Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Bevacizumab

Proprietary Product Name: Avastin

Sponsor: Roche Products Pty Ltd

August 2012

TGA Health Safety Regulation

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- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Contents

I. Introduction to product submission

Submission details

Type of Submission	Extension of Indications
Decision:	Approved
Date of Decision:	23 February 2012
Active ingredient(s):	Bevacizumab
Product Name(s):	Avastin
Sponsor's Name and Address:	Roche Products Pty Ltd PO Box 255, Dee Why, NSW 2099
Dose form(s):	Injection Vial
Strength(s):	100 mg/4mL and 400 mg/16mL
Container(s):	Glass vial
Pack size(s):	1's
Approved Therapeutic use:	In combination with carboplatin and paclitaxel for the first line treatment of patients with advanced (FIGO[1] stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer.
Route(s) of administration:	Intravenous (IV) infusion
Dosage:	The recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an IV infusion. Avastin should be given in combination with carboplatin and paclitaxel for up to 6 cycles of treatment, followed by continued use of Avastin as single agent. It is recommended that Avastin treatment be continued for a total of 15 months therapy or until disease progression, whichever occurs earlier.
ARTG Number (s)	99755 and 99757

Product background

This AusPAR describes the application by the sponsor, Roche Products Pty Ltd, to extend the approved indications of Avastin to include, in combination with carboplatin and paclitaxel, the first-line treatment of patients with epithelial ovarian, fallopian tube or primary peritoneal cancer as follows:

[1] Federation of Gynecology and Obstetrics (FIGO). The FIGO system defines how far the cancer has spread.

> *"Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer- Avastin (bevacizumab) in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer."*

Bevacizumab is a monoclonal antibody produced by recombinant DNA technology in a Chinese hamster ovary (CHO) cell line. It is targeted against human vascular endothelial growth factor (VEGF), a growth factor which mediates the development of new blood vessels in both normal tissues and in tumours. Reduction in the vascularisation of tumours results in inhibition of tumour growth.

The drug is currently registered for use in various tumour types. The proposed dose for the new indication (15 mg/kg every 3 weeks) is consistent with regimens previously approved for other malignancies. For the new indication it is proposed that patients receive carboplatin, paclitaxel and bevacizumab for a total of six 3-week cycles, after which bevacizumab is to be continued as a single agent, until disease progression occurs or the total duration of bevacizumab treatment reaches 15 months.

Regulatory status

Avastin has been registered in Australia since February 2005 when approval was granted for the metastatic colorectal cancer indication[2]. Subsequent approvals have been granted for the other listed indications with the most recent being in February 2010 for the treatment of Grade IV gliomas.

[2]The currently approved indications for Avastin are:
Metastatic Colorectal Cancer Avastin (bevacizumab *rch*) in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of patients with metastatic colorectal cancer.
Locally recurrent or metastatic Breast Cancer
Avastin (bevacizumab *rch*) in combination with paclitaxel is indicated for the first-line treatment of metastatic breast cancer in patients in whom an anthracycline-based therapy is contraindicated. (See Clinical Trials).
Advanced, metastatic or recurrent non-squamous Non Small Cell Lung Cancer (NSCLC)
Avastin (bevacizumab *rch*), in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent, non-squamous, non-small cell lung cancer.
Advanced and/or metastatic Renal Cell Cancer

Avastin (bevacizumab *rch*) in combination with interferon alfa-2a is indicated for treatment of patients with advanced and/or metastatic renal cell cancer.

Grade IV Glioma Avastin (bevacizumab *rch*) as a single agent, is indicated for the treatment of patients with Grade IV glioma after relapse or disease progression after standard therapy, including chemotherapy.

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal cancerAvastin (bevacizumab *rch*) in combination with carboplatin and paclitaxel for the first line treatment of patients with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer.

The proposed indication has been approved in the following countries (Table 1):

Table 1. International regulatory status

Country	Status
EU	Approved 23 December 2011
Switzerland	Not yet approved.
Mexico	Approved 22 September 2011
Philippines	Approved 14 June 2011
Ecuador	Approved 15 June 2011
New Zealand	Not yet approved.

Applications have not been submitted in the USA or Canada.

Product information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

Introduction

The cancers to be treated

The cancers to be treated are epithelial ovarian cancer, fallopian tube cancer and primary peritoneal cancer. The most common of these is epithelial ovarian cancer. All three are histologically equivalent and, as recommended by the International Federation of Gynecology and Obstetrics (FIGO), are treated in the same way. Throughout this evaluation, the term *ovarian cancer* is used to refer to all three diseases.

How are these cancers treated with chemotherapy?

Initially, combination chemotherapy with carboplatin and paclitaxel after surgical debulking are standard-of-care treatment[3]. Although this conclusion of the Cochrane Collaboration is from 1999, an interim review indicated no reason for it to be updated.

Rationale for including bevacizumab

Many studies have attempted to improve first treatment of ovarian cancer. A recent Phase III Study, GOG182/ICON5, that enrolled over 4000 women, showed that the addition of a third cytotoxic agent provided no clinical benefit (as measured in terms of overall or progression free survival) above standard-of-care intravenous carboplatin and paclitaxel[4]. For this reason, other treatments have been investigated, including inhibitors of VEGF. VEGF is a mediator of angiogenesis and is the therapeutic target of the humanized monoclonal antibody, bevacizumab. Studies from Isaiah J Fidler's group over many years on angiogenesis in cancer have shown ovarian cancer to frequently express VEGF. In nude mice, the same group claimed that increased VEGF expression correlates with increased vascularisation, enhanced angiogenesis, ascitic fluid formation and attenuated survival[5].

Bevacizumab as a single agent has been evaluated in two Phase II studies; Study GOG-170D, a single-arm study in patients with relapsed ovarian cancer and Study AVF2949g a single arm trial in patients with platinum-resistant ovarian cancer who had progressed after either topotecan, liposomal doxorubicin, or both. Efficacy results in terms of objective response rates from both of these studies suggested that bevacizumab was an active agent in ovarian cancer, and thus provided the rationale for further evaluating bevacizumab in this clinical setting. Subsequently, the two Phase III studies, BO17707 and GOG-0218, were initiated as first treatment, and were the submitted with this application.

Outline of the application

The application consisted of two Clinical Study Reports (CSRs) based on the final analysis of the data obtained from two studies, GOG-0218 and BO17707.

Study GOG-0218

A Phase III trial of carboplatin and paclitaxel plus placebo versus carboplatin and paclitaxel plus concurrent bevacizumab followed by placebo, versus carboplatin and paclitaxel plus concurrent and extended bevacizumab, in women with newly diagnosed, previously untreated, Stage III or IV epithelial ovarian, primary peritoneal and fallopian tube cancer.

Study BO17707

A randomised, open-label, two-arm, multi-centre Gynaecologic Cancer InterGroup trial of adding bevacizumab to standard chemotherapy (carboplatin and paclitaxel) in patients with epithelial ovarian cancer.

Key differences between the two studies are presented in Table 2 below. In addition, the application included data from one Phase II studies previously conducted with bevacizumab in patients with ovarian cancer, namely a CSR for study AVF2949g entitled

[3] Stewart L, Advanced Ovarian Cancer Trialists Group. Chemotherapy for advanced ovarian cancer. *Cochrane Database of Systematic Reviews* 1999, Issue 1. Art. No.: CD001418. DOI: 10.1002/14651858.CD001418.

[4]Bookman M A, Brady M F, McGuire W P et al. Evaluation of New Platinum-Based Treatment Regimens in Advanced-Stage Ovarian Cancer: A Phase III Trial of the Gynecologic Cancer InterGroup. *J Clin Oncol 27:1419-1425(2009).*

[5] Yoneda J, Kuniyasu H, Crispens M A et al. Expression of Angiogenesis-Related Genes and Progression of Human Ovarian Carcinomas in Nude Mice. *J Natl Cancer Inst 90:447–54 (1998).*

"A multicenter, single-arm, Phase II trial of bevacizumab in subjects with platinum-resistant epithelial carcinoma of the ovary or primary peritoneal carcinoma for whom subsequent doxil or topotecan therapy has failed". This study was reviewed for safety. Also submitted was a publication based on Study GOG-170D entitled "Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: A Gynecologic Oncology Group study", that was not reviewed. The sponsor's Clinical Summary referred to postmarketing safety information from the Global Drug Safety Database held by Roche up to February 25, 2010 (the cut-off date used for the seventh Periodic Safety Update Report) but these data were not submitted.

Table 2. Key differences between Studies GOG-0218 and BO17707

	Study GOG-0218	Study BO17707
Trial design	• Double-blind, placebo-controlled • 3 arms • Bevacizumab 15 mg/kg q3w • Bevacizumab for 15 months	• Open-label • 2 arms • Bevacizumab 7.5 mg/kg q3w • Bevacizumab for 12 months
	• Primary endpoint: INV-assessed PFS • Exploratory: IRC-assessed PFS	• Primary endpoint: INV-assessed PFS • No IRC-assessed PFS
Patient Population	• FIGO Stage III (optimally debullked with macroscopic disease and suboptimally debulked), Stage IV	• High risk FIGO Stage I + IIa (capped at 10%), Stage IIb - IV
Primary Efficacy Analysis	• PFS per RECIST, censored for CA-125 progressions and NPT prior to PD (SAP specified)	• PFS per RECIST
	• GOG: PFS per RECIST inc. CA-125 progressions, not censored for NPT (protocol specified)	• MRC: PFS per RECIST censoring at last clinic visit

FIGO = International Federation of Gynecology and Obstetrics; INV = investigator; IRC = independent review committee; NPT = non protocol antineoplastic therapy; PFS = progression free survival; SAP = statistical analysis plan

Clinical pharmacology

The pharmacokinetics of bevacizumab were not assessed in the two main studies, nor has it been characterised in patients with ovarian cancer (see below). The sponsor's application contained a Summary of Clinical Pharmacology (SCP) that described the following:

- the pharmacokinetics of bevacizumab, which have been characterised previously in patients with solid tumors (that is, colorectal cancer [CRC], hormone-refractory prostate cancer [HRPC] , metastatic breast cancer [mBC] and non-small cell lung cancer [NSCLC] from eight clinical trials in which bevacizumab was administered either as a single agent or in combination with various chemotherapeutic agents.
- the cumulative pharmacokinetic drug-drug interaction (PK-DDI) information between bevacizumab and anti-cancer agents as well as for two chemotherapy agents that were relevant and applicable to Studies GOG-0218 and BO17707. PK-DDI information on carboplatin and paclitaxel was also provided in the SCP from one study conducted in patients with NSCLC (AVF0757g).
- a reference population PK model and an optimised population PK model were presented, based on a population PK analysis of data 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[6]). Four hundred and ninety one patients with mBC, NSCLC, CRC, and other solid tumors were included in this analysis.

Orphan medicinal products

Bevacizumab has been granted orphan drug status for the treatment of malignant glioma.

Pharmacokinetics

Introduction

The sponsor stated that the pharmacokinetics of bevacizumab have been well characterised in a comprehensive analysis across a variety of cancer indications and tumor type has not been shown to alter the pharmacokinetics of bevacizumab. Therefore, the pharmacokinetics of bevacizumab in ovarian cancer patients are expected to be consistent with the pharmacokinetics described by the bevacizumab population pharmacokinetic (PK) model.

Evaluator's comment: The evaluator accepted this argument, noting that the PK results from studies of bevacizumab in tumor types other than ovarian cancer have been similar and consistent with those in the Australian Product Information (PI). In this section, the drug's PK characteristics will be presented and these refer to the population PK models submitted in the sponsor's current Australian application.

Pharmacokinetic characteristics of bevacizumab

The draft Australian PI states that "……the pharmacokinetics of bevacizumab are well described by a two-compartment model. Overall, in all clinical trials, bevacizumab disposition was characterised by a low clearance, a limited volume of the central compartment (Vc), and a long elimination half-life. This enables target therapeutic bevacizumab plasma levels to be maintained with a range of administration schedules (such as one administration every 2 or 3 weeks). In the population pharmacokinetics analysis there was no significant difference in the pharmacokinetics of bevacizumab in relation to age (no correlation between bevacizumab clearance and patient age [the median age was 59 years with 5th and 95th percentiles of 37 and 76 years]). Low albumin and high tumour burden are generally indicative of disease severity. Bevacizumab clearance was approximately 30% faster in patients with low levels of serum albumin and 7% faster in subjects with higher tumour burden when compared with the typical patient with median values of albumin and tumour burden."

Absorption and bioavailability

Not applicable.

Distribution

The typical value for central volume (Vc) was 2.73 L and 3.28 L for female and male patients, respectively, which is in the range that has been described for Immunoglobulin type G (IgG) and other monoclonal antibodies. After correcting for body weight, male patients had a larger Vc (+20%) than female patients.

[6]Population pharmacokinetics of bevacizumab: structural model identification, mean population pharmacokinetic parameter estimation, and covariate analysis. *Genentech Inc. Report* 03-0324-1751. September 2003. *(Submitted with Response to Questions (EMEA/H/C/582/II/015)September 2007, Section 5.4 Vol 2 [8092])*

Metabolism

Assessment of bevacizumab metabolism in rabbits following a single intravenous (IV) dose of radioactively labeled (^{125}I)-bevacizumab suggested that its metabolic profile was similar to that expected for a native IgG molecule which does not bind VEGF.

Elimination

The pharmacokinetics of bevacizumab are linear at doses ranging from 1.5 to 10 mg/kg/wk. The value for clearance is, on average, equal to 0.188 and 0.220 L/day for female and male patients, respectively. After correcting for body weight, male patients had a higher bevacizumab clearance (+17%) than females. According to the two-compartmental model, the elimination half-life ($t_{1/2}$) is 18 days for a typical female patient and 20 days for a typical male patient.

Pharmacokinetics in special populations

The population pharmacokinetics of bevacizumab were analysed to evaluate the effects of demographic characteristics. The results showed no significant difference in the pharmacokinetics of bevacizumab in relation to age.

Children and Adolescents: The pharmacokinetics of bevacizumab have been studied in a limited number of paediatric patients. The resulting pharmacokinetic data suggest that the volume of distribution and clearance of bevacizumab were comparable to that in adults with solid tumours.

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

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

Drug-drug interactions

Interactions are described in the the current Australian PI.

Pharmacokinetics of bevacizumab in the presence of ascites

In response to a TGA enquiry, the sponsor advised that the PK of bevacizumab have not been measured in the presence of ascites, or malignant ascites in ovarian cancer patients, and that its potential impact on systemic levels of Avastin is unknown. The sponsor argued that the presence of ascites in patients treated with Avastin would not signficantly increase either exposure to for toxicity from bevacizumab because any drug resorbed from the ascitic space would result in longer time of exposure but at lower concentrations than those seen in previous clinical studies; and that although the patients in Studies GOG0218 and B017707 had an incidence of pre-study ascites of 72.6% and 40% respectively, "… the overall safety profile from both studies is consistent with previous experience with Avastin across indications". [The incidence of ascites drained at surgery in Study B017707 was actually 53% of patients in the CP arm, and 55% of patients in the CPB7.5+ arm (CSR)].

Evaluator's comment: Both arguments presented make unproven assumptions, but the evaluator did not propose to follow this matter further at this time, except to recommend the addition of a statement to the PK section of the Australian PI informing prescribers that this information is lacking.

Population kinetic models submitted

The population PK analysis referred to as the "Reference Population PK Model" in the SCP provided a reference model for additional population PK analyses of data from other patient populations across tumor types.

Reference population PK model

Patients with mBC, NSCLC, CRC, and other solid tumors 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 week, every 2 weeks, or every 3 weeks.

The model estimated the terminal $t_{1/2}$ of bevacizumab to be approximately 20 days (range: 11-50 days). The predicted time to reach steady state was approximately 100 days. The accumulation ratio, which reflects the extent of drug accumulation at steady state, was estimated to range from 2.7 to 2.9 for a bevacizumab dose of 10 mg/kg given intravenously every 2 weeks on the basis of a comparison of average bevacizumab trough concentration at steady state ($C_{trough, ss}$) with average trough concentration following the first dose ($C_{trough, first}$). The CL of bevacizumab varied with albumin level, body weight, and sex. In patients with low serum albumin levels (< 29 g/L, 5th percentile) and high alkaline phosphatase levels (> 483 U/L, 95th percentile), bevacizumab CL was approximately 23% faster compared with that in the typical patient with median values of these covariates (albumin, 37 g/L; alkaline phosphatase, 102 U/L). The CL for patients at the 95th percentile for body weight (114 kg) was approximately 30% faster than that for patients at the 5th percentile for body weight (49 kg). After correcting for body weight, male patients had a 26% faster bevacizumab CL (0.262 L/day versus 0.207 L/day) and a larger Vc (3.25 L versus 2.66 L) than female patients. CL in two mBC studies (AVF0776g and AVF2119g) was slightly slower compared with CL in the other six studies; this was mainly attributed to the female population in the mBC indication, as females have a slower bevacizumab CL than males.

The slow clearance and long terminal $t_{1/2}$ of bevacizumab allows bevacizumab to be administered every 2 or 3 weeks in combination with chemotherapies depending on the respective chemotherapy administration schedules.

The population PK model also included additional covariates that account for inter-individual variability in the pharmacokinetics 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 pharmacokinetics of bevacizumab. Chemotherapy drugs in these studies were doxorubicin, carboplatin/paclitaxel, 5-FU/leucovorin, capecitabine, and bolus-IFN. The CL of bevacizumab when bevacizumab was given in combination with bolus-IFN was not different from 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 tumor types, possible drug interactions (other than with the bolus-IFN regimen) were not distinguishable from effects of tumor type on bevacizumab CL.

