks.

Baseline data

The baseline demographic data are presented in Table 15.

Table 15. Summary of Baseline Demographic Data: Randomised Population

	CP (N = 764)	CPB7.5+ (N = 764)
Race		
White	737 (96%)	730 (96%)
Asian	17 (2%)	22 (3%)
Black or African American	2 (<1%)	10 (1%)
Other	8 (1%)	2 (<1%)
Unknown	0	0
Age in years		
Mean (SD)	56.7 (10.6)	56.5 (10.4)
Median	57.0	57.0
Range	18 - 81	24 - 82
n	764	764
Weight in kg		
Mean (SD)	65.4 (13.9)	65.5 (13.4)
Median	63.0	63.6
Range	38.0 - 130.9	41.0 - 135.0
n	764	763
Height in cm		
Mean (SD)	162.8 (6.5)	163.1 (6.8)
Median	163.0	163.0
Range	143 - 183	144 - 185
n	764	764
CP = carboplatin + paclitaxel up to 6 cycles; CPB7.5+ = carboplatin + paclitaxel up to 6 cycles + bevacizumab (7.5 mg/kg q3w) up to 18cycles; CPB15+ = carboplatin + paclitaxel up to 6 cycles + concurrent and extended bevacizumab (15 mg/kg q3w) up to 21 cycles.		

Baseline disease characteristics are presented in Table 16.

Table 16: Summary of baseline disease characteristics study BO17707

	CP (N = 764)	**CPB7.5+ (N = 764)**
Performance Status [a]		
0	333 (44%)	307 (41%)
1	375 (49%)	391 (52%)
2	54 (7%)	55 (7%)
n	762	753
FIGO Staging		
IA	16 (2%)	15 (2%)
IB	5 (<1%)	5 (<1%)
IC	44 (6%)	34 (4%)
IIA	10 (1%)	13 (2%)
IIB	30 (4%)	21 (3%)
IIC	40 (5%)	49 (6%)
IIIA	32 (4%)	22 (3%)
IIIB	44 (6%)	45 (6%)
IIIC	432 (57%)	438 (57%)
III	14 (2%)	18 (2%)
IV	97 (13%)	104 (14%)
N	764	764
Primary Site of Cancer		
Ovary	667 (87%)	673 (88%)
Peritoneum	56 (7%)	50 (7%)
Fallopian tube	29 (4%)	27 (4%)
Ovary / fallopian tube	8 (1%)	7 (<1%)
Ovary / fallopian tube /peritoneum	0 (0%)	1 (<1%)

Ovary / peritoneum	4 (<1%)	6 (<1%)
N	764	764
Histologic Type		
Serous adenocarcinoma	529 (69%)	525 (69%)
Clear cell carcinoma	60 (8%)	67 (9%)
Endometrioid adenocarcinoma	57 (7%)	60 (8%)
Mucinous adenocarcinoma	15 (2%)	19 (2%)
Mixed epithelial carcinoma	48 (6%)	40 (5%)
Adenocarcinoma, unspecified	-	-
Other	55 (7%)	53 (7%)
n	764	764
Histologic Grade [b]		
1	56 (7%)	41 (5%)
2	142 (19%)	175 (23%)
3	556 (74%)	538 (71%)
Unknown	0 (0%)	0 (0%)
n	754	754

A greater proportion of patients in the CP arm (7%) were started on NPT prior to disease progression than in the CPB7.5+ arm (3%). The most common of these were surgical and medical procedures (CP: 2%; CPB7.5+: 1%). Antineoplastic therapy given following disease progression (i.e., second-line treatment) was reported in more patients in the CP arm (41%) than in the CPB7.5+ arm (33%). The most common therapies in both treatment arms were cytotoxic antibiotics and platinum compounds. Non-Protocol-Specified bevacizumab administration at any time prior to or post progressive disease was given to 11 (1%) of the patients in the CP arm and 3 (<1%) of the patients in the CPB7.5+ arm.

Numbers analysed

The number of patients included in each analysis population is summarised in Table 17.

Table 17. Summary of analysis population by trial treatment

	CP		CPB7.5+	
	Included	**Excluded**	**Included**	**Excluded**
No. of patients randomized = included in ITT	764		764	
No. of patients included in PPP	659		703	
Total no. of patients excluded from PPP		105		61
• No tumor assessment during treatment		56		27
• No baseline tumor assessment		14		12
Major Protocol Violations				
• Other anti-tumor therapy administered or debulking surgery performed prior to disease progression		32		26
• Failure to receive at least 3 cycles of study treatment (patients who progress or die before cycle 3 will be included in the per protocol analysis)		20		11
No. of patients included in SP	763		746	
• No. of patients excluded from SP (no study treatment received)		11		8
• No. of patients randomized to CP who received bevacizumab [a]		1	1	
• No. of patients randomized to CPB7.5+ who did not receive bevacizumab [a]	11			11

[a] See section 3.1.3

ITT = intent-to-treat; PPP = per protocol population; SP = safety population.

Outcomes and estimation

Primary endpoint

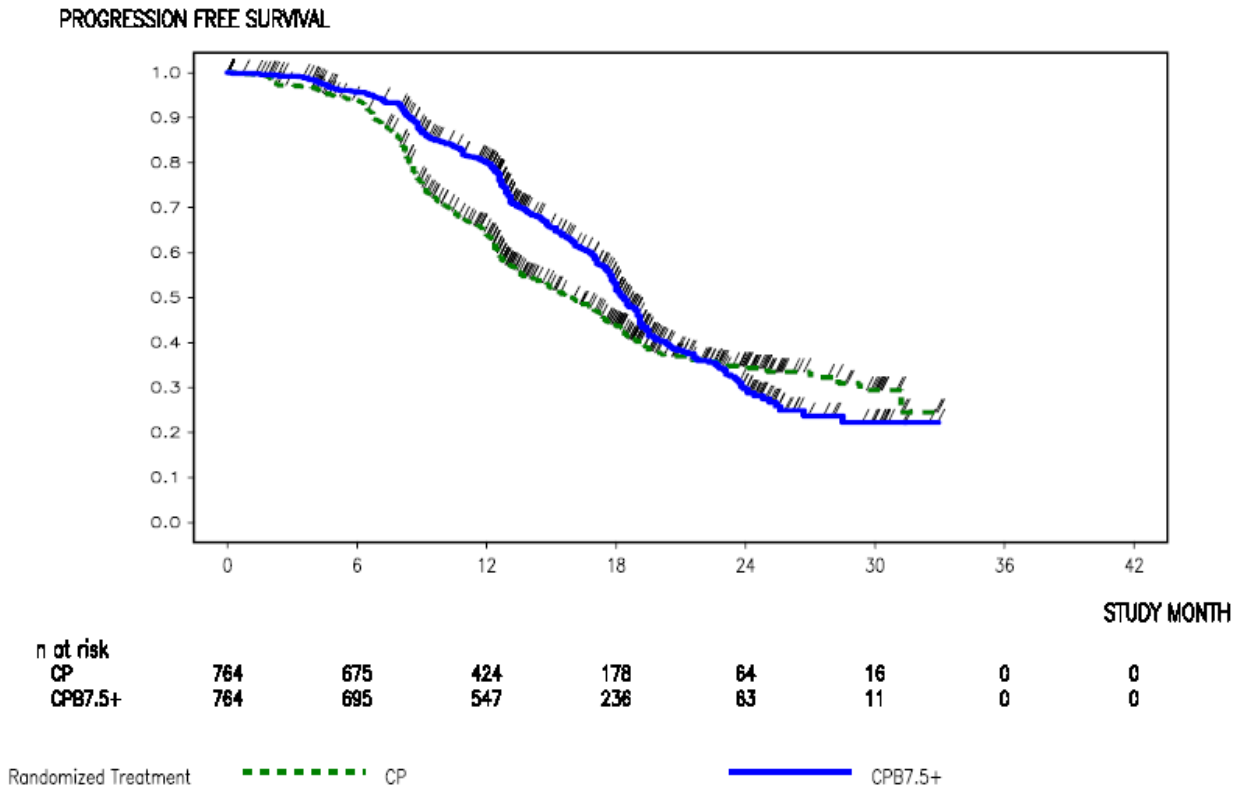
Progression Free Survival

At the time of the data cut-off (February, 2010), the median duration of follow up was 543 days (17.8 months; range 1 – 1059 days) in the CP arm and 557 days (18.3 months; range 1 - 1125 days) in the CPB7.5+ arm. The result of the primary analysis of PFS in study BO17707 is presented in Table 18, and the Kaplan Meier curve is presented in Figure 11.

Table 18. Primary Analysis of Investigator-Assessed Progression-Free Survival Study BO17707: Randomised Population

Progression-Free Survival [a]	**CP (N = 764)**	**CPB7.5+ (N = 764)**
Patients with events	392 (51.3%)	367 (48.0%)
Median - months	16.0	18.3
Hazard ratio (stratified) [b]	0.75	
95% CI	[0.65; 0.86]	
One-sided log-rank p-value	<0.0001	
Hazard ratio (unstratified)	0.79	
95% CI	[0.68; 0.91]	
One-sided log-rank p-value	0.0010	
CP = carboplatin + paclitaxel up to 6 cycles; CPB7.5+ = carboplatin + paclitaxel up to 6 cycles + bevacizumab (7.5 mg/kg q3w) up to 18 cycles.[a] Not censored for NPT and CA-125; b Relative to CP; NOTE: Primary analysis based on an unstratified log-rank test.		

Figure 11. Kaplan Meier Curve of Investigator-Assessed Progression-Free Survival: (Randomised Population)



The results of the updated analysis (cut-off date 30 November 2010) of PFS in study BO17707 are presented in Table 19.