Optimised population PK model

It was not clear to this evaluator what the term "optimized" means in this context. In the analysis, data from 102 patients with metastatic renal cell cancer (mRCC) treated with bevacizumab were used to determine individual bevacizumab concentration-time profiles and individual PK parameters, and compared with the results predicted by the model. This "optimized" model used "reference" model parameters with data from patients with this one tumor type to test the model. Presumably, if significant discrepancies had resulted, the reference model would have needed to be reassessment.

The comparison of the 90% prediction interval with the observed data showed that overall 9.32% of the observations were actually found to lie outside the interval (12.1% outside for troughs and 3.76% for the full profiles). The comparison of the 90% prediction interval with the predicted data showed that overall 6.30% of the individual predictions were found to lie outside the interval (9.5% outside for troughs and none for the full profiles). No clinically relevant differences in PK parameters (that is, clearance, central and peripheral volumes) were found between the mRCC and the reference oncology populations. Inspection of the goodness-of-fit plots showed that the empirical Bayesian estimation based on the reference model was describing the data well without obvious bias.

The conclusion was that no significant difference was apparent in the posterior Bayesian estimates of clearance and central and peripheral volumes between mRCC patients and oncology patients included in the pooled data analysis, a finding that supported the conclusion that the population pharmacokinetics of bevacizumab in the mRCC population was comparable with the population pharmacokinetics of bevacizumab in the oncology patient population with different types of cancer.

Efficacy

Study GOG-0218

A Phase III Trial of Carboplatin and Paclitaxel plus Placebo versus Carboplatin and Paclitaxel plus Concurrent Bevacizumab followed by Placebo, versus Carboplatin and Paclitaxel plus Concurrent and Extended Bevacizuamb, in women with newly diagnosed, previously untreated, Stage III or IV, Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancer.

The aim of this double-blinded randomised study was to determine the effect of adding bevacizamub to the combination of carboplatin and paclitaxel as first-line treatment for ovarian cancer after surgical resection. Five 3-weekly cycles of bevacizamub were administered with 6 cycles of standard chemotherapy, beginning with Cycle 2, then followed by placebo (concurrent, CPB15) or by bevacizumab for a further sixteen 3-weekly cycles (extended, CPB15+), and compared with a third arm of standard chemotherapy combined with placebo administered with the chemotherapy for 6 cycles and then continued for a further 16 cycles (CPP) for a total treatment time of 15 months (22 cycles of treatment and 21cycles of bevacizumab or placebo).

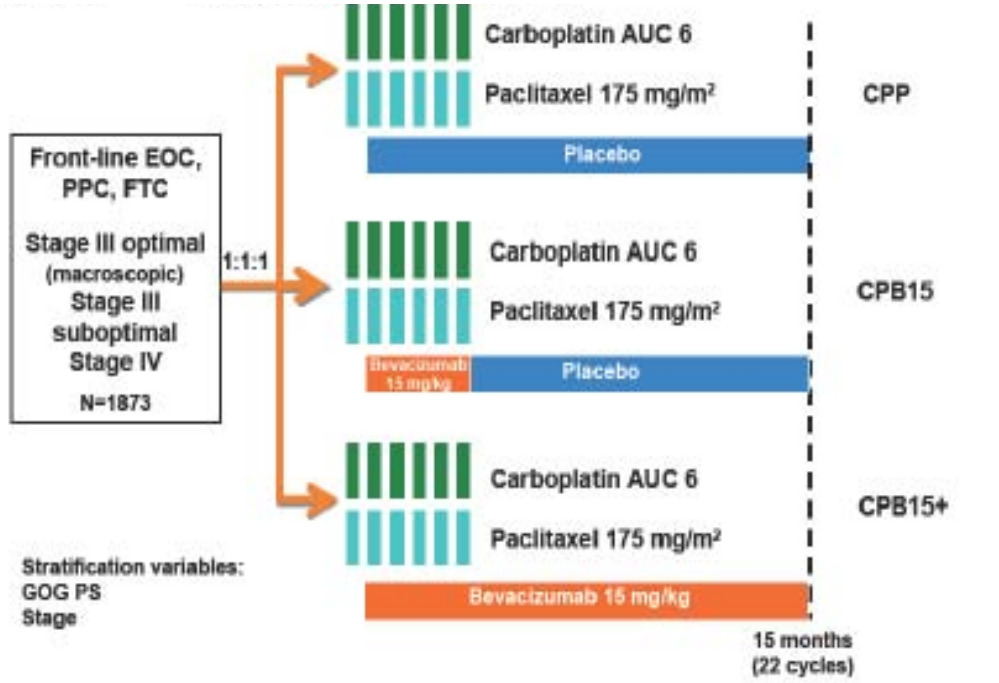
The sponsor was Genentech, and the study began on the 14 October 2005 and was completed on 22 February 2010. The report submitted was dated 17 November 2010. Three hundred and thirty-six investigative sites in Canada, Japan, South Korea, and the United States participated in the study.

Methods

Design

The study was a Phase III, randomised, three-arm, double-blind, placebo-controlled trial in women with newly diagnosed, previously untreated, FIGO Stage III with any gross (macroscopic or palpable) residual disease or FIGO Stage IV epithelial ovarian, primary peritoneal, or fallopian tube cancer. One thousand eight hundred eligible patients were to be randomised in a 1:1:1 ratio to the three treatment arms. The study design is shown in Figure 1 below.

Figure 1. Design of study GOG-0218



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

The protocol specified that full information for the comparisons of Progression Free Survival (PFS) of patients in the two bevacizumab-containing arms designated as CPB15 and CPB15+ compared to those in the standard therapy (CPP) arm would be achieved when 375 PFS events occurred in the standard therapy arm (approximately 1045 events in all three arms, assuming no arm was stopped). One interim PFS analysis was planned at 75% information. In the event that both CPB15 and CPB15+ were statistically superior to CPP with respect to PFS, a PFS comparison between the two bevacizumab-containing regimens would be performed. According to the protocol, full information for this comparison would be achieved when a total of 710 events were observed among patients randomised to CPB15 or CPB15+ who received Cycle 7 treatment or beyond (that is, were progression free at Cycle 6). The National Cancer Institute's Cancer Therapy Evaluation Program informed Genentech on 17 July 2009 that upon reviewing the interim data at 75% information, the Data Monitoring Committee recommended that the study continue.

Objectives

Primary:

- To determine if the addition of 5 concurrent cycles of bevacizumab to 6 cycles of standard therapy (carboplatin and paclitaxel) [CPB15] increases the duration of progression-free survival (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.

Secondary:

- 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 overall survival (OS) when compared with the CPP regimen.
- To determine whether the CPB15 or CPB15+ regimen increased the objective response rate (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.

Outcomes/endpoints

As stated in the objectives above, the primary endpoint of the study was Progression Free Survival (PFS) and secondary endpoints were OS and ORR. The Clinical Overview states that originally the GOG-0218 study had OS as the primary endpoint. This was changed to PFS in May 2008 (the study began in October 2005). When the primary endpoint was OS, patients could only be unblinded to their treatment assignment in the case of a medical emergency. This was to protect the integrity of the OS endpoint and avoid confounding the OS results by differing uses of subsequent therapy. Changing the primary endpoint to PFS allowed patients the option of being unblinded at the time of progression (see below for efficacy of second-line chemotherapy in these patients). Most patients in the study had been recruited in the USA where bevacizumab treatment was already in the national treatment guidelines for ovarian cancer[7] and thus could be offered bevacizumab at recurrence.

Evaluator's comment: It is not known to this evaluator what authority the National Cancer Comprehensive Network has, as it appears to be a commercial organisation associated with the publication of a Journal; however its guidelines agree with those of the National Cancer Institute USA[8]. The indication does not appear in the FDA approved prescribing information for Avastin].

Evaluator's comment: The TGA accepts as valid the primary end-point of PFS, provided it is consistent with international guidelines[9]. Appendix 1 of those guidelines describe the methodological considerations when PFS is used as an endpoint[10]. The sponsor's Clinical Overview stated that both studies (GOG-0218 and BO17707) employed designs consistent with these guidelines except that no Independent Research Committee (IRC) was used in the BO17707 study. This claim will be examined in the following section.

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[7] NCCN Clinical practice Guidelines in Oncology: Ovarian Cancer including fallopian tube cancer. V.2. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp, accessed 17 April 2011.

[8]National Cancer Institute, US National Institutes of Health. Stage III and Stage IV Ovarian Epitehlial Cancer Treatment and Recurrent or Persistent Ovarian Cancer Treatment. http:// www.cancer.gov/cancertopics/pdq/treatment/ovarianepithelial/HealthProfesion, accessed 15 April 2011

[9]Population pharmacokinetics of bevacizumab: structural model identification, mean population pharmacokinetic parameter estimation, and covariate analysis. *Genentech Inc. Report* 03-0324-1751. September 2003. *(Submitted with Response to Questions (EMEA/H/C/582/II/015)September 2007, Section 5.4 Vol 2 [8092])*

[10]EMEA Committee for Medicinal Products for Human Use (CHMP). Guidelines on the Evaluation of Anticancer Medicinal Products in Man. CPMP/EWP/205/95.3/Corr.

Is PFS a valid endpoint for the requested indication?

Section III.1.3 "Study Endpoints" of the European Union (EU) document[9] sets out the conditions for PFS to be acceptable. The present study meets these conditions because recurrence of ovarian disease would require treatment with effective chemotherapy[8], which would complicate analysis of OS. Also survival after disease progression is relatively long, and the toxicity of the test drug in other studies, although significant, is claimed to be not major. The guidelines do require that OS be the secondary endpoint if PFS is the primary endpoint, although under stated conditions, this may not be required for regulatory approval. The guidelines recommend that the estimated treatment effect on OS should be sufficiently precise to ensure there are no negative effects on this endpoint.

Evaluator's comments: The definition used in the study for PFS was the time from randomisation to objective progression, or death from any cause, as in the EU document [11]. The use of PFS in the study is acceptable for establishing efficacy. However its use is not without controversy, especially in the case of inhibitors of angiogenesis, because in some cases prolongation of the PFS does not correlate with an increase in OS. This will be discussed later in the risk benefit analysis. Also required in the document was an analysis of OS data to show that no detrimental effect on OS of the test treatment. This was the case in the present study (see later) as shown by a HR (HR) of 0.81 (95% confidence interval (CI) 0.63; 1.04), although the data were limited at the time of the analysis, as only 15.8% of patients had died and thus a reliable estimate of the duration of OS could not be determined.

Was PFS assessed appropriately?

This question has two parts, firstly, whether the study protocol and the Statistical Analysis Plan (SAP) for assessing PFS were appropriate, and secondly, whether the results show that these procedures were followed. The second question will form part of the results section that follows.

The SAP's plan for analyzing PFS was consistent with the guidelines[11] with reference to managing and assessing deviations and withdrawals after randomisation; frequency and methods of assessment for disease progression, handling deviations from scheduled assessments and the role of the independent review. The plan is presented in brief in the next sections.

Planned assessment and analysis of PFS and OS

Method and time of assessment

Radiographic tumor assessments were to be performed at baseline and subsequently as follows:

- After Cycle 3 (before Cycle 4) of paclitaxel-carboplatin.
- After Cycle 6 of paclitaxel-carboplatin (before Cycle 7, bevacizumab/placebo).
- After completion of carboplatin and paclitaxel chemotherapy, and during treatment with bevacizumab/placebo: Cycle 10 (before Cycle 11), Cycle 14 (before Cycle 15), Cycle 18 (before Cycle 19), Cycle 22 (within 4 weeks as of Day 1).
- After completion of all protocol therapy: every 3 months for 2 years, then every 6 months for 3 years, then annually.

[11]EMEA Committee for Medicinal Products for Human Use (CHMP). Appendix 1 to the Guidelines on the Evaluation of Anticancer Medicinal Products in Man. CPMP/EWP/205/ 95.3/ Corr. Methodological Considerations for Using Progression-Free Survival (PFS) as Primary Endpoint in Confirmation Trials for Registration. EMEA/CHMP/27994/2008.

Additionally, radiographic imaging could be performed at any time if clinical or laboratory findings indicated the possibility of progressive disease, such as rising serum Cancer antigen 125 (CA-125)[12] levels that alone did not meet the criteria for disease progression according to the protocol. The GOG Response Evaluation Criteria in Solid Tumors (RECIST)[13] was used to assess response and included a definition of progression based on rising serum CA-125 levels in the absence of clinical or radiographic evidence of progression but this was modified for the reasons that follow.

Use of CA-125 to determine disease progression

The Overview (Section 2.5, page 15) cited published data evaluating CA-125 concentrations in patients with ovarian cancer receiving bevacizumab or sorafenib, suggesting that there was a small subset of patients in whom CA-125 levels fluctuate or rise gradually for many months, sometimes years, before radiological progression. The Overview concluded that using CA-125 levels to define progression may be less reliable in some patients receiving "antiangiogenics". Further, the benefit of starting second line treatment of patients based solely on CA-125 progression has also been questioned (referenced in the sponsor's application). Because of these findings associated with CA-125 as a marker of progression, and of the potential issues inherent with censored analyses, it was decided that the appropriate primary analysis for the GOG-0218 study was investigator-assessed PFS censored for patients with progression based on CA-125 alone (and patients who received non- protocol antineoplastic treatment [NPT] therapy). The protocol-defined primary analysis of PFS (GOG analysis) did not censor for CA-125 progression nor for NPT.

Evaluator's comments: This deviation from the study protocol was considered acceptable and is the more conservative. An issue in assessing PFS can be if investigators initiate an assessment outside of the scheduled dates for assessment, because in an unblinded study this may introduce "assessment bias"[11]. In Study GOG-0218, however, the study was double-blinded (see below).

Primary efficacy analysis of PFS

The primary efficacy analysis of PFS for the trial was based on the investigator assessment and consisted of all pairwise comparisons of PFS between treatment regimens. Primary efficacy comparisons of CPB15 versus CPP and CPB15+ versus CPP were referred to as "initial primary" comparisons, as they were scheduled to occur earlier than the CPB15 versus CPB15+ comparison referred to as "late primary." As per protocol, the final analysis of the initial primary comparisons was to occur when there were at least 375 PFS events observed among patients randomised to receive standard therapy (CPP). The SAP provided acceptable details for initial and late primary comparisons. The cutoff date for the "final" late primary comparison was the date of the 710th event from patients randomised to CPB15 and CPB15+ who are progression-free for at least 18 weeks. The comparisons to be made are shown in Table 3 below.

[12] CA 125: Cancer antigen 125, a protein normally made by certain cells in the body, including those of the ovaries, Fallopian tubes, uterus, cervix, and lining of the chest and abdominal cavities (the pleura and peritoneum). When CA 125 is found in higher than normal amounts (more than 35 kU/ml), it is considered a marker for cancer. Benign conditions can also raise CA 125 levels.

[13] RECIST (Response Evaluation Criteria In Solid Tumors) is a set of published rules that define when cancer patients improve ("respond"), stay the same ("stable") or worsen ("progression") during treatments. The criteria were published in February, 2000 by an international collaboration including the European Organisation for Research and Treatment of Cancer (EORTC), National Cancer Institute of the United States, and the National Cancer Institute of Canada Clinical Trials Group.

Table 3.

Analyses to Be Performed during Study GOG-0218

Analysis	Comparison	Triggering Event
Initial primary	CPB15 vs. CPP, CPB15+ vs. CPP	Interim and final analyses triggered by the 281st and 375th PFS events in the CPP arm, respectively
Late primary	CPB15 vs. CPB15+	Interim: At either the interim initial primary or final initial primary analysis whenever both CPB15 and CPB15+ were found to be superior to CPP
		Final: 710th PFS event in the CPB15 and CBP15+ arms for patients who were progression free at Cycle 6 (prior to Cycle 7)

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; PFS = progression-free survival.

Because Arms CPB15 and CPB15+ have identical regimens until Cycle 7 (Week 19 of bevacizumab treatment), PFS events that occur prior to Cycle 7 are informative for both efficacy comparisons. Thus, in the formal PFS comparison of CPB15 versus CPP, PFS data from patients randomised to both experimental arms were to be combined. For this comparison, the PFS event times for patients randomised to CPB15+ were to be censored at the date of Cycle 7 treatment. An analogous use of PFS data from Arm CPB15 was to be made in the comparison of CPB15+ versus CPP. This pooling of PFS events was to be used for Kaplan−Meier analysis as well as for the log-rank tests. Log-rank tests and Kaplan-Meier curves for a standard intent-to-treat analysis (without the pooling of PFS events occurring prior to Cycle 7 in the active arms) were also to be reported. If either stratified log-rank test produced statistics greater than thresholds specified for the interim or final analysis and the estimated HR favored the bevacizumab arm over control, then it would be concluded that the corresponding bevacizumab-containing regimen (CPB15 or CPB15+) prolonged PFS compared with standard therapy alone among women with newly diagnosed, previously untreated, FIGO Stage III with any gross (macroscopic or palpable) residual disease or FIGO Stage IV epithelial ovarian, primary peritoneal, or fallopian tube cancer.

Significance level and power

The two hypotheses constituting the initial primary analysis were to be tested simultaneously at a one-sided value of 0.025. Only if both hypotheses were rejected (that is, both CPB15 and CPB15+ were statistically superior to CPP) would the two experimental arms be formally compared. In this case, the late primary analysis was to be tested at a one-sided $\alpha = 0.025$, although the protocol-specified level for this test was a one-sided α value of p of 0.05. Based on the protocol-specified one-sided $\alpha = 0.05$ level test, this design had an approximate 90% chance to correctly identify CPB15+ as superior to CPB15 if extended bevacizumab treatment decreased the conditional hazard of PFS by 20% for bevacizumab-treated patients who were progression free until Week 18. Based on the one-sided $\alpha = 0.025$ level test described previously, the power for this comparison declined to approximately 84%.

As described in the SAP, because of the several analyses (including the interim analysis) involved, 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 hazard ratio (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.