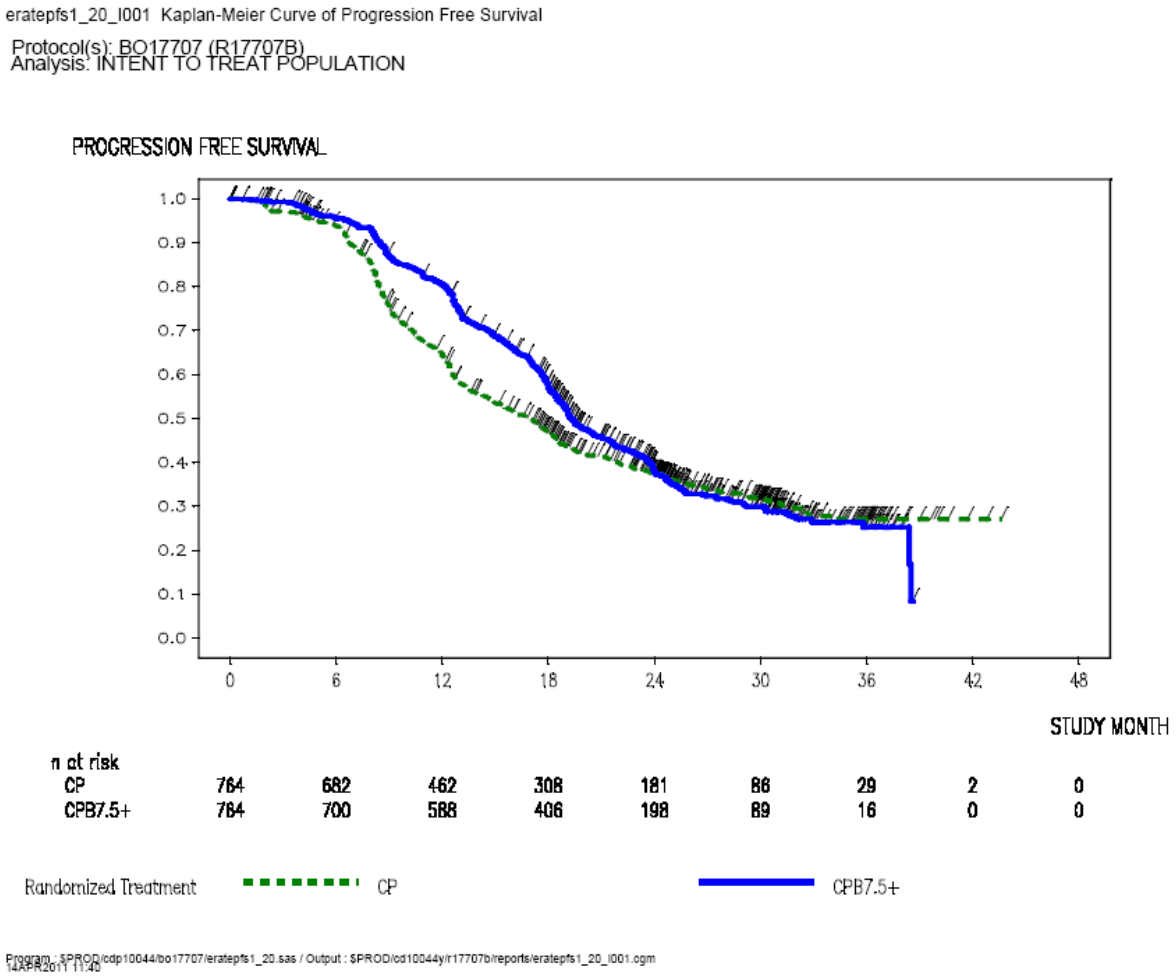
Table 19. Updated Analysis of Progression Free Survival (Study BO17707)

	CP (N=764)		CPB7.5+ (N=764)
Patients with event	464 (60.7 %)		470 (61.5 %)
Patients without events*	300 (39.3 %)		294 (38.5 %)
Time to event (months)			
Median#	16.9		19.3
95% CI for Median#	[14.9;18.2]		[18.7;20.6]
25% and 75%-ile	9.0;.		12.9;38.4
Range##	0.0 to 43.6		0.0 to 38.6
p-Value (Log-Rank Test)		0.0185	
Hazard Ratio		0.86	
95% CI		[0.75;0.98]	

Time to CSPFS [months] (TTMPFS) - Censoring: First Inv PD or Death (CSPFS)
* censored
# Kaplan-Meier estimate
including censored observations

The Kaplan Meier curve of PFS is presented in Figure 12.

Figure 12. Kaplan-Meier Curve of Progression Free Survival (Study BO17707: Updated Analysis)



- **<u>Sensitivity analyses of primary endpoint</u>**

A summary of the results of the various sensitivity analyses of PFS is presented in Table 20.

Table 20. Sensitivity Analysis of PFS

	CP (N = 764)	**CPB7.5+ (N = 764)**
Missing Assessment Analysis		
Patients with events	392 (51.3%)	367 (48.0%)
Median - months [a]	15.9	18.3
Hazard ratio (unstratified) [b]	0.80	
95% CI	[0.69; 0.92]	
One-sided log-rank p-value	0.0020	
Worst Case Analysis		
Patients with events	480 (62.8%)	426 (55.8%)
Median - months [a]	13.4	17.8
Hazard ratio (unstratified) [b]	0.76	
95% CI	[0.66; 0.86]	
One-sided log-rank p-value	<0.0001	
Analysis Before Start of NPT		

Patients with events	336 (44.0%)	339 (44.4%)
Median - months [a]	17.1	18.4
Hazard ratio (unstratified) [b]	0.85	
95% CI	[0.73; 0.99]	
One-sided log-rank p-value	0.0320	
CP = carboplatin + paclitaxel up to 6 cycles; CPB7.5+ = carboplatin + paclitaxel up to 6 cycles + bevacizumab mg/kg q3w) up to 18 cycles. NPT = non protocol antineoplastic therapy. [a] Kaplan-Meier estimates; [b] Relative to CP.		

- **PFS subgroup analyses by disease stage and debulking status**

The PFS subgroup analyses by disease stage and debulking status for study Study BO17707 is provided in Table 21. The cut-off date for this analysis is 30 November 2010.

Table 21. PFS Results by Disease Stage and Debulking Status from Study BO17707

Randomized patients stage III optimally debulked disease [1,2]		
	CP (n = 368)	CPB7.5+ (n = 383)
Median PFS (months)	17.7	19.3
Hazard ratio (95% CI) [3]		0.89 (0.74, 1.07)
Randomized patients with stage III suboptimally debulked disease[3]		
	CP (n = 154)	CPB7.5+ (n = 140)
Median PFS (months)	10.1	16.9
Hazard ratio (95% CI)[3]		0.67 (0.52, 0.87)
Randomized patients with stage IV disease		
	CP (n = 97)	CPB7.5+ (n = 104)
	CP (n = 97)	CPB7.5+ (n = 104)
Median PFS (months)	10.1	13.5
Hazard Ratio (95% CI)[3]		0.74 (0.55, 1.01)

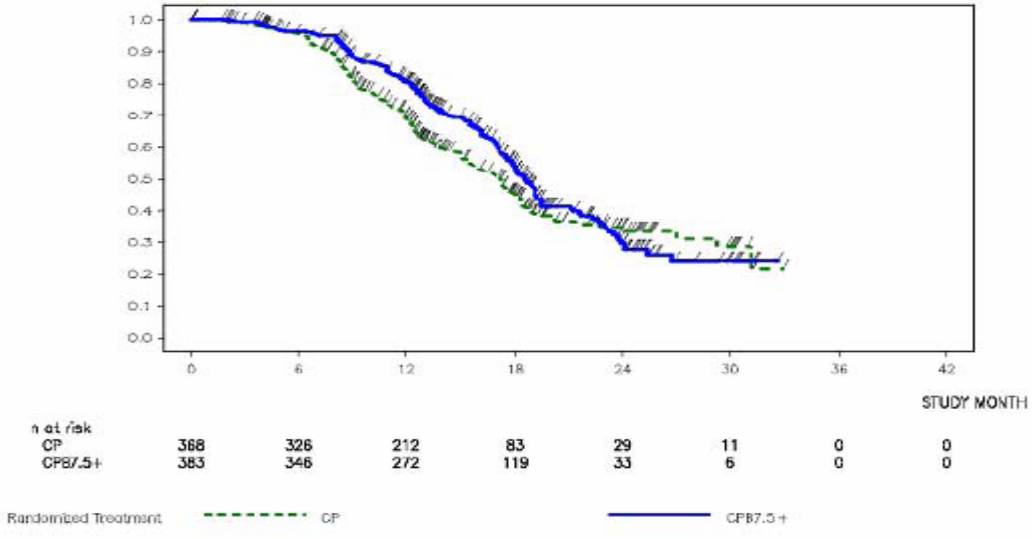
[1]With or without gross residual disease.

[2] 5.8% of the overall randomized patient population had Stage IIIB disease.

[3] Relative to the control arm.

The Kaplan – Meier curve is presented in Figure 13.

Figure 13. Kaplan-Meier Estimates of Progression-Free Survival by FIGO Stage III Optimally Debulked (Study BO17707)



- **Exploratory analyses**

An analysis of the possible impact of bevacizumab on the pattern of relapse or the timing of disease progression in patients who discontinued treatment due to an adverse event has been submitted by the MAH.
The results are presented in Table 22.

Table 22. Summary of Time from Discontinuation of Treatment due to an Adverse Event to Disease Progression or Death (Study BO17707: Updated PFS Analysis)

	CP (N=764)		CPB7.5+ (N=764)
Patients included in analysis	64 (100.0 %)		159 (100.0 %)
Patients with event	39 (60.9 %)		104 (65.4 %)
Patients without events*	25 (39.1 %)		55 (34.6 %)
Time to event (days)			
Median#	9.8		9.7
95% CI for Median#	[8.3;18.4]		[8.3;12.6]
25% and 75%-ile#	5.8;.		4.7;25.3
Range##	0.0 to 39.5		0.0 to 32.4
p-Value (Log-Rank Test)		0.4163	
Hazard Ratio		1.16	
95% CI		[0.81;1.68]	

Time to CSAEPFS [months] (TTMAEPFS) - Censoring: First Inv PD or Death (disc. due to AE) (CSAEPFS)
* censored
# Kaplan-Meier estimate
including censored observations

In addition, the MAH submitted a worst-case sensitivity analysis in study BO17707 in which all patients with early discontinuations were counted as having an event (table 23)

Table 23 Summary of Worst Case Analysis for Progression-Free Survival Accounting for Early Discontinuation (Study BO17707)

	CP (N=764)		CPB7.5+ (N=764)
Patients with event	400 (52.4 %)		403 (52.7 %)
Patients without events*	364 (47.6 %)		361 (47.3 %)
Time to event (months)			
Median#	15.7		18.0
95% CI for Median#	[14.1;17.3]		[17.3;18.5]
25% and 75%-ile	8.9;31.2		11.8;25.1
Range##	0.0 to 32.9		0.0 to 32.9
p-Value (Log-Rank Test)		0.0803	
Hazard Ratio		0.88	
95% CI		[0.77;1.02]	

Time to CSW2PFS [months] (TTMW2PFS) - Censoring: Worst case analysis PFS (Prem. Withdr.) (CSW2PFS)
* censored
# Kaplan-Meier estimate
including censored observations

Secondary endpoints

Overall Survival (OS)

The results of the original and the updated OS analysis are presented in Table 24.