If a p-value ≤ 0.0116 crossed the p-value boundary, it was to be considered statistically significant

Evaluator's comment: As stated above, it is important to note that because of the above statistical considerations, the upper limit of p value for significance was not the usual 0.05, but 0.0116.

Stratification

The stratification factors consisted of those used for patient randomisation, namely GOG performance status and disease stage. Results from an unstratified log-rank test were also to be presented. Kaplan-Meier methodology was to be used to estimate median PFS for each treatment arm.

Secondary efficacy assessment of OS

The analysis for the secondary efficacy endpoint of OS was to occur at either the interim or final PFS analysis. If either experimental regimen decreased the risk of death by 23% compared with the control arm (that is, the median OS extended from 34 to 44 months), and assuming that OS events were anticipated from 90% of patients enrolled (i.e., 10% cure rate), then this design provided approximately 50% and 65% power to correctly identify that regimen as superior to standard therapy at the interim and the final PFS analysis, respectively. The power calculations were based on approximately 290 OS events from an experimental arm and the standard therapy arm at the interim PFS, and approximately 400 OS events at the final PFS analysis.

Evaluator's comment: The low power of the analysis of OS, 50% at the time of interim analysis of PFS and 65% at the time of final analysis of PFS, indicates that no conclusion can be made on OS at these times except that a separate analysis showed the test arms did not worsening survival up to the time of the analysis.

Secondary efficacy assessment of Overall Response Rate (ORR)

Objective response was defined as the occurrence of a complete or partial best overall confirmed response (CR or PR) (per modified 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 a post-baseline tumor assessment was not performed, were considered non-responders in the analysis of objective response. ORRs were formally compared between arms using the Cochran-Mantel-Haenszel test, with GOG performance status and disease stage as stratification factors. This analysis included only patients who had measurable disease at baseline. Patients were grouped according to the treatment arms to which they were assigned at randomisation. For each treatment arm, an estimate of the ORR and its 95% CI was determined; the 95% CI was constructed using the normal approximation to the binomial distribution.

Evaluator's comment: Note that the ORR included only patients with measurable disease at baseline. At baseline, approximately one-third of patients had residual disease with lesions less than 1 cm after surgery (macroscopic optimal debulking) and would not be assessable for ORR. The ORR group was therefore a selected population of patients in whom optimal debulking was not possible or not done. They therefore form a different patient population from all randomised. It is not known if the response rates to chemotherapy in the two patient populations are the same.

Withdrawals, deviations, missing data and protocol violators

The EU Appendix to the Guidelines on the Evaluation of Anticancer Medicinal Products in Man[11] stresses the need to plan prospectively how to manage these problems. In the CSR of the trial and in the SAP this has been done with reference to follow-up for survival (OS), but not for PFS. Such problems affect the times of assessment for disease progression, and so PFS, the primary endpoint in this study.

Evaluator's comment: The failure to specify these procedures for PFS in the SAP could be a problem but the related problems have been appropriately handled in the data analysis by the use of sensitivity analyses (see below).

Total sample size

The total sample size required for the study was 1800 patients.

Analysis populations

The analysis population for primary efficacy was the intent-to-treat population, defined as all patients randomised to study treatment, irrespective of whether or not the assigned treatment was actually received. For efficacy analyses, patients were grouped according to the treatment assigned at randomization.

The primary safety population (PSP) consisted of all randomised patients who received at least one full or partial dose of any study treatment during Cycle 2 or later. This population was defined as such because all three treatment arms were identical prior to Cycle 2. For safety analyses, patients were grouped according to the treatment assigned at randomization.

Independent review committee

An IRC's assessment of the primary endpoint of PFS was added as a sensitivity analysis to provide additional support for the primary endpoint of investigator-assessed PFS. The IRC for this study used radiologic and clinical evidence to detect tumor progression in a retrospective manner. Imaging-based evaluation by the IRC was performed by two radiologists and adjudicated by a third radiologist if necessary. An oncologist reviewed clinical data first and then reviewed both the radiologic and clinical evidence to make a final determination of response and progression status. The reviews were performed in a blinded fashion. CA-125 marker data were not sent to the IRC to determine progression status.

Evaluator's comment: The study was double-blinded so that bias in investigator assessment was unlikely. Nevertheless, the EU Guidance document[11] that "Data on PFS/DFS will be more persuasive if the trial results from the independent, blinded evaluation does not differ from the investigator assessments to an important degree"

Assessment of "Health Related Quality of Life"

The principal measure used in this study to assess the HRQoL was the self-administered Functional Assessment of Cancer Therapy-Ovarian (FACT-O) Trial Outcome Index (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 is the Trial Outcome Index (TOI) which consisted of PWB + FWB + OCS scores. The minimum important difference for the TOI score is 5 points and for the OCS 3 points. A higher score means better health-related quality of life. Each patient was asked to complete the FACT-O questionnaire at the following time points during their participation in the study:

- Timepoint 1: Pre-treatment, baseline (Prior to Cycle 1).
- Timepoint 2: Midpoint of the scheduled chemotherapy treatment phase (Prior to Cycle 4: 9 weeks after starting treatment).
- Timepoint 3: End of the scheduled chemotherapy treatment phase and start of the extended treatment phase (Prior to Cycle 7: 18 weeks after staring treatment).
- Timepoint 4: Approximate midpoint of the scheduled bevacizumab/placebo only extended treatment phase (Prior to Cycle 13: 36 weeks after starting treatment).
- Timepoint 5: End of the scheduled bevacizumab/placebo only extended treatment phase (Prior to Cycle 21: 60 weeks after starting treatment).
- Timepoint 6: Follow-up (6 months after the scheduled end of study treatment: 84 weeks after starting treatment).

The section "Overall FACT-O TOI Score" (in the SAP), provided details on the scoring method under the headings of Deriving a Total Score, Descriptive Summaries, and Hypothesis Testing and Method.

Evaluator's comment: The methodology, as described, was acceptable

Sensitivity analyses

Sensitivity analyses planned for the analysis of trial data were:

1. Assessment of PFS by an Independent Review Committee (IRC)

2. Non–Protocol Cancer Therapy Impact Analyses:

Impact Analysis of Differential Usage of Non-Protocol Therapy (NPT) among Treatment Arms

If a difference of greater than 5% existed between the control arm and either experimental arm in the number of patients who underwent non-protocol-specified cancer therapy prior to experiencing documented disease progression, then a sensitivity analysis was to be performed. The sensitivity analysis was to be a "worst-case" analysis of PFS. Patients in the control arm who received NPT prior to progression were to be censored at the date of their last radiographic tumor assessment prior to the initiation of NPT. Patients in the bevacizumab arms who received NPT prior to progression however, were to be considered to have progressed on the date of their last radiographic tumor assessment prior to the initiation of NPT.

Analyses of PFS without Censoring for Non-Protocol Cancer Therapy

Because the number of patients receiving NPT can be substantial, for each primary analysis of investigator-determined PFS a sensitivity analysis will be performed without censoring PFS data at the last tumor assessment prior to therapy initiation for patients receiving NPT. This sensitivity analysis was performed for the IRC-determined PFS endpoint.

3. Discontinuation Due to Toxicity Impact Analyses

A sensitivity analysis was performed to assess the impact of discontinuation due to toxicity on the PFS comparison. Patients in this study who discontinued study treatment may undergo disease assessments at intervals that are different from those mandated during on-study treatment. In this analysis, the PFS for any patient who discontinued study treatment prior to disease progression was to be censored at the time of the last tumor assessment prior to discontinuation. Additionally, the primary efficacy analysis was to be repeated for the eligible population based on centrally confirmed histologic diagnosis.

4. Worst-Case Analyses Accounting for Missing Data

Two sensitivity analyses were performed to evaluate the potential impact of missing scheduled tumor 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 cutoff, they were to be counted as having progressed on the date of the first of these missing assessments. In the first analysis, the imputation rule was to be applied to patients on an experimental arm only. In the second analysis, the imputation rule was to be applied to patients in both treatment arms. Statistical methodologies analogous to those used in the initial primary analysis of PFS were to be used for this worst-case analysis.

5. Protocol-specified (GOG) PFS analysis: Investigator-assessed PFS with neither NPT nor CA-125 censoring

6. Worst-case analyses accounting for early discontinuation

Analyses of Biomarkers for Angiogenesis. In the study, identification of potential predictive diagnostic biomarkers was sought. Because bevacizumab targets the host tumor vasculature, the study explored not only potential plasma markers but also imaging parameters and genetic profiles that correlate with patient response. Extensive sample collection in the study was to allow a comprehensive analysis of tumor, plasma/serum, and DNA. These results will not be evaluated or reviewed in this report.

Safety Assessment

Adverse event forms were completed after each cycle during the treatment phase of the trial. Thereafter, patients were monitored for delayed toxicity every 3 months for 2 years, then every 6 months for 3 years and then annually during the post treatment period. All patients who discontinued or completed study treatment were followed for survival according to the following schedule: every 3 months when the patient was < 2 years in the post-treatment period and every 6 months when the patient was 2-5 years in the post treatment period. The protocol contained no specific requirement regarding the frequency of survival follow-up when the patient was more than 5 years in the post treatment period. It is GOG standard procedure to follow patients annually after the patient has completed 5 years of follow-up.

Method of Assessment

For all safety analyses, patients were grouped according to the treatment to which they were randomised. Safety endpoints were summarised with descriptive statistics. The NCI CTCAE, v3.0, was used to classify the type and severity of toxicities observed during treatment according to the maximum severity for each organ system or preferred term. The proportion of patients experiencing at least one adverse event was reported by toxicity term and by treatment arm. The safety evaluable population included all randomised patients who received at least one full or partial dose of any study treatment during Cycles 2 or beyond. Patients who did not receive any of their assigned study treatment were not included in these analyses.

Evaluator's comment: Cycle 2 or beyond was selected because the test drug, bevacizumab was first administered in Cycle 2 (see treatment, below). Patients who suffered adverse events from chemotherapy in Cycle 1 were included in the S3 analysis (see below).

Three secondary safety analyses were performed. These analyses differed according to the time period during which the adverse events occurred:

- S1 analysis: Cycle 2 to before Cycle 7
- S2 analysis: Cycle 7 to the end of follow-up

- S3 analysis: prior to Cycle 2

The S1 analysis focused on toxicity during the concurrent chemotherapy phase of treatment. Data from the CPB15 and CPB15+ arms were pooled for the S1 analysis because these regimens were identical during this period. The proportion of patients experiencing at least one adverse event was reported by the toxicity term and according to whether or not the patient was randomised to receive bevacizumab.

The S2 analysis was the primary means for comparing safety between the CPP and CPB15+ and CPB15 regimens beyond the chemotherapy phase (that is, during the extended bevacizumab treatment phase). The proportion of safety evaluable patients experiencing at least one adverse event was reported by the toxicity term and by treatment arm.

The S3 analysis characterised early toxicity from carboplatin + paclitaxel therapy in this patient population. For this analysis, all three treatment arms were pooled because the regimens were identical prior to Cycle 2. The exploratory safety population was used for this analysis and included all patients enrolled to the study, received any of their assigned study treatment.

Protocol amendments

Study GOG-0218, which began on 14 October 2005, was amended eight times prior to the database lock for the primary analysis. Major changes were implemented with Amendments 3 and 4 to address accrual problems that were specifically raised by the investigators.

In *Amendment 3* in July 2007, the entry criteria were expanded to include Stage III optimally debulked patients with macroscopic residual disease. The reason for the amendment was that with the previous study population of patients with Stage III-suboptimal and Stage IV tumors, accrual in the first 18 months of the study was less than half that expected. A survey of the study sites revealed that the majority of patients with epithelial ovarian cancer or primary peritoneal cancer undergoing up front surgery were optimally debulked with no more than 1 cm maximal diameter residual tumor implants. Enrollment of patients with Stage III optimally debulked cancers was limited to only those with macroscopic residual disease at the completion of initial surgery; this was because those with no gross (macroscopic or palpable) residual disease were felt to be at too low a risk for relapse and death to justify their inclusion. Although Mullerian adenocarcinomas of the fallopian tube are much less common than epithelial ovarian and primary peritoneal cancers, due to similarities in response to treatment and prognosis, this disease has been grouped with epithelial ovarian and primary peritoneal cancers in National Cancer Institute trials. This study also included these cancers from October 2008.

In Amendment 4 in May 2008, the primary endpoint was changed from OS to PFS assessed by investigators; unblinding was allowed at disease progression; and the sample size was decreased from 2000 to 1800 patients. An exploratory endpoint of PFS assessed by the IRC was also added to confirm the PFS endpoint.

Evaluator's comment: The Protocol Amendments are acceptable and would not compromise the analyses and conclusions of the study, assuming that the times of assessment for PFS were not changed when PFS was made the primary endpoint rather than OS, 2 years and 7 months after the trial started.

Study participants

The study population consisted of patients with a histologic diagnosis of epithelial ovarian cancer, peritoneal primary carcinoma or fallopian tube cancer; 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 Stage III cancer in which the largest maximal diameter of any residual tumor implant at the completion of this initial surgery was no greater than

1 cm were defined as "macroscopic optimally debulked"; all others were defined as "suboptimally debulked." Measurable disease on postoperative imaging studies was not required for eligibility.

Patients with the following histological epithelial cell types were eligible: serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner tumor, or adenocarcinoma, not otherwise specified. However, the histologic features of the tumor must have been compatible with a primary Müllerian epithelial adenocarcinoma. Patients may have had concurrent fallopian tube carcinoma in situ as long as the primary origin of the invasive tumor was ovarian, peritoneal, or fallopian tube.

Inclusion and exclusion criteria

No special discussion of the criteria is needed except to note the eligible patient population has been selected in such a way as to be very healthy apart from its ovarian cancer.

Planned treatments

Patients were randomised on a 1:1:1 basis to one of the following three treatments:

- 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.

However, it was estimated that of the order of 5% of patients in the population who were eligible for participation in the trial would develop peripheral neuropathy or refractory acute hypersensitivity infusion reactions, which would necessitate discontinuation of paclitaxel.

Docetaxel is a taxane with reduced potential for neurotoxicity compared with paclitaxel. In addition, docetaxel has been safely substituted for paclitaxel in patients experiencing severe acute hypersensitivity to paclitaxel for whom re-challenge was either unsuccessful or deemed unsafe. In order to optimise cytotoxic therapy in all arms of the current trial, reduce the likelihood of protocol violations and avoid imbalances in the type of taxane utilised in each treatment arm, docetaxel was selectively substituted for paclitaxel in circumstances in which peripheral neuropathy or hypersensitivity warranted discontinuation of paclitaxel at the discretion of the investigator.

Rationale of doses used

The bevacizumab dose, 15 mg/kg every 3 weeks, is equivalent to a dose of 5 mg/kg/wk, the standard dose of bevacizumab used in clinical trials across multiple tumor types. This dose was used in previous Phase II trials that demonstrated single-agent activity of bevacizumab in ovarian, fallopian tube, and primary peritoneal cancers.

The dosing approved in the Australian PI for second-line treatment of colon cancer includes 3-weekly treatment with 15mg/kg and is also an option for breast cancer, Grade IV glioma and NSCLS.

Note: A formulation of bevacizumab to be used in the trial was provided to investigators. The use of commercially available Avastin was a protocol violation. The formulation used was stated to be qualitatively the same as that in the Australian PI (neither formulation was quantitative).

Paclitaxel

The dose recommended in the Australian PI in combination with a platinum drug to treat ovarian cancer is 175mg/m^2.

Carboplatin

The recommended dose in the Australian PI as a single agent for advanced ovarian cancer is 400mg/m^2 in patients with normal renal function. This is modified for patients with impaired renal function. With creatinine clearance values of 20-39 mL/min, the dose is 250mg/m^2 and with a creatinine clearance of 0-19 mL/min the dose is 150mg/m^2. In combination with other drugs, the dose is not specified, and "Dosage adjustments should be made according to the treatment regimen adopted and the results obtained from haematological monitoring."

Evaluator's comment: In the present study, GOG0218, the dose of carboplatin was determined from the Clavert formula which uses the glomerular filtration rate (GFR), and a target area under the plasma concentration time curve (AUC) of carboplatin of 6. The formula is Carboplatin dose (mg) = target AUC x (GFR + 25). In this study GFR was equated to the creatinine clearance value. The creatinine clearance value was calculated in turn from the serum creatinine concentration by the formula Ccr = [{98 - [0.8 (age - 20)]} divided by Scr] x 0.9 where Ccr = creatinine clearance in ml/min; age = patient's age in years (from 20-80); and Scr = serum creatinine in mg/dl.

To compare the dose adjustment with that recommended in the Australian PI, the evaluator used in the Calvert formula creatinine clearance values of 20, 39 and 0 and 19 chosen from the values in the PI. This gives values of carboplatin total doses of 230 mg, 384 mg, and 150 mg, and 264 mg respectively. Taking an average figure of 1.6 m^2 for body surface area, this equates to carboplatin doses of 144, 240, and 94 and 165 mg/m^2, respectively. Where the dose recommended in the Australian PI for a creatinine clearance of 20-39 mL/min was 250 mg/m^2 carboplatin, the trial would use doses from 144 to 240 mg/m^2, and if creatinine clearance was 0-19 mL/min doses of 94 to 165 mg/m^2 instead of the PI recommended dose of 150 mg/m2. This indicates that the doses in the study are similar to those in the PI for patients with better renal function but lower than the recommended doses when renal function is more impaired.

It can be argued that use of the formula results in a dose appropriately high when renal function is better and in a lower dose that reduces the risk of nephrotoxicity when renal function is poor. By maintaining the AUC for carboplatin at 6, efficacy would be maintained at all doses. The study was limited to patients whose serum creatinine was increased by no more than 1.5 times above the institution's normal vale. As can be seen from the above formula for calculating Ccr, this would reduce the Ccr value by a third. For a typical normal value of 40 mL/min, patients with a value below 26 mL/min would be ineligible for the study, so dosage of carboplatin in such patients is less of an issue but is relevant for advice to prescribers in the PI, if the product were approved for the requested indication.