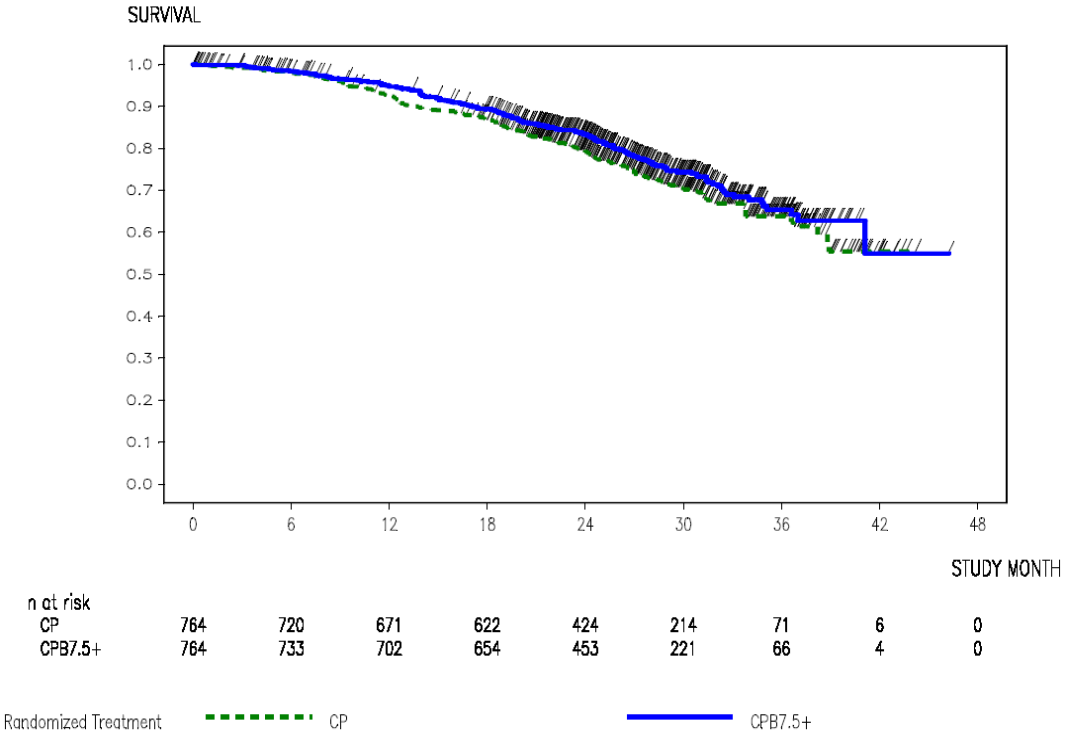
Table 24. Original and Updated Analyses of Overall Survival (Study BO17707)

Overall Survival	**BO17707 Original (CSR) Analysis**		**BO17707 Updated Analysis**	
	CP (N = 764)	**CPB7.5+ (N = 764)**	**CP (N = 764)**	**CPB7.5+ (N = 764)**
No. (%) patients who died	130 (17.0%)	111 (14.5%)	200 (26.2%)	178 (23.3%)
Median survival time – months [95% CI]	NR [NE; NE]	35.1 [32.6; NE]	NR [38.9; NE]	NR [41.1; NE]
Unstratified analysis				
Hazard ratio relative to CP [95% CI]		0.81 [0.63; 1.04]		0.85 [0.70; 1.04]
One-sided log-rank p-value		0.0987		0.1167

CP = carboplatin + paclitaxel up to 6 cycles; CPB7.5+ = CP + bevacizumab (7.5 mg/kg q3w) up to 18 cycles; CPP = carboplatin + paclitaxel up to 6 cycles + concurrent and extended placebo up to 21 cycles; NE = not estimated; NR = not reached.

The Kaplan Meier curve is presented in Figure 14.

Figure 14. Kaplan-Meier Estimate of Overall Survival (Study BO17707: Updated Analysis)



Objective Response Rate (ORR)

A summary of best overall response is presented in Table 25.

Table 25. Summary of Extended Best Overall Response (RECIST) (Study BO17707)

	CP (N=277)		CPB7.5+ (N=272)
Responders$	152 (54.9 %)		176 (64.7 %)
Non-Responders	125 (45.1 %)		96 (35.3 %)
95% CI for Response Rates*	[48.8; 60.8]		[58.7; 70.4]
Difference in Response Rates		9.83	
95% CI for Difference in Response Rates#		[1.5; 18.2]	
p-Value (Chi-squared Test)		0.0188	
Complete Response (CR)	38 (13.7 %)		42 (15.4 %)
95% CI for CR Rates*	[9.9; 18.3]		[11.4; 20.3]
Partial Response (PR)	114 (41.2 %)		134 (49.3 %)
95% CI for PR Rates*	[35.3; 47.2]		[43.2; 55.4]
Stable Disease (SD)	81 (29.2 %)		72 (26.5 %)
95% CI for SD Rates*	[24.0; 35.0]		[21.3; 32.1]
Progressive Disease (PD)	22 (7.9 %)		9 (3.3 %)
95% CI for PD Rates*	[5.0; 11.8]		[1.5; 6.2]
Missing (No Response Assessment)	22 (7.9 %)		15 (5.5 %)

* 95% CI for one sample binomial using Pearson-Clopper method
\# Approximate 95% CI for difference of two rates using Hauck-Anderson method
$ Patients with best overall response of confirmed CR or PR

Duration of ORR

In patients with a confirmed CR or PR by RECIST criteria, the median time between first documentation of the response and disease progression or death was longer in the CPB7.5+ arm (12.4 months) compared to the CP arm (10.6 months) (table 26).

Table 26. Duration of Objective Response: Study BO17707 (Randomised Population)

Duration of Objective Response	CP (N = 277)	CPB7.5+ (N = 272)
RECIST Responders		
Median - months [a]	10.6	12.4
95% CI for median	[9.5; 15.8]	[11.3; 13.6]
Hazard ratio	1.02	
95% CI	[0.79; 1.39]	
Log-rank p-value	0.9043	

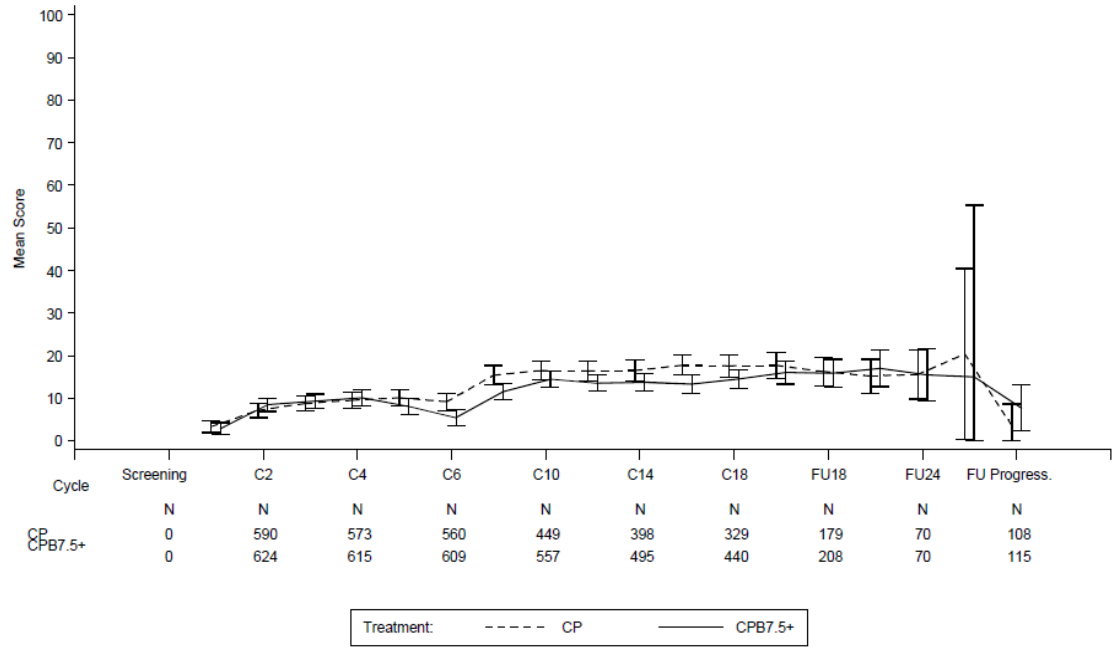
CP = carboplatin + paclitaxel up to 6 cycles; CPB7.5+ = carboplatin + paclitaxel up to 6 cycles + bevacizumab (7.5 mg/kg q3w) up to 18 cycles. [a] Kaplan-Meier estimate.

Quality of Life (QoL)

EORTC QLQ-C30:

Figure 15 illustrates the change from baseline of the global health status/QoL over time (cycles [C1-18], follow-up [15-24 months] and after progression.

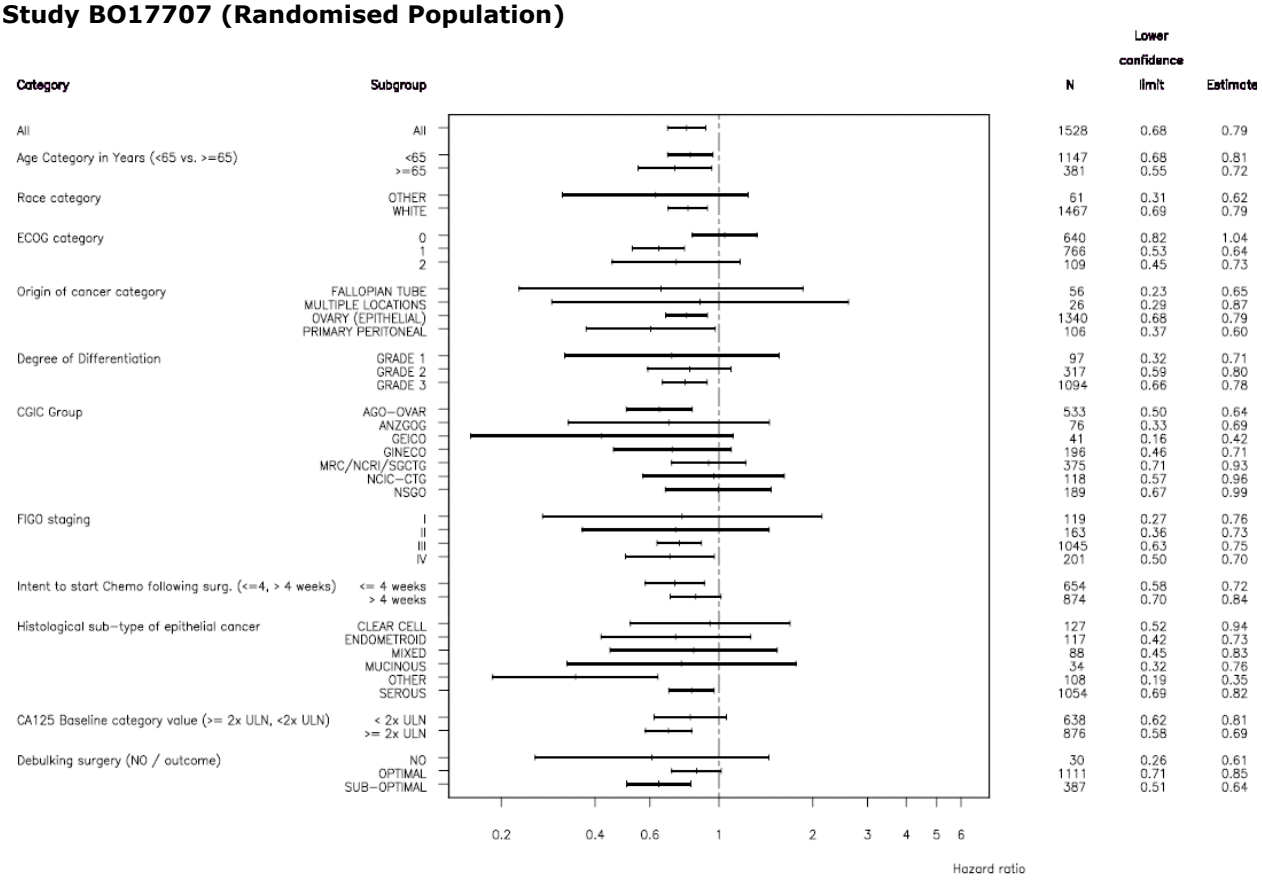
Figure 15. Change in Mean Global Health Status Score QoL From Screening with 95% Confidence Interval Over Time (EORTC QLQ C-30)



The limits of 95% CI are truncated at 0 and 100 if they extend beyond those values

- Subgroup analyses in study BO1717707
  Although many of the subgroups included relatively few patients, the results of each of the analyses of PFS were generally consistent with the results of the primary analysis of all patients (Figure 16).

Figure 16. Forest Plot of Hazard Ratio for Progression-Free Survival by Subgroup: Study BO17707 (Randomised Population)



- Cox Regression Analysis of PFS

An exploratory multiple Cox regression analysis was performed in Study BO17707 with various pre-defined prognostic factors, i.e. treatment and all prognostic factors were included in one model. The stratification factors were also added to the model in the unstratified analysis.

The results showed a statistically significant treatment effect with respect to PFS in favour of the CPB7.5+ arm (HR 0.70; $p < 0.0001$). Significant prognostic factors for PFS were ECOG performance status at baseline (ECOG 1 vs. 0: p=0.0006, ECOG 2 vs. 0: p=0.0001), degree of differentiation (Grade 2 vs. 1: p=0.0079, Grade 3 vs. 1: p=0.0113), FIGO stage and outcome of surgery (FIGO Stage I-III suboptimally debulked vs. Stage I-III optimally debulked: $p < 0.0001$, FIGO Stage IV and inoperable Stage III vs. Stage I-III optimally debulked: $p < 0.0001$), origin of cancer (PPC vs. EOC: p=0.0012), histological sub-type (mucinous vs. serous: $p < 0.0001$) and CA-125 at baseline (≥ 2 x ULN vs. < 2 x ULN, $p < 0.0001$).

Analysis performed across trials (pooled analyses and meta-analysis)

N/A

Clinical studies in special populations

No studies in special populations were submitted.

3.4.3. Discussion on clinical efficacy

Study GOG-0218

Overall the demographic characteristics were well balanced between the three treatment arms. The majority of the patients in all study arms were White (app. 87%), mean age was 65.9-71.6 years, and median body weight was 66.8-68.0 kg.

Baseline disease characteristics were well balanced across the three treatment arms. Study GOG-0218 enrolled patients with optimal (macroscopic) or sub-optimal FIGO stage III or IV EOC, FTC or PPC. The majority of the patients in all arms had Stage III suboptimal debulked disease. The primary site of cancer was the ovary. The majority of patients in all arms had serous adenocarcinoma histologic type. Most patients (73.6% - 75.6%) had poorly differentiated tumours (Grade 3).

Protocol violations were overall equally distributed among treatment arms at relative low numbers. It is considered unlikely that these protocol violations should have threatened the overall integrity of the study.

The CHMP acknowledged that the reliability of CA-125 to determine progression is controversial. Although widely used in clinical practice, there is evidence that initiation of therapy solely based on CA-125 elevations has not resulted in improved OS benefits. This may indicate that frequent controls of CA-125 are not deemed necessary in this palliative setting. However, CA-125 is still considered the most reliable tumour marker with a sensitivity of 85% (all stages) and CA-125 measurements continue to play an important role in the monitoring of patients with ovarian cancer, although limitations exist which should be kept in mind. In GOG-0218 study, criteria for progression based on rising serum CA-125 levels in the absence of clinical or radiographic evidence of progression were given.

Based on the SAP-specified primary analysis of INV-based PFS, patients who progressed solely based on rising CA-125 levels were censored at the last tumour assessment.

Likewise, patients who received NPT for ovarian cancer prior to documented disease progression were censored at the last tumour assessment. These censoring rules may lead to some degree of bias as these biochemical CA-125-progressions will often precede clinical/radiographic progressions ("informed censorings").

Therefore, the GOG-specified sensitivity analysis of INV-based PFS in which CA-125 progressions were also counted as events is considered a more conservative and reliable estimate of the true treatment effect of bevacizumab in the first-line setting of ovarian cancer. It is possible that this analysis may slightly underestimate the true treatment effect of bevacizumab as some of these CA-125 elevations may not precede true disease progressions but rather represent the result of an unclear interaction between CA-125 and bevacizumab. Therefore, the CHMP recommended that the MAH investigates this potential interaction. This analysis is not expected to change the observed benefits as conservative efficacy estimates already were calculated on this basis.

In the updated analysis not censored for CA-125 elevations or NPT, a total of 1252 PFS events had been recorded at the time of data cut-off: 440 (70.4%) in the CPP arm, 435 (69.6%) in the CPB15 arm and 377 (60.5%) in the CPB15+ arm. In the CPB15+ arm, the HR indicated a reduction of 30% in the risk of progression or death compared to the CPP arm (stratified HR 0.70, p-value <0.0001). The median time to progression or death was longer in the CPB15+ arm (14.7 months) compared with the CPP arm (10.6 months). The gain in PFS observed in the updated analysis gives indications of a clinically relevant benefit of the front-line therapy with bevacizumab.

Overall, subgroup analyses of the SAP-defined INV-based PFS assessment demonstrated consistent results, also in patients with poor prognostic factors such as poorer PS, old age, clear cell tumours, poorly differentiated tumours and stage IV disease.

In addition, the results of the PFS analysis for patients with optimally debulked disease for study GOG-0218 (protocol-specified analysis without censoring for CA-125 or NPT) provided reassurance that the results seen in this subgroup analysis are consistent with the PFS analysis in the overall patient population in study GOG-218.

The MAH has submitted exploratory analyses of relapse patterns and of the time between treatment discontinuation due to an AE and disease progression. The median duration of time between discontinuation and progressive disease was the same (8.3 months) in all treatment arms so there was no indication of a rebound effect in the bevacizumab arms. Therefore there is no indication that bevacizumab impacts the pattern of relapse or the timing of disease progression in patients who discontinued treatment due to an adverse event.

The updated OS data set was still not completely mature, with 36% deaths observed. The HR for OS was consistent with previous estimates [0.90 (95% CI: 0.74 – 1.08; p= 0.1253)]. The median OS was 43.4 months in the CPB15+ arm vs. 39.4 months in the CPP. Based on these results, it was possible to conclude that no detrimental effect on OS in patients treated with the CPB15+ regimen was expected, in line with the recommendations provided in the CHMP Guideline on the Evaluation of Anticancer Medicinal Products for Human Use about supportive data on OS when PFS is the primary endpoint.

Furthermore, the MAH has submitted an update of later lines of therapies in both studies. Based on these results, the majority of patients received chemotherapies as secondary or tertiary treatments. In GOG-0218, 67.7% of patients in the CPP arm received chemotherapy vs. 60.5% in the CPB15+ arm. Commercially available Avastin was given to 20.2% in the CPP arm and bevacizumab was continued in 12.2% of patients in the CPB15+ after disease progression. This may confound OS results and limit the interpretability of further follow-up data. Nevertheless, further follow-up is needed to further clarify the benefit-risk of the product and the MAH will be requested to provide this analysis by 31/03/2012 (see Annex II of the PI).

Regarding QoL, although small improvements were observed in favour of the CPB15+ arm, no clinically meaningful differences were observed between treatment arms.

Based on the overview of the ongoing activities in the search of a predictive biomarker for bevacizumab the CHMP requested the MAH to submit the results from the GOG-218 study on the correlation of plasma markers for VEGF-A with PFS and OS analyses in order to be identified whether VEGF-A is of predictive value for the activity of bevacizumab, and refine the understanding on the benefit-risk balance of the product in different subpopulations.

In reply to the CHMP request the MAH committed to submit the plasma biomarker results for VEGF-A from study GOG-218 with PFS and OS analyses by 31/06/2012 (see Annex II of the PI).

Study BO17707

The key demographic characteristics were similar between the treatment arms. The majority of patients were White (96%) and the median age was app. 57.0 years; median body weight was app. 65 kg.

Disease characteristics were equally distributed across the two treatment arms. Approximately 18% of patients enrolled in each study arm in BO17707 had an early Stage of disease at baseline (FIGO stage IA-IIC). However, the majority of patients had Stage IIIC disease (57%) whereas the proportion of patients with stage IV disease only represented 14%. This number was higher in study GOG-0218 (approximately 25%). The primary site of cancer was the ovary (87-88%) and most tumours were serous adenocarcinomas (69%) with poor differentiation (Grade 3: 71-74%).

In general, patients should already have undergone surgical debulking with the aim of maximal surgical cytoreduction before enrolment. With amendment 3, inclusion of patients with inoperable disease in whom initial surgical debulking was not appropriate was allowed provided that the patient had a histological diagnosis and debulking surgery prior to disease progression was not foreseen. These amendments are considered acceptable.

In the updated analysis of PFS, the hazard ratio indicated a 14% reduction in the risk of progression or death in the CPB7.5+ arm compared with the CP arm. Median time to progression or death was longer in the CPB7.5+ arm (19.3 months) compared with the CP arm (16.9 months), translating into a gain in median PFS of 2.4 months.

Furthermore, the results of the PFS analysis for patients with optimally debulked disease in study Study BO17707 demonstrated robustness of the primary analysis of PFS. In response to the concerns expressed by the CHMP, the MAH has furthermore, provided information on the proportion of patients with progression or death at three month intervals for the original PFS analysis, and described the Kaplan-Meier curves in more detail. From the data provided, event rates decreased in both treatment arms over time which does not support the idea of accelerated disease progression upon treatment discontinuation.

In addition, the MAH submitted a worst-case sensitivity analysis in study BO17707 in which all patients with early discontinuations were counted as having an event. This confirmed the result of the primary analysis although the outcome was slightly less favourable as expected from this very conservative estimate.

The MAH has submitted the results of exploratory analyses of relapse patterns and of the time between treatment discontinuation due to an AE and disease progression. In an updated analysis the median time between discontinuation of chemotherapy due to AEs and disease progression was 9.8 months in the CP arm vs. 9.7 months in the CPB7.5+ arm.

In conclusion, these data do not indicate a negative impact of bevacizumab on the pattern of relapse or the timing of disease progression in the subset of patients who discontinued treatment due to AEs.

At the time of the updated OS analysis, only 24% of patients had died. A consistent OS result was observed compared to the original analysis: HR for OS was 0.85 (p= 0.1167). The updated OS analysis allows excluding a detrimental effect of bevacizumab on OS in line with the recommendations provided in the CHMP Guideline on the Evaluation of Anticancer Medicinal Products for Human Use about supportive data on OS when PFS is the primary endpoint. Study BO17707 has a prespecified final analysis for overall survival to be conducted when 715 deaths will have occurred in the study according to the protocol. Further follow-up is needed to further clarify the benefit-risk of the product and the MAH is requested to provide this analysis by 31/12/2013 (see Annex II of the PI).

Overall, there were no documented differences in QoL between treatment arms apart from the results in one EORTC QLQ-OV28 subscale indicating that patients in the CPB7.5+ arm experienced a greater extent of "chemotherapy side effects".

The CHMP expressed their concern regarding the limited evidence of a clinically relevant benefit at an acceptable toxicity level for patients with early high risk stages of EOC at the proposed dosage. As a result, the CHMP excluded this patient population from the indication and included patients with advanced (FIGO stages III B, III C and IV) ovarian cancer. The recommendation on dose and duration of treatment for patients with advanced disease remained the same.

The MAH has submitted an overview of the ongoing activities in the search of a predictive biomarker for bevacizumab. The MAH is expected to submit the plasma biomarker results for VEGF-A from study BO17707 with PFS analysis by 31/06/2012 (see Annex II).