Docetaxel

Docetaxel was to be administered instead of paclitaxel in special cases, mainly of peripheral neuropathy, at a dose of 75 mg/m^2 IV over 1 hour.

Evaluator's comment: Docetaxel (Taxotere) is approved in Australia for the treatment of metastatic carcinoma of the ovary after failure of first line or subsequent chemotherapy. The dose recommended when administered as a single agent for this indication was 100

mg/m^2, and in combination with carboplatin and trastuzumab to treat HER2+[14] breast cancer, 75 mg/m^2. The dose in the present study is therefore acceptable.

Rational of number of treatment cycles

From available data, it was concluded that the absolute number of cycles within a clinically relevant range of between 6 and 8 is unlikely to have a measurable effect on long-term disease control. At present, there are no prospective data to indicate that dose intensity, cumulative dose delivery, or number of cycles has an impact on long-term outcomes following primary therapy with platinum and paclitaxel. There is, however, evidence of increased risk of severe adverse effects of treatment with the combination of paclitaxel and carboplatin beyond the standard 6 cycles. These effects include cumulative platelet toxicity and increased risks of severe hypersensitivity, particularly related to carboplatin, as well as increased risk of high-grade neuropathy related to paclitaxel. The above factors served as the rationale for 6 cycles of induction chemotherapy in the current trial.

Duration of therapy

One question that had not been asked in other studies was the optimal duration of treatment with bevacizumab when used in combination with chemotherapy. Based on the mechanism of action of bevacizumab, there may be a benefit of extended therapy with this agent until disease progression in extending PFS and/or OS in this patient population. It was also decided to investigate whether additional benefit of bevacizumab beyond the general duration of standard primary chemotherapy exists. Therefore, two experimental arms were selected for comparison with standard cytotoxic chemotherapy of paclitaxel and carboplatin (CP): one incorporating 5 cycles of bevacizumab (CPB15) with chemotherapy, and the other with both concurrent and single-agent bevacizumab for an additional 16 cycles after completion of concurrent treatment (CPB15+).

Removal of patients from therapy or assessment

Patients received treatment until disease progression, death, the development of adverse events requiring discontinuation of protocol treatment or completion of 22 cycles of therapy, whichever came first. These rules applied to all patients, including those who had persistent but non-progressive disease after completion of Cycle 6, meaning that no response threshold was required in order to receive maintenance protocol therapy. Patients could voluntarily withdraw from the study at any time. No form of therapy targeted for a patient's cancer other than that specified in the protocol was to be administered until disease progression.

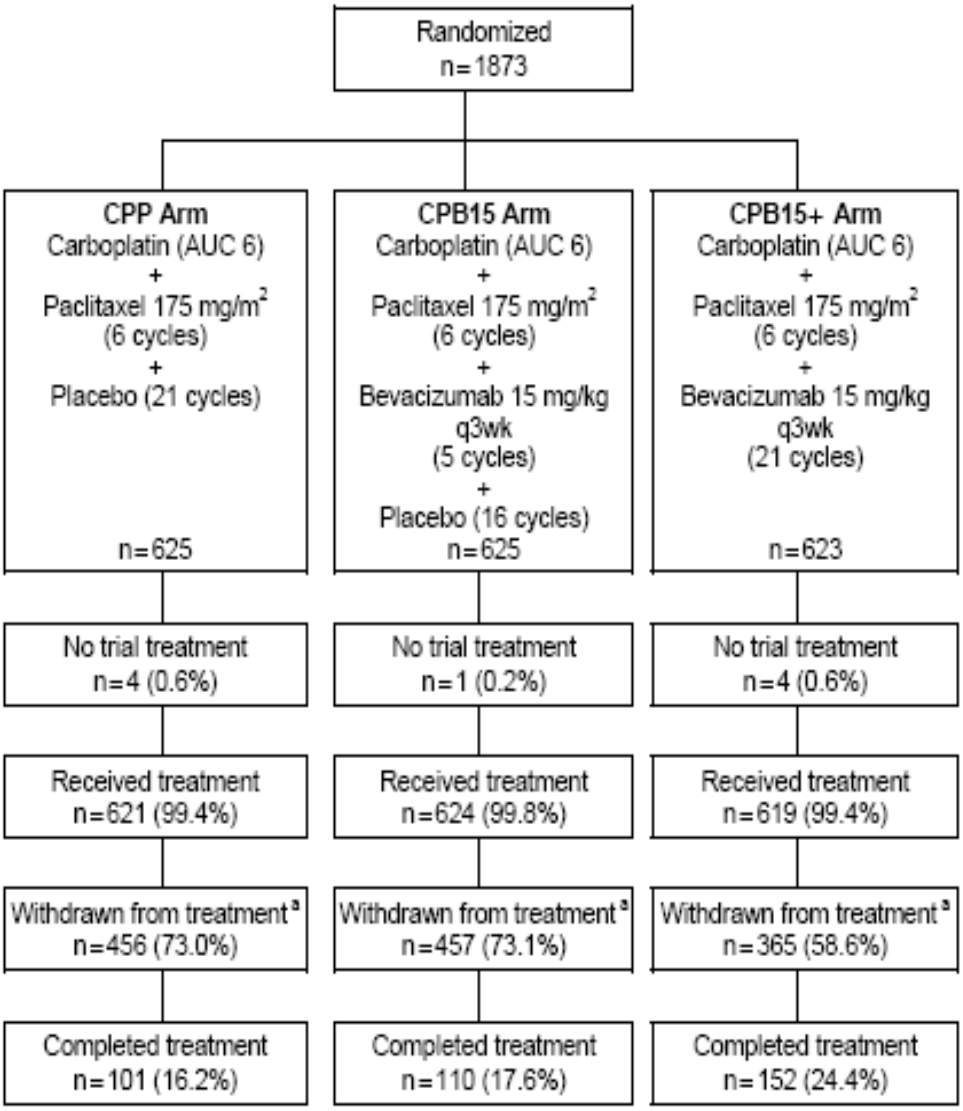
Results-patient population

Participant flow

The disposition of patients and reasons for treatment discontinuation are shown in Figure 2 below.

[14] HER2 is expressed by, and involved in the growth of, some cancer cells. Some breast cancers express HER2 protein. HER2 is a gene that sends control signals to your cells, telling them to grow, divide, and make repairs. A healthy breast cell has 2 copies of the HER2 gene. Some kinds of breast cancer get started when a breast cell has more than 2 copies of that gene, and those copies start over-producing the HER2 protein. As a result, the affected cells grow and divide much too quickly.

Figure 2. Disposition of patients in study GOG-0218



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.

Of the 1873 randomised patients, 9 patients (4 in the CPP arm, 1 in the CPB15 arm, and 4 in the CPB15+ arm) did not receive any study treatment (see Table 4). The primary reason for not receiving treatment was patient withdrawal or refusal for reason other than toxicity. One patient in the CPP arm whose reason for not receiving any study treatment was "other", died before receiving any study treatment

Table 4.

Patient Disposition and Reasons for Treatment Discontinuation: Randomized Patients

Status	CPP (n=625)	CPB15 (n=625)	CPB15+ (n=623)
Received study treatment	621 (99.4%)	624 (99.8%)	619 (99.4%)
Completed study treatment per protocol criteria	101 (16.2%)	110 (17.6%)	152 (24.4%)
Not known to have discontinued study treatment	64 (10.2%)	57 (9.1%)	102 (16.4%)
Discontinued study treatment	456 (73.0%)	457 (73.1%)	365 (58.6%)
Disease progression, relapse during active treatment	310 (49.6%)	270 (43.2%)	173 (27.8%)
Adverse event/side effects/complications	70 (11.2%)	88 (14.1%)	97 (15.6%)
Patient withdrawal/refusal for reason other than toxicity	41 (6.6%)	52 (8.3%)	46 (7.4%)
Death on study	8 (1.3%)	8 (1.3%)	11 (1.8%)
Patient off-treatment for other complicating disease	5 (0.8%)	2 (0.3%)	6 (1.0%)
Other	22 (3.5%)	37 (5.9%)	32 (5.1%)
Patient did not receive study treatment	4 (0.6%)	1 (0.2%)	4 (0.6%)
Patient withdrawal/refusal for reason other than toxicity	3 (0.5%)	1 (0.2%)	4 (0.6%)
Other	1 (0.2%)	(0.0%)	(0.0%)

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.

As shown above, more patients (24.4%) completed study treatment in the CPB15+ arm than in the CPP (16.2%) and CPB15 (17.6%) arms, and when the study closed (Feb 2010) more on the CPB15+ arm were still on treatment. Such patients could continue treatment with bevacizamub up to 22 cycles, whereas patients on the CPB15 and the CPP had already finished chemotherapy and were receiving placebo and were not offered further treatment.

Among patients who discontinued study treatment, the majority of patients (49.6% in the CPP arm, 43.2% in the CPB15 arm, and 27.8% in the CPB15 + arm) discontinued because of disease progression. Higher percentages of patients in the bevacizumab containing arms (14.1% in the CPB15 arm and 15.6% in the CPB15+ arm) compared with the control arm (11.2% in the CPP arm) discontinued study treatment because of an adverse event, side effect or complication. The percentage of patients who discontinued study treatment because of patient's withdrawal of consent or refusal to receive further treatment for a reason other than toxicity or because the patient went off treatment for other complicating disease was comparable in the three treatment arms. Similarly, the percentage of patients who discontinued study treatment because of a death event on study was comparable across the three treatment arms.

Protocol violations

Patient ineligibility

Patient eligibility (see Table 5) was reviewed three times; first, the GOG reviewed the entry checklist of all patients; second, the central GOG Gynecology Management Committee reviewed pre-treatment data forms, operational reports and pathology reports of 95.1% of patients; and third, the Central Pathology Committee reviewed reports and pathology slides of 95.7% of patients.

The results of the first GOG review are shown in Table 6 and those of the second and third reviews in Table 7.

Table 5.

Patient Eligibility: Randomized Patients

	CPP (n=625)	CPB15 (n=625)	CPB15+ (n=623)
Eligible patients			
Yes	594 (95.0%)	581 (93.0%)	580 (93.1%)
No	31 (5.0%)	44 (7.0%)	43 (6.9%)
Inclusion/exclusion criteria not met [a]			
I3.11, E3.21 (Histology; borderline/recurrent)	14 (45.2%)	13 (29.5%)	16 (37.2%)
I3.11 (Histology)	5 (16.1%)	8 (18.2%)	11 (25.6%)
E3.33 (Proteinuria)	5 (16.1%)	7 (15.9%)	6 (14.0%)
I3.11, I3.12 (Histology; epithelial subtype)	2 (6.5%)	11 (25.0%)	2 (4.7%)
I3.12 (Epithelial subtype)	3 (9.7%)	3 (6.8%)	4 (9.3%)
I3.11, E3.25, E3.26 (Histology; synchronous endometrial cancer; other primary within 5 years)	1 (3.2%)	2 (4.5%)	4 (9.3%)
E3.31 (Cardiovascular disease)	1 (3.2%)	(0.0%)	(0.0%)

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.

[a]Details of each of the numbered inclusions and exclusion criteria are detailed in the corresponding numbered subsection of the study protocol.

As shown, a total of 118 of 1873 patients (6.3%) were deemed not eligible by checklist review by the GOG. Most were due to wrong stage of disease and wrongly diagnosing low-risk disease.

Evaluator's comment: The percentage of patients with borderline histology was higher (45%) in the CPP arm than in the CPB15 arm (30%), and with an ineligible epithelial subtype higher in the CPB15 arm (25%) than in either of the other arms (CPP 6.5%, CPB15+ 4.7%). The evaluator assumed that these differences were due to the small numbers of patients involved and to data variability and conclude they would not adversely affect the data analysis.

Table 6 shows similar results for excluded patients, when reviewed by the second and third groups. In the CPP, CPB15 and the CPB15+ arms, the Central Pathology Review excluded 2.3%, 2.8% and 3.9% of patients respectively, and the Gynaecology Management Committee excluded 3.2%, 4.9%, 3.7% of patients, respectively. Pathology characteristics of the cancers were similar in each of the three arms.

Stage III optimally debulked disease with no macroscopic residue

Patients with this stage of disease were ineligible for the study, and so were protocol violators. One hundred and six 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.

Table 6.

Gynecology and Central Pathology Review of Patient Eligibility: Randomized Patients

	CPP (n=625)	CPB15 (n=625)	CPB15+ (n=623)
Patients had central pathology review?			
Yes	596 (95.4%)	599 (95.8%)	597 (95.8%)
No	29 (4.6%)	26 (4.2%)	26 (4.2%)
Central pathology review			
n	596	599	597
Poorly differentiated	431 (72.3%)	439 (73.3%)	434 (72.7%)
Moderately differentiated	99 (16.6%)	84 (14.0%)	97 (16.2%)
Well differentiated	36 (6.0%)	28 (4.7%)	17 (2.8%)
Not graded	16 (2.7%)	31 (5.2%)	26 (4.4%)
Exclusion	14 (2.3%)	17 (2.8%)	23 (3.9%)
Patients had Gynecology Management Committee review?			
Yes	594 (95.0%)	597 (95.5%)	591 (94.9%)
No	31 (5.0%)	28 (4.5%)	32 (5.1%)
Gynecology Management Committee review			
n	594	597	591
Accept	575 (96.8%)	568 (95.1%)	569 (96.3%)
Exclusion	19 (3.2%)	29 (4.9%)	22 (3.7%)

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.

Wrong drug administration

Overall, 60 patients (3.2%) in the three treatment arms had a protocol violation involving incorrect study drug administration (see Table 7). Twenty three patients were given commercial Avastin.

Non-Protocol Antineoplastic Treatment (NPT)

Non-protocol antineoplastic therapy (NPT) was defined as any anti-neoplastic therapy, including surgery, not consistent with protocol specifications. NPT was classified as treatment prior to disease progression and treatment on or after disease progression. Treatment prior to disease progression refers to the investigator's determination of disease progression regardless of the type of progression (radiographic progression based on scans, CA-125 progression based on protocol criteria or symptomatic deterioration) at a time that did not coincide with the protocol determined assessment date.

Table 7.

Protocol Deviations with Study Drug Administration: Randomized Patients

	CPP (n=625)	CPB15 (n=625)	CPB15+ (n=623)
Patients who were given the wrong study treatment	17 (2.7%)	20 (3.2%)	23 (3.7%)
Commercial Avastin®	6 (35.3%)	8 (40.0%)	9 (39.1%)
Phase A drug during Phase B	6 (35.3%)	9 (45.0%)	8 (34.8%)
Other patient's drug	5 (29.4%)	3 (15.0%)	4 (17.4%)
Blinded drug given Cycle 1	(0.0%)	(0.0%)	1 (4.3%)
Phase B drug during Phase A	(0.0%)	(0.0%)	1 (4.3%)

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.

Phase A drug: carboplatin+paclitaxel at Cycles 1–6; bevacizumab/placebo at Cycles 2–6.
Phase B drug: bevacizumab/placebo at Cycles 7–22.

Non-Protocol Antineoplastic Treatment Administered Prior to Disease Progression

The total number of such patients was 139 (7.4%) of the total 1873 patients. The incidence was comparable across the treatment arms (CPP: 7.2%; CPB15: 8.2%; CPB15+: 6.9%). Most NPTs were systemic therapy (such as chemotherapy and/or biologic); 3 patients in the CPP arm and 2 patients in the CPB15 + arm received hormonal therapy. Sixteen (16) patients received commercially available Avastin prior to disease progression. Overall, there was no difference in the pattern of NPT treatment before disease progression across the three treatment arms.

Non–Protocol Antineoplastic Treatment on or after Disease Progression

This treatment was defined as the first postprogression anti-neoplastic treatment for patients in the study. Because more patients in the CPP arm and the CPB15 arm had progressed, more patients in these two treatment arms were administered subsequent therapy (43.8% of patients in the CPP arm; 40.8% of patients in the CPB15 arm) compared with the CPB15+ arm (33.4%). A total of 737 of the 1873 (39.3%) patients received NPT on or after disease progression.

Evaluator's comment: The total number of protocol violators was high when the above figures were combined. The number included 118 who were ineligible because of violations of inclusion or exclusion criteria, 106 with low risk ovarian cancer and so were not eligible, 60 administered the wrong study drug, 139 who received NPT before protocol defined progression and 737 who received NPT after progression. The last group was anticipated and can be excluded as protocol violators, leaving a total of 376 "true" violators, or 22.5% of the 1873 randomised patients. This high number raises two questions: does it affect the analysis and conclusion of the study and what implication does it have for applying the trial treatment to a general patient population with ovarian cancer?

Possible effect on the study analysis and conclusions

The study remained double blinded throughout the occurrence of these events that were evenly distributed among the three arms of the trial, so the analysis and conclusions would not be affected in a comparative sense. The caveat, as was expected, is that the absolute value for the time of overall survival would be determined not only by the trial treatment but also by the additional NPT given to a significant number of patients. The

sensitivity analyses (see above) provide an assessment of possible effects of NPT on endpoints.

Patient population

The high number of protocol violators indicates that it would be difficult for physicians outside a trial setting to select the same patient population as that in the trial and therefore their treatment outcomes could well differ from those of the trial.

Analysis populations

Three analysis populations are summarised in Table 8. The intent-to-treat population consisted of 1873 randomised patients and was used for all analyses in the CSR except the safety and extent-of-exposure analyses.

Table 8.

Analysis Populations: Randomized 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.