3.4 Conclusions on the clinical efficacy

The CHMP considered that both studies GOG-0218 and BO17707 provide robust evidence for clinically significant effects of front-line bevacizumab treatment either only concurrently with carboplatin and paclitaxel or concurrently with carboplatin and paclitaxel followed by extended bevacizumab treatment, in women with newly diagnosed previously untreated, Stage IIIB, IIIC and IV ovarian cancer.

The CHMP has requested the following obligations to be included as conditions in Annex II:

- To submit results from the pre-specified final analysis for Overall Survival from study BO17707 by 31/12/2013.

- To submit final OS data from study GOG-0218 by 31/03/2012.

- To submit results from the plasma biomarker for VEGF-A from study BO17707 with PFS analysis as well as the results from the GOG-218 study on the correlation of plasma markers for VEGF-A with PFS and OS analyses by 31/06/2012.

3.5. Clinical safety

The cut-off date for safety data in study GOG-0218 was February 5, 2010. The primary safety analysis in study GOG-0218 was performed on the safety-evaluable population (N = 1816), which comprised all randomised patients who received at least one full or partial dose of any study treatment during Cycle 2 or later. The cut-off date for safety data in study BO17707 was February 28, 2010. The safety analysis population in study BO17707 comprised all patients exposed to study drug (N = 1509).

Patient exposure

The extent of exposure to chemotherapy and bevacizumab/placebo in studies GOG-0218 and BO17707 is summarized in Table 27.

Table 27. Studies GOG-0218 and BO17707: Extent of Exposure to Study Treatment (Safety Population)

	GOG-0218			BO17707	
	CPP (n=601)	CPB15 (n=607)	CPB15+ (n=608)	CP (n=763)	CPB7.5+ (n=746)
Total number of carboplatin cycles					
n	601	607	608	760	746
Mean(SD)	5.8 (0.7)	5.8 (0.8)	5.7 (0.8)	5.8 (0.9)	5.9 (0.6)
Median	6.0	6.0	6.0	6.0	6.0
Range	2 - 7	2 - 9	2 - 7	1 - 6	1 - 6
25th-75th %ile	6 - 6	6 - 6	6 - 6	6 - 6	6 - 6
Total number of paclitaxel cycles					
n	597	594	600	761	746
Mean(SD)	5.7 (1.0)	5.7 (1.1)	5.6 (1.0)	5.6 (1.1)	5.7 (1.0)
Median	6.0	6.0	6.0	6.0	6.0
Range	1 - 7	1 - 9	1 - 7	1 - 6	1 - 6
25th-75th %ile	6 - 6	6 - 6	6 - 6	6 - 6	6 - 6
Total number of docetaxel cycles					
n	32	36	34		
Mean(SD)	3.3 (2.0)	3.9 (2.1)	3.0 (1.9)		
Median	3.0	4.5	3.0		
Range	1 - 6	1 - 6	1 - 6		
25th-75th %ile	1 - 5	2 - 6	1 - 4		
Duration of BV/placebo (months)					
n	591	593	592		746
Mean(SD)	8.1 (4.4)	8.1 (4.6)	8.8 (5.0)		9.6 (3.7)
Median	7.7	8.1	9.0		11.6
Range	0 - 19	0 - 17	0 - 19		0 - 16
25th-75th %ile	5 - 12	5 - 12	5 - 14		8 - 12
Total number of BV/placebo cycles					
n	591	593	592		746
Mean(SD)	11.8 (6.1)	11.9 (6.4)	12.7 (6.7)		14.1 (5.1)
Median	11.0	12.0	13.0		17.0
Range	1 - 21	1 - 22	1 - 21		1 - 18
25th-75th %ile	7 - 17	7 - 17	7 - 20		12 - 18

BV = bevacizumab; CP = carboplatin + paclitaxel; CPP = CP + up to 21 cycles of placebo; CPB15 = CP + up to 5 cycles of BV 15 mg/kg + up to 16 cycles of placebo; CPB15+ = CP + up to 21 cycles of BV 15 mg/kg; CPB7.5+ = CP + up to 18 cycles of BV 7.5 mg/kg; SD = standard deviation.
Per protocol, docetaxel may be substituted for paclitaxel in GOG-0218 and may not be substituted for paclitaxel in BO17707.
Duration of BV/placebo was calculated as last BV/placebo dose date minus first BV/placebo dose date in BO17707 and last BV/placebo dose date minus first BV/placebo dose date plus 1 in GOG-0218

Adverse events

An overview of adverse events in studies GOG-0218 and BO17707 is presented below:

Table 28. Studies GOG-0218 and BO17707: Overview of AEs (Safety Population)

Parameter	GOG-0218			BO17707	
	CPP N = 601	CPB15 N = 607	CPB15+ N = 608	CP N = 763	CPB7.5+ N = 746
No. of patients (%) with any adverse event (any grade)[a]	600 (99.8)	607 (100.0)	607 (99.8)	755 (99.0)	746 (100.0)
Grade 3–5 adverse events – with lab data[b]	559 (93.0)	577 (95.1)	574 (94.4)		
– without lab data[b]	274 (45.6)	307 (50.6)	337 (55.4)	414 (54.3)	482 (64.6)
adverse events leading to death (Grade 5 AEs)	4 (0.7)	9 (1.5)	14 (2.3)	7 (0.9)	4 (0.5)
any serious adverse events/NCI AdEERS[c]	128 (21.3)	144 (23.7)	157 (25.8)	179 (23.5)	281 (37.7)
AEs leading to discontinuation of study treatment[d]	58 (9.7)	83 (13.7)	100 (16.4)	68 (8.9)	164 (22.0)
All deaths	145 (24.1)	148 (24.4)	131 (21.5)	131 (17.2)	107 (14.3)

All events were graded according to NCI-CTCAE v3.0. Maximum severity was selected for each event for each patient. AE: adverse event.

The most common adverse events in both studies occurred in the system organ classes gastrointestinal disorders (abdominal pain, constipation, diarrhoea, nausea, vomiting), nervous system disorders (headache, peripheral sensory neuropathy), general disorders and administration site conditions (fatigue), skin and subcutaneous tissue disorders (alopecia), and musculoskeletal and connective tissue disorders (myalgia).

The majority of patients in study GOG-0218 reported Grade 4 events (range 60.9%–66.0% across treatment groups) whereas the majority of patients in study BO17707 reported Grade 3 events (range 45.2–54.6% across treatment groups). The number of patients who experienced an adverse event leading to death (Grade 5 AEs) was 27 patients in GOG-0218 and 11 patients in study BO17707.

- Adverse events of special interest

Adverse events of special interest are summarised in the following table:

Table 29. Studies GOG-0218 and BO17707: AEs of special interest (Safety Population)

Parameter	GOG-0218			BO17707	
	CPP N = 601	CPB15 N = 607	CPB15+ N = 608	CP N = 763	CPB7.5+ N = 746
No. of patients (%) with an AE of special interest (AESI)[e]	585 (97.3)	592 (97.5)	591 (97.2)	362 (47.4)	552 (74.0)
arterial thromboembolic events	14 (2.3)	19 (3.1)	19 (3.1)	12 (1.6)	26 (3.5)
bleeding (CNS)	0 (0.0)	0 (0.0)	3 (0.5)	0 (0.0)	3 (0.4)
bleeding (non-CNS)	96 (16.0)	216 (35.6)	223 (36.7)	84 (11.0)	294 (39.4)
congestive heart failure	0 (0.0)	0 (0.0)	3 (0.5)	3 (0.4)	3 (0.4)
febrile neutropenia	21 (3.5)	31 (5.1)	27 (4.4)	15 (2.0)	21 (2.8)
fistulae and abscesses	7 (1.2)	5 (0.8)	12 (2.0)	9 (1.2)	13 (1.7)
gastrointestinal perforation	2 (0.3)	11 (1.8)	12 (2.0)	3 (0.4)	10 (1.3)
hypertension	81 (13.5)	143 (23.6)	196 (32.2)	49 (6.4)	191 (25.6)
neutropenia–neutrophil count decreased[f]	574 (95.5)	577 (95.1)	577 (94.9)	8 (1.0)	13 (1.7)
neutropenia term[f]	40 (6.7)	52 (8.6)	51 (8.4)	211 (27.7)	199 (26.7)
proteinuria	39 (6.5)	32 (5.3)	51 (8.4)	17 (2.2)	33 (4.4)
reversible posterior leukoencephalopathy syndrome	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
venous thromboembolic events	24 (4.0)	21 (3.5)	25 (4.1)	34 (4.5)	51 (6.8)
wound-healing complications	27 (4.5)	29 (4.8)	22 (3.6)	12 (1.6)	34 (4.6)

All events were graded according to NCI-CTCAE v3.0. Maximum severity was selected for each event for each patient. AE: adverse event.

The proportion of patients with any AE of special interest was similar across the three treatment arms of GOG-0218, but in BO17707 was higher in the CPB7.5+ arm than in the CP arm.

The proportion of patients with AESIs in GOG-0218 CPB15+ arm was higher than in the BO17707 CPB7.5+ arm (97.2% vs. 74.0%); the difference is mainly accounted for by neutropenia (95.4% vs. 28.3%) and is due to the differences in the collection of laboratory parameters and hence reporting of AEs between the studies. There were also small differences between the studies in the proportion of patients in the bevacizumab arms with hypertension.

Arterial Thromboembolic Events

The incidence of arterial thromboembolic events was higher in the bevacizumab-containing treatment arms than in the respective control arms across both studies. The incidence of events was higher after the chemotherapy treatment than during chemotherapy. The majority of events were Grade ≥ 3 in severity. In GOG-0218 the two grade 5 events were in the bevacizumab treatment arms. In BO17707, one grade 5 event occurred in the control arm and two in the bevacizumab arm.

In both studies, adverse events with a MedDRA preferred term of "embolism" without further qualification or characterization by the investigator were categorized as arterial thromboembolic events according to the standard coding practices of the sponsors. Medical review found that 35 of the 52 arterial thromboembolic events in study GOG-0218, and 13 of the 38 arterial thromboembolic events in study BO17707 reported as "embolism" were venous thromboembolic events.

Bleeding (CNS and Non CNS)

The incidence of all bleeding events in both studies was higher in all bevacizumab arms compared with the respective control arms. The majority of bleeding events in both studies were non-CNS bleeding events (in particular, epistaxis), and the majority of those events were Grade 1 or 2 in severity. CNS bleeding events were reported for three patients in each study. Most events were reported during the chemotherapy treatment phase.

Congestive Heart Failure (CHF)

In study GOG-0218, CHF events were reported only in the CPB15+ arm (3 patients, 0.5%), all of whom experienced Grade 3 left ventricular systolic dysfunction during the period from Cycle 2 to the start of Cycle 7. One of these patients also reported Grade 3 cardiomyopathy. In study BO17707, three patients in each arm experienced CHF events.

Febrile Neutropenia

In study GOG-0218, the incidence of febrile neutropenia in the two bevacizumab-containing treatment arms was higher than that in the CPP arm. All events of febrile neutropenia were either Grade 3 or 4 in severity. All events were reported prior to Cycle 7. In study BO17707, the incidence of febrile neutropenia was higher in the CPB7.5+ arm than the CP arm. Most febrile neutropenia events were Grade 3 or 4 in severity.

Fistula/Abscess

Overall incidence rates of fistulae and abscesses were similar across both studies, with a higher incidence of events recorded in both extended bevacizumab treatment arms. There were no Grade 5 fistulae or abscesses in either study.

Gastrointestinal Perforation

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 GI perforations leading to death.

The majority of GI perforations (any grade) reported in study GOG-0218 occurred prior to Cycle 7, with the exception of two patients in the CPB15+ arm who experienced large-intestine perforations after Cycle 7. The longer course of bevacizumab treatment did not appear to lead to an increased incidence of GI perforations compared to the shorter course of bevacizumab treatment. The majority of GI perforations were Grade ≥ 3 events. Six patients experienced large-intestine perforations leading to death: 4 patients in the CPB15 arm, and 2 patients in the CPB15+ arm. No Grade 4 or 5 GI perforations were reported for patients in the CPP arm. All fatal events occurred prior to Cycle 7.

In study BO17707, all GI perforations were Grade ≥ 3 events and most occurred after the chemotherapy phase. One patient in the CPB7.5+ arm had an intestinal perforation that resulted in death. An additional patient in the CPB7.5+ arm experienced a serious adverse event of "abdominal pain" which led to death, but the cause of death was recorded as "gastrointestinal perforation". This patient does not appear under GI perforations in any summary tables of adverse events. There were no Grade 5 GI perforations reported for patients in the control arm. In BO17707, there were no GI perforation events in patients with early stage (FIGO I and FIGO II) disease.

Overall the incidence rates of GI perforation were within the known safety profile of the drug: up to 2% across all labelled indication within the current product information.

Hypertension

In study GOG-0218, a higher incidence of hypertension was observed in the bevacizumab-containing treatment arms compared with the CPP arm. During the period from Cycle 2 to the start of Cycle 7, the proportions of patients reporting hypertension events was comparable in the two bevacizumab treatment arms and higher than the control arm. During the period from Cycle 7 onwards, patients in the CPB15+ arm had a higher incidence of hypertension. The majority of events were Grade 1 or 2 events.

In study BO17707, more patients in the CPB7.5+ arm experienced hypertension events compared with the CP arm. The numbers of patients reporting hypertension events was similar during and after the chemotherapy phase. The majority of hypertension events were Grade 1 or 2.

There were no Grade 5 hypertension events in either study.

Neutropenia

The rate of neutropenia was higher in the GOG-0218 study compared to the BO17707 study due to the methods of data. In GOG grade ≥ 3 laboratory values were recorded as AEs regardless of whether the investigator considered them clinically relevant.

In study GOG-0218, the majority of patients experienced an adverse event of decreased neutrophil count, the incidence rate of which was similar across all three treatment groups. More patients reported neutropenia during the chemotherapy phase than in the period from Cycle 7 onwards. The majority of events were Grade ≥ 3 events.

The incidence of adverse events reported as "neutropenia" in GOG-0218 separate from the grading of laboratory values was higher in the bevacizumab-containing treatment arms (CPB15: 8.6%; CPB15+: 8.4%) than in the control arm (CPP: 6.7%). One patient in the CPB15 arm and three patients in the CPB15+ arm had adverse events of neutropenia leading to death which occurred during the period from Cycle 2 to the start of Cycle 7. There were no Grade 5 neutropenia events in the CPP arm.

In study BO17707, the overall incidence of adverse events reported as neutropenia was essentially the same in both arms (CP 28.7% and CPB7.5+ 28.3%) consistent with that seen in other studies with bevacizumab across indications. Most events occurred during the chemotherapy phase and there were no Grade 5 neutropenia events in either study arm.

The incidence of adverse events reported as neutropenia cannot be compared between the GOG-0218 and BO17707 studies because of the differences in data collections.

Proteinuria

In study GOG-0218, the highest incidence of proteinuria was observed in the CPB15+ treatment arm and the lowest incidence was observed in the CPB15 arm (CPP 6.5%, CPB15 5.3%, CPB15+ 8.4%). Most events were either Grade 1 or 2. There was no Grade 5 proteinuria events reported.

In study BO17707, the incidence of proteinuria was higher in the CPB7.5+ arm than in the CP arm (CPB7.5+: 4.4%; vs. CP: 2.2%). The majority of events of proteinuria in the two treatment arms were Grade 1 or 2 in severity.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

In study GOG-02018, there was one case of RPLS reported. There were no reports in study BO17707 of any patients experiencing RPLS.

Venous Thromboembolic Events

In study GOG-0218, the incidence of venous thromboembolic events was similar across the three treatment arms (around 4%). Most events occurred during the chemotherapy period. The majority of these events were Grade 3.

In study BO17707, 6.8% of patients in the CPB7.5+ arm experienced a venous thromboembolic event compared with 4.5% in the CP arm. The majority of events occurred during the chemotherapy phase. Grade $\geq$ 3 venous thromboembolic events were reported in 12 patients (1.6%) in the CP arm and 30 patients (4.0%) in the CPB7.5+ arm. Eleven patients (1.5%) in the CPB7.5+ arm had a Grade 4 event compared with two patients (0.3%) in the CP arm.

There were no Grade 5 venous thromboembolic events in either study.

Adverse events with a preferred term of "embolism" unqualified were categorized as arterial thromboembolic events. However, medical review revealed that 35/52 arterial thromboembolic events across treatment groups in study GOG-0218 and 13/38 arterial thromboembolic events across treatment groups in study BO17707 reported as "embolism" were venous thromboembolic events.

Wound Healing Complications

In study GOG-0218, the incidence of wound-healing complications/dehiscence events was similar across the treatment arms (around 4%). One patient in the CPB15 arm and one patient in the CPB15+ arm experienced Grade 4 wound complications. There were no wound-healing complications leading to death.

In study BO17707, wound-healing complications were reported in 4.6% of patients in the CPB7.5+ arm compared with 1.6% in the CP arm. The majority of wound-healing complications in the two treatment arms were Grade 1 or 2 events. Grade 3 wound-healing complications were recorded for one patient (0.1%) in the CP arm and nine patients (1.2%) in the CPB7.5+ arm. No Grade 4 or 5 wound-healing complications were reported in either treatment arm.

Serious adverse event/deaths/other significant events

Deaths

Study GOG-0218

The primary cause of death was categorized by the investigator on the study GOG-0218 follow-up form as due to "this disease", "protocol treatment", "other cause", or "unknown".

At the time of the safety data cut-off for study GOG-0218, a total of 424 patients (23.3%) from the safety-evaluable population had died. Overall fewer patients in the CPB15+ arm died compared with the CPB15 and CPP arms (21.5% vs. 24.4% and 24.1%, respectively), and this is specifically due to the lower number of deaths classified as due to this disease (19.4% vs. 22.9% and 22.5%, respectively). Ovarian cancer/ progressive disease (i.e. death due to this disease) was the most common cause of death. The number of deaths due to protocol treatment was lowest in the chemotherapy-alone arm (CPP: 0.5%) and highest in the extended bevacizumab arm (CPB15+: 1.3%). The number of deaths due to other causes was lower in the two bevacizumab-containing treatment arms (CPB15: 0.7%; CPB15+ 1.0%) compared with the CPP arm (1.2%), and the number of deaths with unknown cause was equal across all three treatment arms (0.5%). Ten patients had multiple primary causes of death.

Study BO17707

At the time of the safety data cut-off for study BO17707, a total of 238 patients (15.8%) from the safety population had died (131 patients in the CP arm, and 107 patients in the CPB7.5+ arm). Table 924 summarizes all causes of death, with deaths due to disease progression and those deaths with no obvious association to ovarian cancer progression presented separately. The number of deaths was lower in the CPB7.5+ arm than in the control arm (14.3% vs. 17.2%), reflecting the lower number of patients who died as a result of disease progression in the bevacizumab-containing treatment arm (11.8% in the CPB7.5+ arm vs. 15.1% in the CP arm; classification based on the primary cause of death reported).

Adverse Events Leading to Death (Grade 5 AEs)

Study GOG-0218

In study GOG-0218, 27 patients were reported either on the toxicity form or in NCI Adverse Event Expedited Reporting System (AdEERS) as having an adverse event leading to death. Note that deaths due to disease progression, when reported as an adverse event by the investigator, were included in this analysis.

The number of patients with adverse events leading to death was higher in the two bevacizumab-containing treatment arms than in the control arm (9 and 14 patients in the CPB15 and CPB15+ arms, respectively, vs. 4 patients in the CPP arm). These adverse events include neutropenic infections and gastrointestinal perforations observed during the period that bevacizumab was combined with chemotherapy. With the exception of two patients in the CPB15+ arm who died after Cycle 7 of treatment (patient nos. 023-0218-012 [sudden death] and 023-0218-022 [disease progression]), all other deaths from adverse events occurred during the first six cycles of therapy.

Study BO17707

In study BO17707, seven patients in the CP arm and four patients in the CPB7.5+ arm were reported on the AE CRF page as having an AE leading to death. Two patients in each treatment arm died following a gastrointestinal disorder, three patients died from nervous system disorders (CP: 2 patients; CPB7.5+: 1 patient), and two patients in the CP arm had a cardiac disorder leading to death.

One patient in the CP arm had an adverse event of disease progression leading to death, and one patient in the CPB7.5+ arm had an adverse event of malignant neoplasm leading to death; both patients were classified as death due to disease progression following clinical review. One patient was

reported to have had a Grade 5 adverse event of abdominal pain but the cause of death was recorded as gastrointestinal perforation on the study completion form.

Other Serious Adverse Events

Serious Adverse Events (SAEs) in GOG-0218 were defined as those requiring expedited reporting to AdEERS, and SAEs in BO17707 were defined according to standard SAE criteria defined by the protocol and based on the ICH GCP.

The incidence of all-grade adverse events reported to AdEERS or as SAEs was slightly higher in all bevacizumab-containing treatment arms compared with the corresponding control arms. System organ classes comprising common adverse events associated with laboratory parameters (i.e., investigations, metabolism and nutrition disorders, and blood and lymphatic system disorders) cannot be compared across studies due to differences in data collection and AE reporting. The most common types of AEs reported to AdEERS or as SAEs in the two studies by body system were gastrointestinal disorders, infections and infestations, and vascular disorders.

In study GOG-0218, the only adverse event that was reported to AdEERS with ≥ 1% higher incidence in a bevacizumab-containing treatment arm relative to the control arm was large intestine perforation (CPP: 0 patients, 0.0%; CPB15: 7 patients, 1.2%; CPB15+: 6 patients, 1.0%). In study BO17707, the following adverse events reported as SAEs occurred with ≥ 1% higher incidence in the CPB7.5+ arm relative to the CP arm: abdominal pain, hypertension, vomiting, constipation, embolism, pulmonary embolism, and wound complication.

Laboratory findings

In summary, the majority of patients in both study arms showed no change in NCI-CTC grade for any laboratory test parameter during the treatment phase. The most common Grade 3/4 haematologic laboratory abnormalities during the study were low neutrophil count and low white blood cell count, whereas the incidence of Grade 3/4 abnormalities in clinical chemistry laboratory parameters was low and not markedly different between the study arms.