The safety evaluable population (n = 1816) included all randomised patients who received at least one full or partial dose of any study treatment during Cycle 2. The exploratory safety evaluable population (n = 1864) consisted of patients who received at least one cycle of any study treatment (chemotherapy-only phase). This population was used for the summary of adverse events occurring before Cycle 2 (chemotherapy-only phase). Almost all (99.5%) of the randomised patients received at least one dose of any study treatment component, while 9 randomised patients did not receive any study treatment and 48 patients (2.6%) did not receive treatment beyond Cycle 1.

Demographics

Overall, patient demographic characteristics were similar across the three treatment arms. The median age of all randomised patients was 60 years, with a range from 22 to 89 years. The proportion of patients older than 65 years was 27.9%. The majority of patients (88%) enrolled were of an ethnicity other than Hispanic or Latino and the majority of patients (87.2%) were Caucasian.

Baseline characteristics

Overall, baseline disease characteristics were balanced across the three treatment arms. The majority of patients (92.8%) had a baseline PS of either 0 or 1. Approximately one-third of patients (n = 639; 34.1%) had Stage III macroscopic optimally debulked disease, 751 patients (40.1%) had Stage III disease that was suboptimally debulked and 483 patients (25.8%) had Stage IV disease. Baseline performance status and disease stage were stratification factors used in the randomisation and were well balanced across the three treatment arms. To be eligible, patients with Stage III optimally debulked disease had to have macroscopic (visible or palpable) residual disease after surgery. However, 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 (that is, these patients had Stage III microscopic optimally debulked disease and were considered protocol violations; see *Protocol Violations* above).

The primary site of cancer in the majority of patients (1558 patients; 83.2%) was the ovary, followed by the peritoneum (279 patients; 14.9%) and the fallopian tube (36 patients; 1.9%). The majority of patients (1591 patients; 84.9%) had serous adenocarcinoma. Smaller numbers of patients had histologic types with worse prognosis; specifically, 4.2% and 1.7% of patients had clear cell and mucinous adenocarcinoma, respectively; the percentages were comparable across the treatment arms. There were 73 patients (3.9%) who had more than one histologic type, mostly a combination of serous and endometrioid adenocarcinomas. The majority of patients (1359 patients; 72.6%) had ascites prior to initial staging surgery. Approximately two-thirds of patients (1192 patients; 63.6%) had measurable disease at baseline. At study entry, most patients (1768 patients; 94.4%) had elevated CA-125 (greater than the upper limit of normal (ULN)).

Patient medical history

Overall, patient medical history and previous or concomitant use of medications at study entry were balanced across the treatment arms. Medical history included smoking history, diabetes history and use of associated medications, autoimmune disease history and peptic ulcer history.

Collection of concomitant medications focused specifically on use of corticosteroids and non-steroidal anti-inflammatory drugs.

Results - efficacy

An overview of the primary and secondary efficacy results is shown in Table 9.

Primary efficacy results for PFS

According to the SAP, data for patients who progressed solely on the basis of CA-125 criteria were to be censored at the last tumor assessment for which the patient was known to be progression free and data for patients who received NPT for ovarian cancer prior to disease progression were censored at the last tumor assessment prior to initiation of NPT. As a result, although there were 375 events in the control arm per protocol criteria to define the data cutoff date, there were fewer events reported in the control arm in the primary analyses of PFS presented in the following section because of these censoring rules.

For each comparison between an active arm and the control arm (each initial primary PFS comparison), events prior to Cycle 7 from the other active arm were pooled for both the Kaplan–Meier analysis and the log-rank test because patients randomised to the two active arms received identical protocol treatment prior to Cycle 7. As a result, the number of patients shown in an active arm in the initial primary analyses (n = 1248) represents the number of patients from both active arms; however, only events prior to Cycle 7 from the other active arm were counted in the number of patients with an event.

Compared to patients treated with chemotherapy (carboplatin and paclitaxel) alone, patients who received bevacizumab at a dose of 15 mg/kg every three weeks (q3w) in combination with chemotherapy and who continued to receive bevacizumab alone had a clinically meaningful and statistically significant improvement in PFS, as assessed by investigators (36% reduction in the risk of progression or death; stratified HR 0.64, 95% CI 0.54; 0.77, one-sided log-rank p-value <0.0001). Median duration of PFS was increased by 6.2 months in the CPB15+ arm compared to the CPP arm (18.2 compared to 12.0 months). The results are shown as a Kaplan-Meier plot in Figure 3 below.

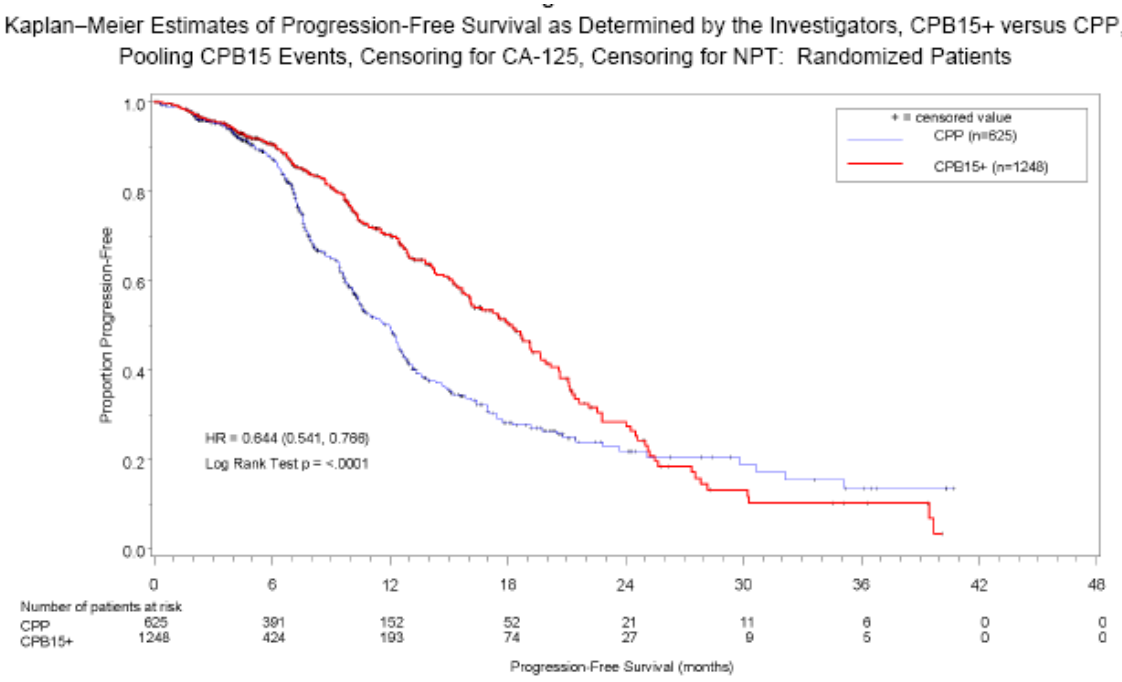
Patients who received bevacizumab in combination with chemotherapy and who did not continue to receive bevacizumab alone (CPB15 arm) had neither a clinically meaningful nor a statistically significant improvement in PFS compared to patients who received chemotherapy alone (CPP arm) (stratified HR 0.84, 95% CI 0.71; 0.99: one-sided log-rank

p-value=0.0204). The results of the unstratified analyses of PFS showed essentially the same results.

For patients randomised to the CPB15 or CPB15+ arm who received Cycle 7 treatment or beyond, an exploratory analysis showed that between the Cycle 7 date and data cutoff date for the primary analyses, 184 PFS events were reported in the CPB15 arm and 127 events were reported in the CPB15+ arm. The stratified analysis yielded a HR of 0.605 (95% CI: 0.481, 0.761) favouring the CPB15+ arm, with no p value calculated.

Note: The analyses above were censored for Ca125 and NPT (see footnote b, Table 9).

Figure 3.



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; GOG=Gynecologic Oncology Group; HR=hazard ratio; NPT=non–protocol-specified therapy. The one-sided p-value and stratified hazard ratio are shown and HR was estimated by stratified Cox regression method. The strata were GOG performance status (0 vs. 1 or 2) and disease stage (Stage III macroscopic optimally debulked, Stage III suboptimally debulked, and Stage IV).

Table 9. Overview of efficacy results. Study GOG-0218

	CPP (N = 625)	CPB15 (N = 1248 [a])	CPB15+ (N = 1248 [a])
Primary Efficacy Parameter			
Progression-Free Survival (INV-assessed) [b]			
Patients with events	277 (44.3%)	305 (24.4%)	248 (19.9%)
Median - months [c]	12.0	12.7	18.2
Hazard ratio [95% CI] (stratified) [e]		0.84 [0.71; 0.99]	0.64 [0.54; 0.77]
One-sided log-rank p-value [e]		0.0204	<0.0001
Hazard ratio [95% CI] (unstratified) [d]		0.86 [0.73; 1.02]	0.65 [0.55; 0.78]
One-sided log-rank p-value [e]		0.0383	<0.0001
Secondary Efficacy Parameters			
Overall Survival			
Patients with event	157 (25.1%)	178 (14.3%)	156 (12.5%)
Median - months [c]	39.4	38.8	39.8
Hazard ratio [95% CI] (stratified) [d]		1.09 [0.87; 1.35]	0.90 [0.72; 1.13]
One-sided log-rank p-value		0.2256	0.1909
Best Objective Response (INV-assessed)			
No. of patients with measureable disease	396	393	403
No. (%) of patients with an obj. response	251 (63.4%)	260 (66.2%)	266 (66.0%)
95% CI for response rates	[58.6%; 68.1%]	[61.5%; 70.8%]	[61.4%; 70.6%]
Difference in response rates [95% CI]		2.8% [-3.9%; 9.4%]	2.6% [-4.0%; 9.2%]
One-sided log-rank p-value (stratified)		0.2341	0.2041

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; CPP = carboplatin + paclitaxel up to 6 cycles + concurrent and extended placebo up to 21 cycles; INV = investigator-assessed.

[a] Events from the CPB15 and CPB15+ arms were pooled prior to Cycle 7 for PFS and OS as specified in the SAP; [b] SAP analysis censored for CA-125 and NPT; [c] Kaplan-Meier estimates; [d] Relative to CPP; [e] Based on the total one-sided α, the final p-value boundary for statistical significance for each comparison was ≤0.0116.

Sensitivity analyses

The sensitivity analyses of PFS explored the effect that independent assessment of progression (IRC analyses), censoring rules (censoring for CA-125 and/or NPT), missing assessments and early discontinuation had on the PFS results.

1. IRC analyses

PFS assessed by the IRC supported the primary investigator assessment for the CPB15+ arm versus the CPP arm (stratified HR 0.63, 95% CI 0.51; 0.77: log-rank p-value <0.0001), and for the CPB15 versus the CPP arm (HR 0.94, 95% CI 0.78: 1.14: log rank p-value 0.2663).

2. Censoring for CA-125 and/or NPT

A sensitivity analysis of PFS comparing CPP and CPB15+ in which the pre-progression use of NPT was not censored yielded results consistent with those from the primary analysis (HR [CI] = 0.67 [0.57, 0.78]). The effect of censoring for NPT on the analysis of IRC-assessed PFS was minimal.

3. Missing assessments

Two worst-case analyses were performed in which patients who missed two or more tumor assessments prior to the data cutoff were assumed to have progressed on the date of the first missed assessment. In the first analysis (first worst case), only patients in the arms receiving bevacizumab who met this criterion were assumed to have progressed. The report states that this assumes a very unrealistic scenario in which 100% of patients in the bevacizumab arms who met this criterion experienced progression, while none of patients in the control arm who met this criterion experienced progression.

In the second analysis (second worst case), the imputation rule was applied equally to patients in all arms. The first worst-case analysis of PFS comparing the CPP and CPB15+ arms yielded a HR of 0.91 (CI: 0.78, 1.08). Results from the second worst-case analysis were closer to those observed in the primary analysis (HR [CI] = 0.76 [0.65, 0.88]).

4. Early discontinuation

For the first of these analyses, patients who discontinued protocol treatment prior to Cycle 22 without documented disease progression or death or because of an adverse event, were considered to have progressed on the date of last tumor assessment prior to treatment discontinuation. Similar to results from the other sensitivity analyses, a comparison of PFS for CPP versus CPB15+ demonstrated a significant increase in favor of the CPB15+ arm (HR [CI] = 0.75 [0.64, 0.87]). A second analysis was conducted exploring the effect of early discontinuation–censored PFS at the time of the last tumor assessment prior to pre-progression treatment discontinuation. This comparison of PFS for CPP versus CPB15+ also yielded results in favor of the CPB15+ arm (HR [CI] = 0.59 [0.49, 0.71]).

Evaluator's comment: All the sensitivity analyses were consistent with the primary analysis of PFS except for the first of the worst case missing assessment analyses, which was based on an unrealistic assumption.

Secondary endpoints for efficacy (OS, ORR)

Overall Survival (OS)

A total one-sided $\alpha = 0.0135$ was allocated to each primary analysis of OS comparing an experimental arm with the control arm. As of the cutoff date, 157 (25.1%), 154 (24.6%) and 140 (22.5%) deaths had occurred in the CPP, CPB15 and CPB15+ arms, respectively. Table 9 shows data when the events in the bevacizumab arms up to Cycle 7 were combined, the number of deaths then being 157 (25.1%), 178 (14.3% of the total patient numbers combined in the CPB15 and CPB15+ arms) and 156 (12.5%) in the CPP, "CPB15", and "CPB15 +arms", respectively. Of the 178 deaths shown in the CPB15+column, 154 occurred during the study period in the CPB15 arm and 24 in the CPB15+ arm up to the end of Cycle 7, at which time both arms had used the same treatment. These data were therefore pooled. Analysis of OS using data without pooling gave similar results. Kaplan Meier plots of the survival data comparing CPB15+ with CPP (with pooling) are shown in Figure 4. Median follow-up was 20.7, 19.7 and 19 months for patients in the CPP, CPB15, and CPB15+ arms, respectively. At this time the median survival for the CPP arm was 39.4 months (CI 34.0-45.5); CPB15, 38.8 (32.6-NE); and CPB15+, 39.8 (39.1-NE).

Although the data were limited due to the relatively short follow-up, no detrimental effect on OS was observed in patients who received bevacizumab in combination with chemotherapy and continued to receive bevacizumab alone (CPB15+ arm) as shown by a (stratified) HR of 0.90 (95% CI 0.72-1.13).

Updated results for OS

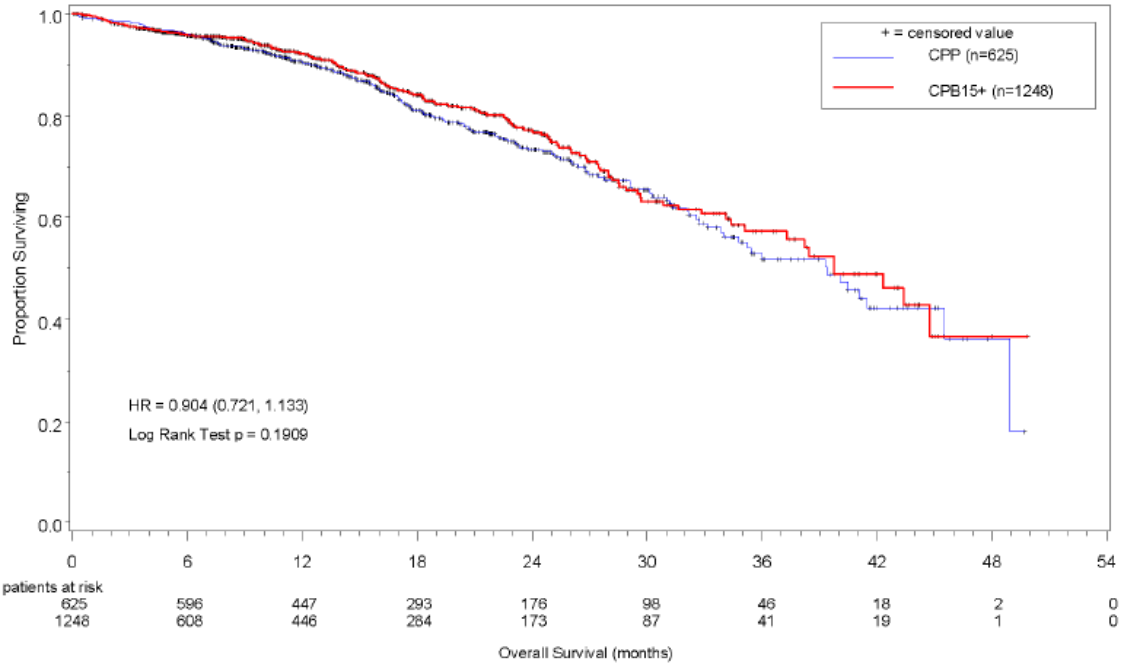
On request, the sponsor provided an updated analysis of OS that included a further 10 months of follow-up results. At this time, 36% of enrolled patients had died as compared to24% previously. A comparison of the CPB15+ arm with the CPP arm found the HR values unchanged with a stratified HR of 0.90, 95% CI [0.74; 1.08] and a one sided p value of 0.125; and an unstratified HR of 0.91, 95% CI [0.75; 1.10] with a p value of 0.159. The median survival of 43.4 months [CI 38.2-49.1 months] for patients in the CPB15+ arm was longer compared to the previous value of 39.4 months (CI 35.3-43.3 months] for the CPP arm but the CI intervals of each still overlapped. The new analysis still showed no statistically difference in OS between the CPP and the CPB15+ arms.

Response rate

There was a no significant difference in the percentage of responders (CR + PR) in patients who received bevacizumab in combination with chemotherapy and continued to receive bevacizumab alone (CPB15+ arm) compared to chemotherapy alone (CPP arm).

Figure 4.