Safety in special populations

- Safety in special populations

The effects of age (< 65, ≥ 65 years) and race (white, non-white) on adverse events of special interest and primary cause of death were evaluated for patients treated in studies GOG-0218 and BO17707. A breakdown of the patient populations in the two studies by age and race is provided in Table 30. The majority of patients across both studies were under 65 years old (range 66.7%–75.7%), and the majority of patients were white (range 86.7%–96.5%).

Table 30. Studies GOG-0218 and BO17707: Summary of Patient Demographic Characteristics (Safety Population)

	GOG-0218			BO17707	
	CPP (n=601)	CPB15 (n=607)	CPB15+ (n=608)	CP (n=763)	CPB7.5+ (n=746)
Age (yr)					
n	601	607	608	763	746
Mean (SD)	58.8 (10.8)	59.7 (10.2)	58.9 (10.6)	56.7 (10.7)	56.4 (10.4)
Median	60.0	60.0	59.0	57.0	57.0
Range	24 - 85	23 - 87	22 - 89	18 - 81	24 - 82
Age group (yr)					
n	601	607	608	763	746
<65	409 (68.1%)	405 (66.7%)	425 (69.9%)	569 (74.6%)	565 (75.7%)
>=65	192 (31.9%)	202 (33.3%)	183 (30.1%)	194 (25.4%)	181 (24.3%)
Race					
n	601	607	608	763	746
White	527 (87.7%)	528 (87.0%)	527 (86.7%)	736 (96.5%)	713 (95.6%)
Non-White	74 (12.3%)	79 (13.0%)	81 (13.3%)	27 (3.5%)	33 (4.4%)

BV = bevacizumab; CP = carboplatin + paclitaxel; CPP = CP + up to 21 cycles of placebo; CPB15 = CP + up to 5 cycles of BV 15 mg/kg + up to 16 cycles of placebo; CPB15+ = CP + up to 21 cycles of BV 15 mg/kg; CPB7.5+ = CP + up to 18 cycles of BV 7.5 mg/kg; SD = standard deviation.

Safety by Age Group

Overall, a slightly higher proportion of patients in the ≥ 65 year age group experienced a Grade ≥ 3 AESI compared with the under-65 year age group across both studies.

In study GOG-0218, the generally higher incidence of Grade ≥ 3 AESIs among bevacizumab-treated patients compared with patients in the CPP arm did not appear to be more pronounced for one age subgroup than the other, with the possible exception of congestive heart failure and hypertension: the three patients in the CPB15+ arm who reported Grade ≥ 3 CHF were all aged ≥ 65 years old, and the incidence of Grade ≥ 3 hypertension was higher in patients aged ≥ 65 years compared with patients under 65 years old.

In study BO17707, the higher incidence of Grade ≥ 3 hypertension in the bevacizumab arm relative to the control arm was more pronounced in the ≥ 65 year age group than the < 65 year age group. In the older age group, a higher proportion of patients in the CP arm reported neutropenia than the bevacizumab treatment arm. A higher proportion of patients in the ≥ 65 year age group experienced AEs reported to NCI AdEERS in study GOG-0218 or serious adverse events in study BO17707.

In study GOG-0218, the proportion of patients who died in the ≥ 65 year age group was higher than that in the < 65 age group. In study BO17707, the proportion of patients who died in the ≥ 65 year age group was higher than that in the < 65 year group.

Safety by Race

A comparison of the adverse events of special interest to bevacizumab in white and non-white subgroups has been presented. The percentages of white and non-white patients who reported at least one Grade ≥ 3 AESI were similar across treatment arms within the two studies.

Discontinuation due to adverse events

In study GOG-0218 a higher proportion of patients in the bevacizumab-containing treatment arms discontinued study treatment because of an AE, side effect, or complication than in the CPP arm (CPP: 58 patients, 9.7%; CPB15: 83 patients, 13.7%; CPB15+: 100 patients, 16.4%).

In study BO17707, more patients in the bevacizumab-containing treatment arm than in the chemotherapy-alone arm discontinued any component of treatment due to adverse events (CP: 68 patients, 8.9%; CPB7.5+: 164 patients, 22.0%).ae11disca_s001 This difference between the two

treatment arms reflects patients who discontinued bevacizumab (CPB7.5+: 118 patients, 15.8%) and also reflects to some extent the longer treatment duration in the CPB7.5+ arm compared with the CP arm (up to 18 cycles versus 6 cycles, respectively). Around half of all patients who discontinued bevacizumab did so during the six cycles when bevacizumab was administered concurrently with chemotherapy, and the remainder discontinued bevacizumab during the 12 additional cycles when bevacizumab was administered alone. The most common AE leading to discontinuation of bevacizumab treatment in the CPB7.5+ arm was hypertension (22 patients, 2.9%). Discontinuation of either carboplatin or paclitaxel due to AEs during the six cycles of chemotherapy was similar between the two treatment arms.

Post marketing experience

The total number of patients exposed to bevacizumab in the post-marketing setting or in clinical trials over the six-year period covered by the Periodic Safety Update Reports (from February 26, 2004 to February 25, 2010) is estimated to be approximately 812 640.

During the six-year period from February 26, 2004 to February 25, 2010, a total of 32 266 adverse events, of which 27 222 were serious, were reported in 18 103 (2.2%) patients. In 1950 (0.2%) cases, the outcome was fatal.

3.5.1. Discussion on clinical safety

Overall, the review of AEs in the light of bevacizumab known safety profile did not reveal any unexpected findings.

Safety data have not been pooled due to differences in study design, populations and collection of safety information. In particular, the number of all-grade events laboratory events was significantly higher in all treatment arms in study GOG-0218 in which events associated with abnormal haemoglobin, neutrophil count, platelet count, and white blood cell count were routinely collected on the toxicity form, compared with study BO17707 that had stricter criteria for reporting laboratory abnormalities as AEs.

The exposure to carboplatin/paclitaxel was similar across treatment arms and studies (median of 6 cycles). In GOG-0218, patients in the CPB15+ arm received a median of 13 cycles of bevacizumab. In BO17707, patients in the CPB7.5+ arm received a median of 17 cycles of bevacizumab. The overall exposure and the extent of the safety database are considered satisfactory for the safety evaluation.

The most common AEs observed were gastrointestinal disorders, general disorders (fatigue), musculoskeletal disorders (myalgia/ arthralgia), nervous disorders (peripheral neuropathy) and skin and subcutaneous disorders (alopecia).

Common AEs associated with carboplatin are myelosuppression (particularly thrombocytopenia), nausea/vomiting and peripheral neuropathia. Common adverse events associated with paclitaxel are nausea/vomiting, myelosuppression, arthralgia/myalgia, peripheral neuropathy, alopecia and infections. As expected, these chemo-related toxicities were most frequently observed during the first 6 cycles of therapy.

Common AEs associated with bevacizumab are epistaxis, stomatitis, nausea/diarrhoea, hypertension, dyspnoea, headache, arthralgia, fatigue. In GOG-0218, dysarthria was more common than previously observed (11.8% in the CPB15+ arm), but it was Grade 1 in 90% of patients. In BO17707, the incidence of diarrhoea was higher than expected (35% in the CPB7.5 arm).

At the time of data cut-off in study GOG-0218, the number of deaths was relatively low, and most deaths were due to progressive disease with the highest incidence in the control arm. Also, in study

BO17707 the number of deaths was relatively low at the time of data cut-off and most deaths were attributed to disease progression. Since the distinction between AEs leading to death and deaths due to progressions was not very clear in all cases presented, the CHMP reviewed all the cases of deaths from causes other than progressive disease as well as the timing and causality (most plausible agent responsible). In some cases the most plausible causes of death were uncertain which is often the case in patients with advanced cancer. Most deaths occurred during the concomitant treatment phase which makes it difficult to attribute the causality to an individual element of the treatment. No definite pattern can be seen regarding timing. In terms of causes, intestinal perforation was considered a possible treatment-related cause in 6 out of 17 deaths. In study BO17707, 2 out of 5 cases of grade 5 events were caused by intestinal perforation in the CPB7.5 arm. Intestinal perforation was also the only AE that was reported to AdEERS (SAE) with ≥ 1% higher incidence in a bevacizumab-containing treatment arm relative to the control arm in study GOG-0218 (CPP: 0 patients, 0.0%; CPB15: 7 patients, 1.2%; CPB15+: 6 patients, 1.0%). Intestinal perforation is a well-known risk associated with treatment with bevacizumab. In the review of events of special interest, the incidence of gastrointestinal perforations was not higher in this population of ovarian cancer patients than the incidence observed in patients with CRC. The CHMP concluded that based on the observations above, more focus should be put on this risk in patients with ovarian cancer in the RMP and in upcoming PSURs. In reply to CHMP concern, the MAH has updated the RMP in order to include intestinal perforation in the setting of ovarian cancer for bevacizumab and to have additional focus on this risk in future PSURs. Furthermore, the MAH is requested to submit a cumulative analysis of GIP cases by grade with the upcoming PSURs.

In study GOG-0218, SAEs were reported in 25.8% of patients in the CPB15+ arm compared to 23.7% in the CPB15 arm and 21.3% in the CPP arm. Only large intestine perforation was reported with ≥ 1% higher incidence in a bevacizumab-containing arm compared to the control arm. In study BO17707, SAEs were reported in 37.7% of patients in the CPB7.5+ arm and in 23.5% of patients in the control arm. SAEs occurred with ≥ 1% higher incidence in the CPB7.5+ arm relative to the CP arm included abdominal pain, hypertension, vomiting, constipation, embolism, pulmonary embolism, and wound complication.

More patients in the bevacizumab-containing arms discontinued treatment because of AEs, particularly in study BO17707 (22%). Half of the patients discontinued treatment during the concomitant chemotherapy/bevacizumab phase. The most common cause of discontinuation was hypertension (2.9%).

The CHMP concluded that the safety profile in study BO17707 does not support a reduction of the bevacizumab dosage to 7.5 mg/kg q3w as more toxicity was observed with the lower bevacizumab dose; however these results should be interpreted with caution due to the limitations in the design of this study that mentioned above.

3.5.2. Conclusions on the clinical safety

In conclusion, safety results and adverse drug reactions encountered with the combination of carboplatin, paclitaxel and bevacizumab from pivotal studies GOG-0218 and BO17707 are as it can be expected from the present knowledge of the safety profile of the three drugs. No new safety concerns have been identified.

The following pharmacovigilance activity has been included in RMP:

The MAH should submit a cumulative analysis of GIP cases by grade with the upcoming PSURs.

3.6. Pharmacovigilance

Risk Management Plan

The Risk Management Plan was updated in the course of the assessment of this variation application.