Kaplan–Meier Estimates of Overall Survival, CPB15+ versus CPP,
Pooling CPB15 Deaths prior to Cycle 7: Randomized Patients



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

ed p-value and stratified hazard ratio are shown and the HR was estimated by stratified Cox regression method. The strata ince status (0 vs. 1 or 2) and disease stage (Stage III macroscopic optimally debulked, Stage III suboptimally debulked,

Exploratory analyses

Subgroup analyses

Subgroups analysed were age (<40, 40-60, >60); race; PS (0, 1or 2); stage; site; cell type; tumour grade; baseline sum of the longest diameters [SLD] (< or > median SLD); baseline CA-125 (normal, abnormal). The HRs in all subgroups were less than 1 and were close to the stratified HR of 0.644 reported in the primary analysis of PFS. The difference in the median PFS between the CPB15+ and CPP arms in the various subgroups was also close to the 6.2-month benefit reported in the primary analysis of PFS. Subgroup analyses of either the short-duration bevacizumab or long-duration bevacizumab arms versus the control arm showed that the OS results in the various subgroups varied considerably from the OS, a result to be expected because of the small number of deaths overall and in each subgroup.

Analysis of overall survival between the two active arms

As planned in the SAP, exploratory analyses of survival between the two experimental arms was performed when at least one was found to be superior in the improvement of PFS over the control arm. The stratified analysis yielded a HR of 0.739 and a p value of 0.0288, favoring the CPB15+ arm but not statistically significant.

Objective Response Rate as determined by the IRC

In the control arm (CPP) the ORR was 68.8% (326 of 474 patients); in the CPB15 arm it was 75.4% (347 of 460); and in the CPB15+ arm it was 77.4% (386 of 499).

Evaluator's comment: The differences in ORR of 6.7% and 8.6% between CPB15 and CPB15+ versus CPP, respectively, were small and not of clinical significance. In addition, the patient population was selected, being that with measurable residual disease after surgery.

Quality of Life Assessments

Method

Quality of life was assessed using the Functional Assessment of Cancer Therapy for Ovarian Cancer (FACT-O) questionnaire as described previously.

Results

The FACT-O TOI score improved in all three treatment arms during the treatment period. The improvements were clinically meaningful (≥ 5points) at all points except at the assessment in the middle of the chemotherapy for the CPB15/CPB15+ arm. At the time-point prior to Cycle 13, the mean changes from baseline were similar in all three arms. At the time point prior to Cycle 21 (that is, at the end of the scheduled bevacizumab/placebo maintenance phase), the mean changes from baseline were larger for patients in the CPB15 and CPB15 + arms compared to those for patients in the CPP arm: 9.8 points for CPP, 12.0 points for CPB15 and 11.6 points forCPB15+.

Evaluator: The difference is small and did not exceed the "minimum important difference" of 5 points and so is unlikely to be of clinical significance.

When a mixed effects model was used to test three pre-specified hypotheses, the results showed that:

- There was a some improvement in TOI scores in the second half of the chemotherapy phase (between Cycles 4 and 7) for patients in the CPB15 and CPB15+ versus the CPP arm. This was not statistically significant.
- Although there was a greater improvement in TOI scores for patients in the CPB15+ arm versus the CPP arm between the second half of the chemotherapy phase (Cycles 4 and 7) and the latter portion of the single agent placebo/bevacizumab treatment phase (Cycles 13 and 21), the change (2.6 points) did not exceed the minimally important difference of 5 points.
- There was no difference between the CPB15 and CPB15+ arms in TOI scores during the latter portion of the extended treatment phase (Cycles 13 and 21).

The ovarian cancer subscale score also increased over time in all three arms and the improvements were clinically meaningful when compared to baseline values but not when the arms were compared.

Evaluator's comment and conclusion on QOL assessment

The data show that the quality of patients' lives improved over baseline values during and after all three chemotherapy treatments in a clinical meaningful way but with no consistently maintained difference between them. As stated in the sponsor's Clinical Summary "Prespecified hypothesis testing demonstrated a statistically greater, although clinically insignificant, improvement in TOI score for patients in the CPB15+ arm compared with patients in the control arm."

Evaluator's summary and conclusions on efficacy

Progression free survival:

1. No significant difference in PFS found after 5 cycles of added bevacizumab

The study's first primary objective was to investigate the effect on PFS of adding 5 concurrent cycles of bevacizumab to 6 cycles of standard therapy (carboplatin and paclitaxel (CPB15) and comparing this to 6 cycles of standard therapy alone (CPP). The results were not statistically significant with an increase in the duration of PFS of 0.7 months from 12.0 to 12.7 months, a HR of 0.84 and a p value of 0.0204 for the comparison (statistical significance required a p value of 0.0116 or less). The results were obtained analying data in which results of the CPB15 and the CPB15+ arms prior to Cycle 7 were pooled and compared to the results of the CPP arm, with censoring of all CA-125 and NPT data, based on the investigator's assessment of progressive disease.

2. A significant increase in PFS in the "academic" population of patients with extended use of bevacizumab

The second objective was to investigate the effect of adding 5 concurrent cycles of bevacizumab followed by bevacizumab extended for 16 cycles beyond the 6 cycles of standard therapy (carboplatin and paclitaxel (CPB15+). The extended use of bevavizumab increased the PFS by 6.2 months (52%) from 12 to 18.2 months when compared to 6 cycles of standard therapy (CPP), with a HR of 0.644 and a p value of <0.0001. These data were pooled and censored as above.

3. The increase in PFS with extended use of bevacizumab did not depend on using NPT

An important result in applying the study results to oncology practice was given in the study report; In oncology practice, NPTs would be used, so the effect of added bevacizumab in this setting is important. The results were similar to those of the primary analysis (NPTs censored) with the addition of bevazizumab increasing the PFS by 6.1 months from 12.9 to 18.8 months, a HR of 0.622 and a p value of <0.0001, showing the effect did not depend on the additional use of NPT.

An exploratory analysis comparing the extended use of bevacizumab in the CPB15+ arm to its use up to 6 cycles in the CPB15 arm, suggested a better result for the extended use (HR 0.605, CI 0.481 to 0.761) but p values were not obtained.

The sensitivity analyses were supportive of the primary analysis. That by the Independent Review Committee (IRC) was reassuring, showing no investigator assessment bias affected the primary analysis, as expected since the study was double blinded.

Overall Response Rate and Overall Survival

Of these secondary objectives, the ORR as assessed by the IRC was higher in both experimental arms (CPB15, 75.4%,; CPB15+ 77.4%) than in the standard treatment arm (CPP, 68.8%), the one-sided p values being 0.0106 (CPB15 cf CPP) and 0.0012 (CPB15+ cf CPP). Note however that the patient population was that with measurable disease, about 75% of those in the study. The data for OS was too immature (15 to 20% deaths) for any firm conclusion except that the experimental arms showed no shortening of survival compared to the standard therapy arm.

Quality of life

The quality of patients' lives improved over baseline values during and after all three chemotherapy treatments, in a clinical meaningful way but with no consistently maintained difference between them. As stated in the sponsor's Clinical Summary: "Prespecified hypothesis testing demonstrated a statistically greater, although clinically insignificant, improvement in TOI score for patients in the CPB15+ arm compared with patients in the control arm."

Conclusions

The efficacy of adding bevacizumab at the study dose to the standard treatment of carboplatin and paclitaxel for an extended period of 22 cycles in total increased PFS by 6.2 months, a clinically significant period, without significantly improving the patients' quality of life above that seen with standard chemotherapy. The increase in PFS occurred whether or not the patients also received non-protocol treatment during the study. No detrimental effect on overall survival was seen and to date, no statistically or clinically significant increase in the OS of patients treated with CPB15+ compared to the standard treatment with CPP.

Study B-17707 (ICON7)

A randomised, two-arm, multi-centre Gynaecologic Cancer InterGroup trial of adding bevacizumab to standard chemotherapy (carboplatin and paclitaxel) in patients with epithelial ovarian cancer.

This randomised study aimed to determine the effect of adding bevacizamub to the combination of carboplatin and paclitaxel as first-line treatment for ovarian cancer after surgical resection. The control was standard chemotherapy with carboplatin and paclitaxel (CP), the former administered to give an AUC value of carboplatin of 6 and paclitaxel given IV 175 mg/m^2 IV every 3 weeks for 6 cycles. Bevacizumab was added to CP in the second arm (CPB7.5+), in which carboplatin and paclitaxel were given at the same doses as in the first arm and bevacizumab was given at 7.5 mg/kg IV every 3 weeks for 6 cycles followed by bevacizumab 7.5 mg/kg IV every 3 weeks for 12 cycles. The sponsor was the Gynaecology International Group. The first patient was randomised on December 18 2006 with the clinical data cut-off on February 28, 2010. The trial was conducted at 263 centers in 8 European countries (Germany, United Kingdom (UK) France, Norway, Denmark and Spain) and 3 non-European countries (Canada, Australia and New Zealand). The Medical Research Council (MRC), UK, provided regulatory sponsorship for the trial.

Methods

Study BO17707 was a randomised, controlled, open-label Phase III trial in patients with high risk early stage (FIGO Stage I or IIA clear cell or Grade 3 carcinoma) or advanced stage (FIGO Stage IIB or greater, all grades and all histological subtypes) epithelial ovarian carcinoma, primary peritoneal carcinoma or fallopian tube carcinoma, to evaluate the addition of bevacizumab to standard chemotherapy with carboplatin and paclitaxel. In the absence of an Independent Committee to review assessments, the study attempted to limit bias by using the same assessment schedule in both the research and control arms. The study outline is shown in Figure 5 below.

The primary outcome measure was PFS. The planned sample size was 1444 patients randomised over a period of 24 months with an additional 12 months follow-up after the last patient was randomised. 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, that is, a HR (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 overall survival. 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, that is, 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.

Figure 5. BO17707 trial design

The carboplatin dose recommended for Study BO17707 was AUC 6 (unless predetermined as being different by individual GCIG group, please refer to Section 2.4.5.2 for further details).
**Bevacizumab could be omitted from the first cycle if cytotoxic chemotherapy had to start within 4 weeks of surgery. Please refer to Section 2.4.2.1 for further details.

Objectives

1. Primary

To determine whether the addition of bevacizumab to standard chemotherapy improves PFS when compared to standard chemotherapy alone.

2. Secondary

To evaluate whether the addition of bevacizumab to standard chemotherapy will result in improved duration of OS, objective response rate, duration of tumor response, biological progression free interval (defined by increasing CA-125 [Biological Progression Free Interval, PFIBIO]). Other secondary aims include safety (adverse events, laboratory results and performance status), quality of life and cost effectiveness assessments. Also included were associated translational research endpoints such as tissue and circulating markers of angiogenesis and circulating markers of early clinical progression and other potential prognostic and diagnostic markers for ovarian cancer. These were not described in the current application and are to be reported separately.

Outcomes/endpoints

As stated in the Objectives above, the primary endpoint of the study was PFS and secondary endpoints included OS and ORR. PFS and OS were defined as in the previous trial (GOG-0218), from the time of randomisation to the time of the event. For PFS, if death occurred first, the time of death was taken as the time for PFS and patients who had neither progressed nor died at the time of the clinical cut-off or who were lost to follow-up were censored at the date of the last tumor assessment. Patients for whom no post baseline tumor assessments were available were censored at Day 1. Unlike the previous study, no independent assessment of PFS was carried out and data were not censored for CA-125 progression nor NPT (see Table 2).

ORR, Duration of Response, and Biological Progression Free Interval (PFIbiol)

These outcomes were included as secondary objectives.

Evaluator's comment: For these outcomes to be assessable, patients needed measurable disease or an abnormal CA-125 concentration or both, with conditions. The use of CA-125 concentrations alone to determine both response and progression was prohibited in the previous study. [15]

Validity of PFS as an endpoint

As discussed previously in this evaluation, PFS is acceptable in principle as an endpoint in these studies. However, unlike the previous study, the present study was not blinded and so was open to assessment bias by the investigators, especially in the absence of independent reviews of assessments. This was most likely when an investigator decided a patient had progressive disease at times before the scheduled assessment dates. The study attempted to limit this by using the same assessment schedule in both the research and control arms.

Planned assessment and analysis of endpoints

The analysis of time-to-event endpoints was based on the survivor function, which is the probability to survive or to have no disease progression beyond a certain point in time. The log rank test (stratified and unstratified) was used to compare survivor functions between treatment arms. The primary analysis of this trial (PFS) was a non-stratified 2-sided log-rank test at an α level of 5%. *Note*: the use of this test required the risk of the event to be uniform through the test period. This did not prove to be the case in this trial). RECIST criteria were used to assess response in the sub-population of patients with measurable disease at baseline. The difference in ORR between the two arms was tested with a Chi-squared test (2-sided). No formal testing was done for Duration of Response. Assessments of efficacy and safety were performed as shown in Table 3.

Data analysis

The hypotheses of interest when comparing time-to-event endpoints between treatment groups were: H0: "There is no difference in the survivor functions of the treatment and the reference group" versus H1: "There is a difference in the survivor functions of the treatment and the reference group". The Kaplan-Meier curves for each of the treatment groups and censored observations were presented and stratified and unstratified HRs calculated using Cox Regression models. The primary analysis of this trial was a non-stratified log-rank test.

[15] Sponsor comment: Study GOG-0218 also used CA-125 determined progression (Protocol Specified Analysis).

Sensitivity analyses

These analyses assessed possible assessment bias in an unblinded study of this type and are described with their results in the Results section of this report (Section 3.2.4.1, page 53, this evaluation).

Stratification

A stratified analysis served as a sensitivity analysis to check the robustness of the results. Stratification factors were:

- 3 categories of FIGO Staging (Cat 1: I-III with residual disease ≤ 1 cm; Cat 2: I-III with residual disease > 1 cm; Cat 3: IV and inoperable III)
- 2 categories of intent to start of chemotherapy following surgery (Cat 1: ≤ 4; Cat 2: > 4 weeks)

Although the GCIG groups were planned as a third stratification factor (Study Synopsis), this was not done "because it was [had been] only included for logistical reasons." (sponsor's Study Report).

Assessment of Health Related Quality of Life (HRQoL)

Health-related quality of life (HRQoL) was assessed using two questionnaires devised by The European Organization for the Research and Treatment of Cancer (EORTC) and an additional questionnaire of the EuroQoL (EQ) groups. Three questionnaires, EORTC QLQ-C30, EORTC QLQ-OV28 and EQ-5D, were used. Completion of the three HRQoL questionnaires occurred before medical assessments were performed, or chemotherapy was administered. The first QoL assessment was completed by the patient during the screening visit. The HRQoL measures were completed at the onset of every chemotherapy cycle, then every 6 weeks until the end of the first year and then every 3 months until progression or to the end of Year 2. HRQoL was also measured on Day 1 of the first cycle of chemotherapy at first relapse and in the cohort at three years from randomisation.

Safety assessment

Summaries of adverse events for the following were produced: All AEs, serious AEs, related AEs, AEs with an incidence rate of at least 2%, 5% and 10%; most extreme intensity of adverse events summarised according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 (CTCAEv3.0); AEs that occurred with at least 2%, 5% and 10%; difference between the bevacizumab treatment and the control arm and for AEs of Grade 3 and higher that occurred with at least 2% difference between the treatment arms.

Protocol amendments

The protocol for Study BO17707 was amended four times after the first version dated June 2006. Most changes were for clarification and of a minor nature, except those in the third amendment of July 2007, which were as follows: Inclusion Criterion 3 was modified to allow enrolment of inoperable Stage III patients for whom de-bulking surgery was not foreseen prior to disease progression; Inclusion Criterion 5 was modified to increase maximum time allowed between surgery and study treatment start from 6 to 8 weeks; an amendment to include hepatic toxicity safety information; and an amendment to include fistulae safety information, and to define it as a BO17707 Notable Event.

Study participants

A total of 1528 patients with newly diagnosed epithelial ovarian, fallopian tube or primary peritoneal cancer that was histologically confirmed with core biopsy from a disease site (cytology alone was insufficient for diagnosis) were enrolled and randomised (1:1) to treatment with either carboplatin and paclitaxel or bevacizumab plus carboplatin and

paclitaxel . The histology of the cancers also had to meet the criteria shown in Table 10 below.

Table 10. Histological eligibility criteria

FIGO Stage	Eligible		
	Grade 1[1]	Grade 2[1]	Grade 3[1]
Ia	No[2]	No[2]	Yes
Ib	No[2]	No[2]	Yes
Ic	No[2]	No[2]	Yes
IIa	No[2]	No[2]	Yes
IIb	Yes	Yes	Yes
IIc	Yes	Yes	Yes
III	Yes	Yes	Yes
IV	Yes	Yes	Yes

[1]Grade refers to 1 (well differentiated), 2 (moderately differentiated) and 3 (poorly differentiated)
[2]Except patients with clear cell carcinoma who are eligible regardless of FIGO stage

Evaluator's comment: The table shows that patients with well and moderately differentiated early stage (Stages Ia, Ib, Ic, and IIa) cancers were not eligible but all stages with poorly differentiated cancers were.

Inclusion and exclusion criteria

Evaluator's comment: The inclusion and exclusion criteria were similar to those of the preceding trial, except that patients with earlier stage disease (high risk Stages I, IIa, IIb) were eligible as well as later Stages III and IV.

Planned treatments

Patients were randomised to the treatments shown in Figure 5; either Arm A consisting of carboplatin at a IV dose to give an AUC of 6, with paclitaxel at an IV dose of 175 mg/m^2 over 3 hours both given every 3 weeks for 6 cycles; or Arm B consisting of the same combination of carboplatin and paclitaxel together with bevacizumab at an IV dose of 7.5 mg/kg every 3 weeks for 5 or 6 cycles. In Arm B, after completion of the 5 or 6 cycles (18 weeks), bevacizumab treatment alone was continued at the same dose every 3 weeks for 12 cycles (36 weeks).

Rationale of doses used

The doses of bevacizumab that were used in previous Phase II studies (3 - 20 mg/kg every 2 or 3 weeks, or 1.5 - 10 mg/kg/week) had been selected to be within the linear pharmacokinetic range and to result in serum bevacizumab concentrations in excess relative to circulating VEGF concentrations. During the design stage of the protocol, new data became available which utilised two different doses of bevacizumab. In colorectal cancer studies, a dose of 2.5 mg/kg/week was shown to be effective, in addition to a higher dose of 5 mg/kg/week. The dose of bevacizumab used in Study BO17707, 7.5 mg/kg q3w, is an extrapolation of the current licensed dose for colorectal cancer of 5 mg/kg two weekly, an approved dosage in the current Australian PI for Avastin.

Note: As in the previous study, a formulation of bevacizumab to be used in the trial was provided to investigators. The formulation used was qualitatively the same as that in the current Australian PI (neither provided quantitative formulation).

The doses of paclitaxel were in accordance with the approved doses in the Australian PI for this indication. The dose of carboplatin was discussed in above.

Rationale of number of treatment cycles

No rationale was given in the study report for the number of the cycles in the study. Six cycles of carboplatin and paclitaxel are standard practice, with often significant neurotoxicity from paclitaxel seen after six cycles. The extended use of bevacizumab for a further 12 cycles would test whether such an extension is more effective than carboplatin

combined with paclitaxel alone. It would not test if extended use of bevaxizumab for 12 cycles are more effective than 6 cycles given with standard chemotherapy.

Removal of patients from therapy or assessment

A patient was permitted to withdraw or be withdrawn from trial treatment for the following reasons:

- Progression whilst on therapy
- Unacceptable toxicity
- Intercurrent illness which prevented further treatment
- Withdrawal of consent for treatment by patient
- Any alterations in the patient's condition which justified the discontinuation of treatment in the investigator's opinion

Patients who withdrew from trial treatment were encouraged to remain in the trial and follow the same visit schedule for the purposes of follow-up and data analysis.

Results – patient population

Participant flow

Patients who received no treatment

Of the 1528 randomised patients, 19 patients (11 in the CP arm, 8 in the CPB7.5+ arm) did not receive any study treatment. Nine of the patients randomised to the CP arm withdrew consent. Two patients died prior to receiving any study treatment. Six of the CPB7.5+ patients withdrew consent and one patient violated selection criteria at entry. One patient in the CPB7.5+ arm developed a pulmonary embolism and was withdrawn before receiving any study treatment.

Withdrawals: Note: Patients could be withdrawn from treatment with any one of carboplatin, paclitaxel or bevacizumab or from any combination of these treatment components.

Withdrawals due to insufficient response

Sixteen (2.1%) patients in the CP arm and 97 (12.7%) patients in the CPB7.5+ arm discontinued at least one component of study treatment due to insufficient therapeutic response. Of note, the incidence of patients withdrawn because of insufficient therapeutic response was similar during Cycles 1 - 6 when patients were receiving carboplatin and paclitaxel with (1.7%) or without (2.1%) bevacizumab.

Evaluator's comment: The high rate of 12.7%, noted above, was observed in patients continuing treatment with bevacizumab for an additional 36 weeks, a total time of 54 weeks, compared to the 18 weeks duration of the CP treatment. This extra time of treatment with bevacizumab would account for the higher percentage of withdrawals, since patients in the CP arm who were not on treatment during the extended time would not be classified as having an insufficient response if they were not receiving treatment at that time.

Withdrawals due to other events

The proportion of withdrawals for reasons other than insufficient therapeutic response or death was higher in the CPB7.5+ treatment arm (26%) compared with the CP arm (10%) due to a higher percentage of patients in the CPB7.5+ arm withdrawing due to adverse events, withdrawal of consent, refusal of treatment/did not cooperate and administrative and other reasons. A significant proportion of the premature withdrawals of patients in the CPB7.5+ arm (66/200 [33%]) occurred after the 6 cycles of CP chemotherapy had

been completed and reflect withdrawals because of bevacizumab. Sixty-three (8.2%) patients in the CP arm and 154 (20.2%) patients in the CPB7.5+ arm withdrew from study treatment prematurely due to an adverse event.

Withdrawals by treatment component

The percentage of patient withdrawals from *bevacizumab* in the CPB7.5+ arm was 36%. This was mainly due to patients having an adverse event (15%) and to patients having insufficient therapeutic response or death (14%). Withdrawals for other reasons were 7%.

The percentage withdrawal from *carboplatin* treatment was slightly higher in the CP arm (8%) than in the CPB7.5+ arm (5%). There were more withdrawals due to adverse events in the CP arm (3%) than in the CPB7.5+ arm (2%) and more withdrawals due to insufficient therapeutic response (CP: 2%; CPB7.5+: < 1%). The frequency of withdrawals due to other reasons was similar in both arms (CP: 3%; CPB7.5+: 2%).

The percentage of withdrawals from *paclitaxel* treatment was similar in both treatment arms (CP: 13%; CPB7.5+:12%). There were slightly more withdrawals due to insufficient therapeutic response in the CP arm (2%) than in the CPB7.5+ arm (<1%). The frequency of withdrawals due to adverse events was similar in both arms (CP: 8%; CPB7.5+: 9%) and the frequency of withdrawals due to reasons other than adverse events and insufficient therapeutic response was not markedly different between the treatment arms (CP: 3%; CPB7.5+: 2%)

Evaluator's comment: The data show that withdrawals from either carboplatin (8%, 5%) or paclitaxel (13%, 12%) treatment with or without bevacizumab respectively were of similar frequency, indicating no significant adverse effect on tolerance of C and P because of the addition of bevacizumab. The larger number of withdrawals in the bevacizumab arm (36% in total compared to 12% in the CP arm) was due to the extended time of treatment with that drug, although 60% occurred during the 6 cycles with C and P. The effect of the large number of withdrawals from the CPB7.5+ arm would be conservative for the ITT population, underestimating the effect of bevacizumab on PFS. On the other hand, it also shows the difficulty in administering the intended treatment with bevacizumab, since 26% of patients withdrew for reasons other than progressive disease.

Protocol violations

Patient ineligibility

Twenty two (22%) of enrolled patients were in violation of the inclusion criteria. The most common violations of the inclusion/exclusion criteria were inadequate coagulation parameter (CP: 110 patients 14%, CPB7.5+: 98 patients 13%), proteinuria at baseline (CP: 48 patients 6%, CPB7.5+: 53 patients 7%), inadequate liver function (CP: 34 patients 4%, CPB7.5+: 35 patients 5%) and inadequate bone marrow function (CP: 18 patients 2%, CPB7.5+: 17 patients 2%).

Wrong drug

There was one patient in the CP arm that received bevacizumab in error and 11 patients in the bevacizumab arm that never received bevacizumab.

Evaluator's comment: This compares with 3.2% (60 patients) in the previous study who were administered the wrong drug.

Non-Protocol Specified Antineoplastic Therapy (NPT)

More patients in the CP arm (44%) were started on non-protocol antineoplastic treatment (including surgical and medical procedures) than in the CPB7.5+ arm (38%). Of these therapies, 41% in the CP arm and 33% in the CPB7.5+ arm were initiated after disease progression. The drugs used were more or less balanced between the two arms.

Protocol violators

Fifty five patients (7%) in the CP arm and 26 patients (3%) in the CPB7.5+ had additional antineoplastic treatment (NPT) *prior* to disease progression. The most common treatments were surgical and medical procedures (CP: 2%; CPB7.5+: 1%). In addition, there were 23 patients (3%) in the CP arm and 28 patients (4%) in the CPB7.5+ arm who received NPT but did not develop progressive disease.

Evaluator's comment: The total percentages of protocol violators who received NPT before or without progressive disease were therefore 10% in the CP arm and 7% in the CPB7.5+ arm, higher than desired but not high enough to bias the outcome of the data analysis.

Patient populations analysed

The patient populations analysed were the Intention to Treat (ITT) population, the Per Protocol (PP) population, and the Safety Population (SP). Table 11 shows the numbers in and exclusions from these populations. The formal definitions follow the table.

Table 11. Summary of analysis populations 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.

The ITT population was defined as all patients randomised to the study regardless of whether they actually received any dose of study medication and was the primary population for the efficacy analyses. The ITT population comprised all 1528 patients randomised to treatment (764 in each treatment arm).

The PPP was defined as those patients in the ITT population who adhered to the protocol and who received at least 3 cycles of study treatment (any component of the paclitaxel, carbo-/cisplatin, bevacizumab combination) and patients who terminated treatment before 3 cycles because of disease progression or death. Patients included in this analysis population should have had a baseline tumor assessment, at least one tumor assessment during treatment if they didn't die before the first scheduled assessment and no major protocol violation.

The following were defined as major violations leading to exclusion from the PPP:

- Absence of documentation of epithelial ovarian, primary peritoneal or fallopian tube cancer (must have at least a core biopsy for histologic diagnosis).
- Absence of documentation of Grade 3 or clear cell histology for Stage I-IIa disease.
- Failure to receive at least 3 cycles of study treatment (patients who progress or die before cycle 3 were included in the per protocol analysis).

- Other anti-tumor therapy administered or debulking surgery performed prior to disease progression.
- Absence of written informed consent.

The PPP excluded 105 patients from the ITT population of the CP arm and 61 patients from the ITT population of the CPB7.5+ arm. The most common reasons for exclusion from the PPP in both treatment arms were not having a tumour assessment during treatment or receiving other anti-tumour therapy or having debulking surgery prior to disease progression. Thus, the PPP comprised 659 patients in the CP arm and 703 patients in the CPB7.5+ arm.

The SP was defined as all patients randomised and exposed to study treatment (any component of the paclitaxel, carbo-/cisplatin, bevacizumab combination). Patients were assigned to treatment groups based on the treatment they actually received. Patients who received one or more administrations of bevacizumab were assigned to the bevacizumab treatment group even if this administration was given in error (that is, the patient was randomised to receive the CP arm but received one or more doses of bevacizumab). Patients who were randomised to bevacizumab but did not receive bevacizumab were included in the non-bevacizumab arm. Nineteen patients were excluded from the SP, 11 in the CP arm and 8 in the CPB7.5+ arm. One patient randomised to the CP arm received one dose of bevacizumab in error on Day 1 of Cycle 1 only. For the purposes of the safety analyses, this patient was included in the CPB7.5+ arm. Eleven patients randomised to the CPB7.5+ arm did not receive any dose of bevacizumab before disease progression. For the purposes of the safety analyses, these patients were included in the CP arm. As a result, all analyses using the safety population included 763 patients in the CP arm and 746 patients in the CPB7.5+ arm.

Demographics

The demographic characteristics of the ITT population were well balanced between the study arms. The large majority of patients were white (96% in both CP and CPB7.5+ arms). The median age was 57 years in both arms (range 18-81 years in the CP arm and 24-82 years in the CPB7.5+), and overall 25% of patients were 65 years or older in both arms. The youngest patient was 18 years (CP arm) and the oldest was 82 years of age (CPB7.5+ arm). Weight, smoking status, reproductive status and ECOG[16] performance at baseline were comparable in both arms. The demographic characteristics of the PPP were similar to those for the ITT population.

Baseline characteristics

The majority of patients had epithelial ovarian cancer (CP: 87%; CPB7.5+: 88%) followed by primary peritoneal cancer (7% in both CP and CPB7.5+ arms) and fallopian tube cancer (4% in both CP and CPB7.5+ arms) or a mixture of the three sources (2% in both CP and CPB7.5+ arms). The most common histological subtype of epithelial ovarian cancer was serous carcinoma (69% in both CP and CPB7.5+ arms arm) followed by clear cell (CP: 8%; CPB7.5+: 9%), endometroid (CP: 7%; CPB7.5+: 8%), mucinous (2% in both CP and CPB7.5+ arms arm) other histological subtypes (7% in both CP and CPB7.5+ arms) or a mixture of subtypes (CP: 6%; CPB7.5+: 5%). The *FIGO stages* were well balanced between the treatment arms. The most common staging was FIGO Stage III (68% in both CP and CPB7.5+ arms) followed by FIGO Stage IV (CP: 13%; CPB7.5+: 14%), FIGO Stage II (CP: 10%; CPB7.5+: 11%) and FIGO Stage I (CP: 9%; CPB7.5+: 7%). The majority of the patients in each treatment arm (CP: 74%; CPB7.5+: 71%) had poorly differentiated (Grade 3) primary tumors at baseline, followed by moderately differentiated primary tumors (CP: 19%; CPB7.5+: 23%) and well differentiated primary tumors at baseline (CP: 7%; CPB7.5+: 5%). Target or non-target lesions at baseline were recorded in 462 patients in the CP and 463 patients in the CPB7.5+ arm. The most frequently reported target and non-target lesions were in the peritoneum (CP: 38%; CPB7.5+: 43%), ascites (confirmed or

[16] Eastern Cooperative Oncology Group (ECOG) status: These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

assumed malignant) (40% in both treatment arms), lymph nodes (37% in both treatment arms) and liver (CP: 18%; CPB7.5+: 22%).

Previous and Current Disease

Previous and/or current diseases at study entry other than primary ovarian cancer were reported in 76% of patients in the CP arm and 78% of patients in the CPB7.5+ arm. The most common disorder was hypertension in 24% of patients in the CP arm and 22% of patients in the CPB7.5+ arm. Overall, the type and incidence of diseases were comparable between the study arms. Of diseases other than primary ovarian cancer, the most common condition which was ongoing at the time patients were enrolled into the study was hypertension (CP: 23%; CPB7.5+: 21%).

Previous and concomitant treatment and procedures

Debulking surgery was performed in the majority of patients (98% in both treatment arms).

Evaluator's comment: A major difference in the patient population in this study compared to that in the previous study was that the percentage of patients who had disease defined as being optimally debulked (residual disease less than 1cm) was 74% in this study compared to 34% in the previous study, in which such patients were ineligible if they had no macroscopic residual disease. Suboptimally debulked patients (residual disease >1 cm) were eligible for the previous study, in which lower risk patients (optimally debulked with no macroscopic residual disease) were excluded.

Ascites was drained intra-operatively in 53% of patients in the CP arm and in 55% of patients in the CPB7.5+ arm. Most previous and concomitant therapies were of similar nature and frequency in both arms of the trial. The incidence of concomitant treatments other than for primary ovarian cancer showing a difference of greater than 5% between the study arms included analgesics (CP: 23%; CPB7.5+: 33%) especially paracetamol (CP: 19%; CPB7.5+: 27%), non-steroidal anti-inflammatories (CP: 23%; CPB7.5+: 31%), penicillins (CP: 16%; CPB7.5+: 22%) and surgical and medical procedures (CP: 13%; CPB7.5+: 20%).

Results - efficacy

An overview of the primary and secondary efficacy results is shown in Table 12.

Primary efficacy results for PFS

Median follow up was not markedly different between the two treatment arms; the median duration of follow up was 543 days (17.8 months; range 1 – 1059 days) in the CP arm compared with 557 days (18.3 months; range 1 - 1125 days) in the CPB7.5+ arm.

At the time of the data cut-off (February 28, 2010) for this final analysis of PFS, 759 (49% of patients) progression events had occurred, 392 (51.3%) in the CP arm and 367 (48%) in the CPB7.5+ arm. For 7 of the 392 patients in the CP arm (1.8%) and 6 of the 367 patients in the CPB7.5+ arm (1.6%), the progression event was death. For the remaining patients, the triggering event for the PFS analysis was progressive disease, most of which were determined by radiological tumor measurement (CP; 373 [95.2% of progression events]; CPB7.5+: 347 [94.6%]). A few progressive disease (PD) events were solely due to symptomatic deterioration (CP: 12 [3.1%]; CPB7.5+: 13 [3.5%]).

The HR indicated a 21% reduction in the risk of progression or death in the CPB7.5+ arm (unstratified HR 0.79, 95% CI 0.68; 0.91, log-rank p-value = 0.001) compared with the CP arm. Median time to progression or death was longer (2.3 months, a 14.4% increase) in the CPB7.5+ arm (18.3 months) compared with the CP arm (16.0 months).

The Kaplan-Meier graph (Figure 6) shows separation of the curves in favor of the CPB7.5+ arm after 6 months. A crossing of the curves at approximately 22 months was observed. At this time, 87 patients (11.4%) in the CP arm and 89 patients (11.6%) in the CPB7.5+ arm had not been censored and had not progressed. In the CP arm, 130 (17%) of patients had died and 111 (14.5%) in the CPB7.5+ arm at the time of analysis that gave a preliminary value for the median OS of patients in the CPB7.5+ arm of 35.1 months (Table 12).

The results of the stratified analysis also showed a statistically significant reduction in the risk of progression or death in the CPB7.5+ arm (HR 0.75, 95% CI 0.65; 0.86, log-rank p-value < 0.0001) compared with the CP arm.

Figure 6. Kaplan meier curve of duration of progression free survival (ITT population).