Table 31: Summary of the Risk Management Plan

Safety Concern	*Proposed PhV activities (planned and ongoing)*	*Proposed risk minimisation activities (planned and ongoing)*
Important identified risks		
Haemorrhage	- prospective data collection in study BO17920 on the use of aspirin and other anti-platelet prophylactic antiaggregation therapy - evaluation of the effect of anticoagulation in study E1505	Routine. EU SmPC section 4.4: Haemorrhage 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 bleeding when treated with a full dose of warfarin and Avastin concomitantly. Labelled in section 4.8 of the EU SmPC.
Pulmonary haemorrhage	- routine PhV	Routine. EU SmPC section 4.4: Pulmonary

Safety Concern	*Proposed PhV activities (planned and ongoing)*	*Proposed risk minimisation activities (planned and ongoing)*
		Haemorrhage/Haemoptysis 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. Labelled in section 4.8 of the EU SmPC
Arterial thromboembolic events (ATE)	- prospective data collection on the use of aspirin and other anti-platelets as well as history of arterial disease and risk factors for ATE - guided questionnaire	Routine. EU SmPC section 4.4: 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. Labelled in section 4.8 of the EU SmPC.
Hypertension	- prospective data collection for evaluation of incidence and reversibility	Routine. EU SmPC section 4.4: 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. Labelled in section 4.8 of the EU SmPC.
Proteinuria	- prospective data collection for evaluation of incidence and reversibility	Routine. EU SmPC section 4.4: Patients with a history of hypertension may be at in-creased 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). Labelled in section 4.8 of the EU SmPC.
Congestive heart failure	- in defined studies - safety monitoring plan - sequential regular LVEF monitoring - consider inclusion of cardiology expert in DSMBs - cardiac advisory board - guided questionnaire	Routine. EU SmPC section 4.4: 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

Safety Concern	*Proposed PhV activities (planned and ongoing)*	*Proposed risk minimisation activities (planned and ongoing)*
		significant cardiovascular disease or pre-existing congestive heart failure with Avastin. Labelled in section 4.8 of the EU SmPC.
Wound healing complications	- prospective data collection to evaluate incidence and risk factors - evaluation of the safety of surgery in study MO18725 - monitoring by DSMB will be implemented in planned Roche-sponsored glioblastoma studies to assess safety on an ongoing basis.	Routine. EU SmPC section 4.4: 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. Labelled in section 4.8 of the EU SmPC. 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, intratumoural interstitial therapy, radiosurgery).
Gastrointestinal perforations	AVF4095g in ovarian cancer patients A cumulative analysis of GIP by Grade will be presented in the next PSUR.	Routine. 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. Labelled in section 4.8 of the EU SmPC.
Reversible posterior leukencephalopathy syndrome (RPLS)	- routine PhV	Routine. EU SmPC section 4.4: There have been rare reports of Avastin-treated patients developing signs and symptoms that are consistent with Reversible Posterior

Safety Concern	*Proposed PhV activities (planned and ongoing)*	*Proposed risk minimisation activities (planned and ongoing)*
		Leukoencephalopathy Syndrome (RPLS), 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 RPLS requires confirmation by brain imaging. In patients developing RPLS, 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 RPLS is not known. Labelled in section 4.8 of the EU SmPC.
Neutropenia	- routine PhV	Routine. 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. Labelled in sections 4.5 and 4.8 of the EU SmPC.
Venous thromboembolic events (VTE)	- routine PhV	Routine. 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. Labelled in section 4.8 of the EU SmPC.
Fistula (other than gastrointestinal)	- data collection in BO17920	Routine. EU SmPC section 4.4: Patients may be at increased risk for the development of fistulae when treated with Avastin. Permanently discontinue Avastin in patients with TE

Safety Concern	*Proposed PhV activities (planned and ongoing)*	*Proposed risk minimisation activities (planned and ongoing)*
		(tracheoesophageal) fistula or any grade 4 fistula. Limited information is available on the continued use of Avastin in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of Avastin should be considered. Labelled in section 4.8 of the EU SmPC.
Thrombotic microangiopathy	- routine PhV	Routine. Labelled in section 4.8 of the EU SmPC.
Pulmonary hypertension	- routine PhV	Routine. Labelled in section 4.8 of the EU SmPC.
Ovarian failure	-routine PhV	Routine. Wording has been suggested for SmPC sections 4.4, 4.6 and 4.8.
Hypersensitivity and Infusion Reactions	-routine PhV	EU SmPC section 4.4 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. Labelled in section 4.8 of the EU SmPC
Important potential risks		
Embryo-foetal development disturbance	- routine PV	Routine. Labelled in section 5.3 of the EU SmPC.
Physeal dysplasia	- routine PhV Study BO20924	Routine. Labelled in section 5.3 of the EU SmPC.
Peripheral sensory neuropathy	- routine PhV	Routine. Labelled in section 4.8 of the EU SmPC.
Cardiac disorders (excl. CHF and ATE)	- cardiac monitoring in BO17920 - QTc study should results from cardiac monitoring in BO17920 indicate it is	Routine. Supraventricular tachycardia is labelled in section 4.8 of the EU SmPC.

Safety Concern	*Proposed PhV activities (planned and ongoing)*	*Proposed risk minimisation activities (planned and ongoing)*
	necessary.	
Osteonecrosis of the Jaw	-routine PhV and monitoring of cases using check list (see Annex 7b)	EU SmPC section 4.4 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 simultaneously or sequentially. Invasive dental procedures are also an identified risk factor. A dental examination and appropriate preventive dentistry should be considered prior to starting the treatment with Avastin. In patients who have previously received or are receiving IV bisphosphonates invasive dental procedures should be avoided, if possible. Labelled in section 4.8 of the EU SmPC DHPC on osteonecrosis of the jaw distributed in the EU in November 2010
Important missing information		
Safety profile of the different treatment combinations in patients with non-squamous NSCLC	- guided questionnaire (to be replaced with an internal checklist)	Routine. 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. EU SmPC section 4.8: *Paediatric population* The safety of Avastin in children and adolescents has not been established.
Patients with renal impairment	- routine PhV	Routine. EU SmPC section 4.2: safety and efficacy have not been studied in patients with renal impairment.
Patients with	- routine PhV	Routine EU SmPC section 4.2: safety and efficacy have not been studied in

Safety Concern	*Proposed PhV activities (planned and ongoing)*	*Proposed risk minimisation activities (planned and ongoing)*
hepatic impairment		patients with hepatic impairment.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
The MAH should perform a cumulative analysis of GIP cases by grade with the upcoming PSURs	PSUR cycle

3.8 Changes to the Product Information

The MAH proposed to update sections 4.1, 4.2, 4.8 and 5.1 of the SmPC to reflect the change in the indication. The PL has been updated accordingly. In addition, ''Batch'' has been replaced by ''lot'' in Annex IIIA. Finally, Annex II has been updated in order to include the new version number of the Risk Management Plan and the list of conditions.

The CHMP agreed with the proposed changes.

3.9 Benefit-Risk Balance

Benefits

- Beneficial effects

Both pivotal studies of bevacizumab in combination with carboplatin and paclitaxel in the front-line treatment of ovarian cancer (study GOG-0218 and study BO17707) showed a statistically significant increase in PFS in patients receiving bevacizumab in combination with chemotherapy followed by extended bevacizumab compared to patients in the control arms. The absolute difference in PFS was between 2-4 months and the reduction in risk of progression or death was about 30%.Furthermore, the observed PFS benefit (4.1 months) in study GOG-218 has proven to be very robust in sensitivity analyses and consistent in subgroup analyses.

No detrimental effect was shown for OS in any of the studies. Nevertheless, further follow-up is needed to further clarify the benefit-risk of the product and the MAH is requested to provide this analysis by 31/03/2012 for study GOG-0218 and by 31/12/2013 for study BO17707 (see Annex II of the PI).

There were no detrimental effects on quality of life according to the results on patient reported outcomes.

- Uncertainty in the knowledge about the beneficial effects

There were uncertainties regarding the limited evidence of a clinically relevant benefit at an acceptable toxicity level for patients with early high risk stages of EOC at the proposed dosage. Therefore this patient population has been excluded from the indication and the updated applied indication includes patients with advanced (FIGO stages III B, III C and IV) ovarian cancer. The recommendation on dose and duration of treatment for patients with advanced disease remained the same.

Risks

- Unfavourable effects

Overall, the review of AEs in the light of bevacizumab known safety profile did not reveal any unexpected findings. Safety results and adverse drug reactions encountered with the combination of carboplatin, paclitaxel and bevacizumab from pivotal studies GOG-0218 and BO17707 are as it can be expected from the present knowledge of the safety profile of the three drugs. No new safety concerns have been identified.

The most common adverse events observed were gastrointestinal disorders (83-87% across treatment arms), general disorders (fatigue), musculoskeletal disorders (myalgia/ arthralgia), nervous disorders (peripheral neuropathy) and skin and subcutaneous disorders (alopecia). Of note, common adverse events associated with carboplatin are myelosuppression (particularly thrombocytopenia), nausea/vomiting and peripheral neuropathia. Common adverse events associated with paclitaxel are nausea/vomiting, myelosuppression, arthralgia/myalgia, peripheral neuropathy, alopecia and infections. As expected, these chemo-related toxicities were most frequently observed during the first 6 cycles of therapy. Common AEs associated with bevacizumab are epistaxis, stomatitis, nausea/diarrhoea, hypertension, dyspnoea, headache, arthralgia and fatigue.

In study BO17707, 2 out of 5 cases of grade 5 events were caused by intestinal perforation in the CPB7.5 arm. Intestinal perforation was also the only AE that was reported to AdEERS (SAE) with ≥ 1% higher incidence in a bevacizumab-containing treatment arm relative to the control arm in study GOG-0218 (CPP: 0 patients, 0.0%; CPB15: 7 patients, 1.2%; CPB15+: 6 patients, 1.0%). Intestinal perforation is a well-known risk associated with treatment with bevacizumab.

Benefit-risk balance

- Importance of favourable and unfavourable effects

A reduction in the risk of disease progression or death of 30% and an improvement between 2-4 months in median PFS represents an important benefit to patients. In addition, the 4.1 months benefit of PFS in study GOG-218 has proven to be very robust in sensitivity analyses and consistent in subgroup analyses.

When adding bevacizumab to a chemotherapy regimen more adverse events and serious adverse events were reported for the combination arm than for the chemotherapy alone as expected. However, the safety profile for bevacizumab was largely consistent with observations in previous bevacizumab studies. No new safety concerns have been identified.

In conclusion, the AEs encountered with the combination of carboplatin, paclitaxel and bevacizumab are as would be expected from the present knowledge of the safety profile of the three drugs.

Discussion on the benefit-risk balance

Efficacy in terms of progression free survival was demonstrated in both GOG-0218 and BO17707 trials. The adverse events reported were considered acceptable for a patient population with advanced ovarian cancer. The safety profile for bevacizumab is known and generally manageable.

Therefore the CHMP concluded that the benefit-risk balance of Avastin in combination with carboplatin and paclitaxel for the front-line treatment of advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer is considered as positive, as the demonstrated statistically significant improvement of PFS outweighs the added toxicity of bevacizumab.

3.10 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. See appendix 1.

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(s) 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

Extension of indication to add the treatment of Avastin in combination with carboplatin and paclitaxel for the front-line treatment of advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer. Sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated to reflect the change in the indication. The Risk Management Plan, Annex II and the Package Leaflet have been updated accordingly. In addition, a minor change was made to the Labelling.

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

This CHMP recommendation is subject to the following new conditions:

Conditions and requirements of the marketing authorisation

Obligation to complete post-authorisation measures

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

Description	Due date
The MAH shall submit results from the pre-specified final analysis for Overall Survival from study BO17707.	31/12/2013
The MAH shall submit final OS data from study GOG-0218.	31/03/2012
The MAH shall submit results from the plasma biomarker for VEGF-A from study BO17707 with PFS analysis as well as the results from the GOG-218 study on the correlation of plasma markers for VEGF-A with PFS and OS analyses	31/06/2012