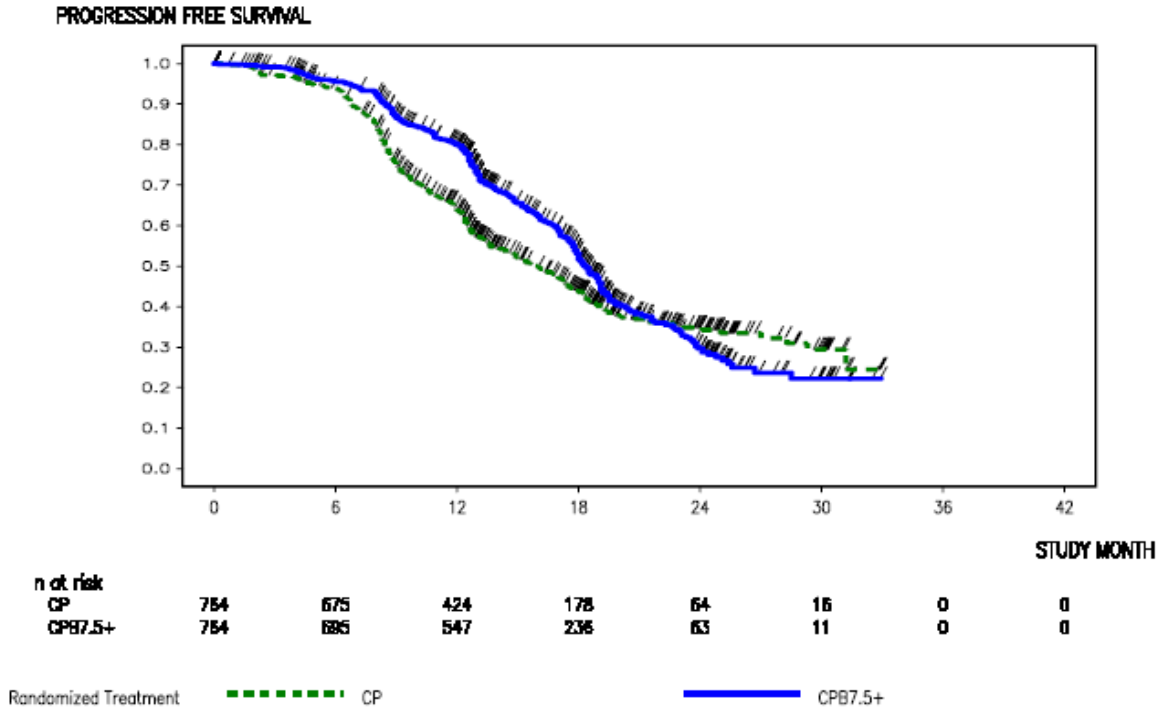


Table 12. Summary of overall efficacy

	CP (N=764)		CPB7.5+ (N=764)
Primary Efficacy Parameter			
Progression Free Survival			
Patients with event	392 (51.3 %)		367 (48.0 %)
Patients without events**	372 (48.7 %)		397 (52.0 %)
Time to event (months)			
Median###	16.0		18.3
p-Value (Log-Rank Test)		0.0010	
Hazard Ratio (unstratified)		0.79	
95% CI		[0.68;0.91]	
Secondary Efficacy Parameters			
Best Objective Response (Recist Responders)			
No, of patients with measureable disease….	.277		272
Responders$	116 (41.9 %)		168 (61.8 %)
95% CI for Response Rates*	[36.0; 47.9]		[55.7; 67.6]
Difference in Response Rates		19.89	
95% CI for Difference in Response Rates#		[11.5; 28.3]	
p-Value (Chi-squared Test)		<.0001	
Complete Response (CR)	12 (4.3 %)		39 (14.3 %)
Partial Response (PR)	104 (37.5 %)		129 (47.4 %)
Stable Disease (SD)	115 (41.5 %)		79 (29.0 %)
Progressive Disease (PD)	16 (5.8 %)		8 (2.9 %)
Missing (No Response Assessment)	30 (10.8 %)		17 (6.3 %)
Duration of Objective Response (Recist Responders)			
Time to event (months)			
Median#	10.6		12.4
95% CI for Median#	[9.5;15.8]		[11.3;13.6]
Range##	3.1 to 30.9		2.0 to 23.0
p-Value (Log-Rank Test)		0.9043	
Hazard Ratio		1.02	
95% CI		[0.75;1.39]	
Overall Survival			
Patients with event	130 (17.0 %)		111 (14.5 %)
Patients without events**	634 (83.0 %)		653 (85.5 %)
Time to event (months)			
Median###	.		35.1
p-Value (Log-Rank Test)		0.0987	
Hazard Ratio		0.81	
95% CI		[0.63;1.04]	
Biological Progression Free Interval			
Patients with event	166 (21.7 %)		162 (21.2 %)
Patients without events**	598 (78.3 %)		602 (78.8 %)
Time to event (months)			
Median###	.		.
p-Value (Log-Rank Test)		0.2398	
Hazard Ratio		0.88	
95% CI		[0.71;1.09]	

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

Sensitivity analyses

All sensitivity analyses supported the results of the analysis of the primary efficacy endpoint above.

1. Time to censoring analysis

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 A Kaplan-Meier plot of the time to censoring in the different treatment arms was generated to investigate the effect of differences in follow-up time. This showed a similar censoring pattern between the CP and the CPB7.5+ arms, with no significant difference (p= 0.23).

2. Missing assessments analysis

The analysis was performed to investigate the effect of missing assessments followed by an assessment of PD/recurrence. In the analysis the missing assessment was considered to

be PD/recurrence. In this analysis, a reduction of 20% [21% in the primary analysis] in the risk of progression or death was seen in the CPB7.5+ arm compared with the CP arm (HR 0.80 [compared to 0.79], 95% CI 0.69; 0.92, log-rank p-value = 0.0020). Median duration of PFS was 15.9 months in the CP arm and 18.3 months in the CPB7.5+ arm [same values as in primary analysis]

3. Worst case analysis

This analysis was used to assess the effect of incomplete tumor assessment follow-up information (in this type of analysis, all patients with incomplete tumor assessment follow-up were considered as having an event). For the PFS endpoint, patients with incomplete tumor 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 randomization and 6 months during Years 2 and 3 after randomization. There was no scheduled tumor 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.

The results of this analysis were similar to the primary analysis: There was a 24% [compared to 21%] reduction in the risk of progression or death in the CPB7.5+ arm compared with CP (HR 0.76, 95% CI 0.66; 0.86 [cf 0.79], log-rank p-value < 0.0001). The median duration of PFS was 13.4 months in the CP arm and 17.8 months [compared to 18.3 months] in the CPB7.5+ arm,

4. Before start of non-study antineoplastic treatment analysis

The PFS before the start of non-study antineoplastic 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 which included surgery for ovarian cancer. There was a 15% [compared to 21%] reduction in the risk of progression or death in the CPB7.5+ arm compared with the CP arm (HR 0.85 [compared to 0.79], 95% CI 0.73; 0.99, log-rank p-value = 0.0320). The median duration of PFS was 17.1 months [compared to 16 months in the primary analysis] in the CP arm and 18.4 months [compared to 18.3 months] in the CPB7.5+ arm.

Evaluator's comment: While all sensitivity analyses supported the conclusion s of the primary analysis, the last analysis, before start of non-study antineoplastic treatment (or non-protocol surgery), requires special mention. The analysis considers the period before an effect of non-protocol treatment occurs and thus more accurately shows the effects of the trial drugs as defined in the protocol and therefore provides a more rigorous comparison. Data show that 336 (44%) of patients in the CP arm and 339 (44.4%) in the CPB7.5+ arm had events as defined. As shown above, the time to the event was a median of 17.1 months and 18.4 months with the 95% CIs 15.6 to 18.3, and 17.8 to 19.1 months, respectively. The p value was 0.032 and the HR was 0.85 (0.73-0.99). The overlapping CI values and the small difference of 1.3 months in median duration of the PFS times shows a small benefit of added bevacizumab, of doubtful clinical significance, when non-protocol treatment was excluded. For comparison, no CIs overlapped in the sensitivity analyses 1 to 3 above.

Secondary efficacy results

Overall response rate (ORR)

Primary analysis – measurable disease

The primary analysis of ORR was based on patients with measurable disease, assessed by RECIST criteria. In patients with measurable disease at baseline, the percentage of patients with a best objective response of CR or PR was higher in the CPB7.5+ arm (168 of 272 patients; 61.8%) compared with the CP arm (116 of 277 patients; 41.9%) (Table13). The

absolute difference in response rate between the CPB7.5+ arm and the CP arm was 19.9%, with a p-value < 0.0001.

Measurement of CA-125 (see Use of CA-125 to determine disease progression)

The analysis of objective response rate based on CA-125 response criteria (defined previously) was performed in all patients (ITT population). The percentage of patients with a CA-125 response was higher in the CPB7.5+ arm (430 of 764 patients; 56.3%) when compared with the CP arm (380 of 764 patients; 49.7%). The absolute difference in response rates between the CPB7.5+ arm and the CP arm was 6.5%, with a p-value of 0.0104.

Combined ORR based on measurable disease and CA-125

The percentage of patients with a combined response was higher in the CPB7.5+ arm (495 of 764 patients; 64.8%) when compared with the CP arm (433 of 764 patients; 56.7%). The absolute difference in response rates between the CPB7.5+ arm and the CP arm was 8.1%, with a p-value of 0.0012.

Evaluator's comment: Given the controversial use of CA-125 to assess response (see previously), the evaluator considered only the primary analysis of ORR above. The other ORR results are provided for interest only.

Overall survival

At the time of the data cut-off for the analysis of progression free survival, the data on overall survival were not mature and therefore only an informal interim analysis was performed. Two hundred and forty one (15.8%) patients had died; 130 (17.0%) in the CP arm and 111 (14.5%) in the CPB7.5+ arm. No detrimental effect in overall survival was seen when comparing the CPB7.5+ arm with the CP arm (HR 0.81, 95% CI 0.63; 1.04, log-rank p-value = 0.0987). Due to the low number of events, a reliable estimate of the median duration of overall survival could not yet be determined.

Updated results for OS

On request, the sponsor provided an updated analysis of OS that included a further 9 months of data. At this time, 24% compared to 15.8% of enrolled patients had died. A comparison of the CPB7.5+ arm with the CP arm found an unstratified HR of 0.85, 95% CI [0.70; 1.04], and a p value of 0.117. Due to the low number of events, an estimate of the median survival times in both arms could not be determined

Duration of response

The patients in this analysis were responders and so were not a randomised population. The analysis was therefore informal, with no hypothesis tested.

Patients with measurable disease

Of 116 responders in the CP arm, 70 (60.3%) had progressed at the time of data cut-off, with a median duration of response of 10.6 months, compared to 168 responders in the CPB7.5+ arm in which 99 (58.9%) had progressed with a median duration of response of 12.4 months. The statistical comparison showed overlapping values for the 95%CIs, 9.5 to 15.8 months 11.3 to 13.6 months, respectively. The p value was 0.904 and the HR 1.02.

Evaluator's comment: Because of the uncertainties of using CA-125 to measure response with inhibitors of angiogenesis (see above), the results for the duration of response based on CA-125, and that combined with those with measurable disease and the biological progression free interval will not be presented here.

Table 13. Summary of best overall response (patients with measurable disease at baseline).

	CP (N=277)		CPB7.5+ (N=272)
Responders$	116 (41.9 %)		168 (61.8 %)
Non-Responders	161 (58.1 %)		104 (38.2 %)
95% CI for Response Rates*	[36.0; 47.9]		[55.7; 67.6]
Difference in Response Rates		19.89	
95% CI for Difference in Response Rates#		[11.5; 28.3]	
p-Value (Chi-squared Test)		<.0001	
Complete Response (CR)	12 (4.3 %)		39 (14.3 %)
95% CI for CR Rates*	[2.3; 7.4]		[10.4; 19.1]
Partial Response (PR)	104 (37.5 %)		129 (47.4 %)
95% CI for PR Rates*	[31.8; 43.5]		[41.4; 53.5]
Stable Disease (SD)	115 (41.5 %)		79 (29.0 %)
95% CI for SD Rates*	[35.7; 47.6]		[23.7; 34.8]
Progressive Disease (PD)	16 (5.8 %)		8 (2.9 %)
95% CI for PD Rates*	[3.3; 9.2]		[1.3; 5.7]
Missing (No Response Assessment)	30 (10.8 %)		17 (6.3 %)

Best Overall Response (RECIST) (BORESP)
* 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
Missing category includes patients who did not receive study treatment, patients with no baseline or post baseline tumor assessment, patients who received Antineoplastic therapy not defined in the protocol before first tumor assessment, patients whose first tumor assessment occurred more than 70 days after date of last dose of last component of study treatment and patients who had their last tumor assessment before 42 days from start of study therapy

Subgroup and exploratory analyses

Exploratory analyses (subgroup analyses and Cox regression) on PFS were performed to assess the influence of prognostic factors that were expected to affect the efficacy endpoints. The subgroup analysis calculated the HRs, comparing the PFS outcome in each treatment arm for the selected group.

Evaluator's comment: The point estimates of the HR were below 1 in all subgroups except one (ECOG PS 0 at baseline), indicating a potential benefit in PFS in the CPB7.5+ arm in comparison with the CP arm. However, the upper value of the CI interval was unity or greater in 23 of the 38 cases, leaving only 15 subgroups (39%) with a confirmed benefit of CPB7.5+ over CP.

In the subgroup analysis using Multiple Cox Regression, the outcomes of subgroups with different prognostic factors were compared, irrespective of treatment..

Evaluator's comment: A comparison of the two groups, that treated with CPB7.5+ compared to that treated with CP, showed a significantly reduced risk of disease progression (HR 0.7, CI 0.6-0.81, p<0.0001) in the CPB7.5+ group. Other covariates showed the following factors conferred a greater risk in both treatment groups: ECOG PS 1 and 2 compared to 0; peritoneal cancer compared to EOC; FIGO I-III sub-optimally debulked compared to FIGO I-III optimally debulked; FIGO IV and inoperable III compared to FIGO I-III optimally debulked; CA-125 more than 2 times the upper limit of normal (ULN) at baseline compared to < 2x ULN; Grade 2 differentiation compared to Grade 1; Grade 3 differentiation compared to Grade 1; mucinous sub-type compared to serous subtype. The results are consistent with the known role of these factors in determining prognosis in this disease.

Restricted mean PFS time

The crossing curves observed on the Kaplan-Meier plot for progression free survival in Figure 6 indicated that the proportional hazards assumption might not be applicable. The plot to assess the proportional hazards assumption confirmed that the treatment effect was not constant over time. An unplanned, exploratory, restricted means survival time analysis, which is a measure independent of the proportional hazards assumption, was performed in order to further quantify the difference between the two treatment groups. This analysis uses the area under the survival curves up to a specified time point to estimate the mean time-to-event. The largest event times in both treatment arms are 31.2 months in the CP arm and 28.5 months in the CPB7.5+ arm. Therefore the restriction time of 30 months was chosen.

The restricted mean progression free survival time in the CP arm was estimated to be 17.8 months in the CP arm and 19.0 months in the CPB7.5 arm, a difference of 1.2 months (6.7%), with a 95%CI for the difference of 0.10 to 2.18 months. No p value was given for significance.

Evaluator's comment: That the proportional hazards ratio changed during the course of the trial further complicates the interpretation of the results. With the corrected values of the restricted mean PFS time, above, the benefit of the CPB7.5+ treatment over CP treatment is a median of 6 weeks but possibly as short as 0.1 month (lowest CI value). The differences are of unstated statistical significance and the clinical significance doubtful.

Quality of life

The number of assessments was balanced between treatment arms during chemotherapy and follow-up and was approximately 20% lower in the CP arm during the phase when bevacizumab was administered alone (Cycles 7 -18) in the CPB7.5+ arm.

The results were similar with the different questionnaires, which showed improved QOL of patients in both arms during the first 6 cycles of chemotherapy and no difference between the two arms during this time. A reduction in QOL occurred in patients continuing on bevacizumab. Analysis of the change from first to last assessment showed that the CPB7.5+ arm versus the CP arm for subscales of the EORTC QLQ-OV28 showed one statistically significant result for one scale, "chemotherapy side effects". In comparison to the CP arm, patients in the CPB7.5+ arm had a higher change from baseline in score for "chemotherapy side effects" (CP: 0.1 mean change; CPB7.5+: 2.9 mean change, p = 0.0044) where higher scores on this scale reflect a greater extent to which patients experienced symptoms or side effects.

Evaluator's summary of efficacy in Study B17707

This trial was by its design less rigorous than the preceding trial (GOG-0218) for reasons that follow, and while it showed the test treatment to be effective in prolonging the PFS compared to standard treatment, the increase was small and of doubtful clinical benefit.

How significant was the prolongation of PFS in the primary analysis?

The addition of bevacizumab to standard therapy of carboplatin and paclitaxel for 6 cycles followed by 12 cycles of bevacizumab alone was compared to 6 cycles of carboplatin and paclitaxel alone and was found to prolong the PFS by 2.3 months (14.4%) from 16 to 18.3 months, with a HR of 0.79 (CI 0.68 to 0.91) and a p value of 0.001 in the primary analysis. The increase in PFS was small, the upper limit of the CI close to unity and the p value doubtful, because the log-rank test was wrongly used in its determination since the treatment effect was not constant throughout the trial (see below).

Issues about the trial

While the sensitivity analyses showed that time to censoring, missing assessments and incomplete assessment information (worst case analysis) did not affect the analyses, the following issues require comment.

1. Management of possible investigators' assessment bias

Because the trial was not blinded, an attempt was made to reduce investigators' assessment bias by setting fixed times of assessment. However, this would not fully remove this risk. An independent review of the assessments, as in the previous study, would be preferable.

2. Protocol violations from stopping one of the three components of the trial medication

The numbers of patients who stopped either carboplatin or paclitaxel during the first 6 cycles of treatment but continued with the other drug or drugs were small and unlikely to affect the analysis of results. However, 33% of the total withdrawals (n=66) in the CPB7.5+ arm occurred during the 36 weeks of treatment with bevacizumab that followed the 18 weeks of initial treatment. In that arm, 466 of 764 patients (61%) completed the planned 18 cycles of treatment. Of the 39% who did not complete the treatment, 14% did so because of insufficient therapeutic response and 15% because of adverse events. The latter group did not receive the planned treatment with bevacizumab so its effect on PFS for patients in that treatment arm would be underestimated.

3. The Use of Non-Protocol Specified Antineoplastic Therapy (NPSAT/NPT)

NPT was administered under three circumstances. The usage after disease progression was expected and formed part of the trial protocol. The incidence was 41% in the CP arm and 33% in the CPB7.5+ arm. The other uses, protocol violations, were administration before disease progression (7% in the CP and 3% in the CPB+arms) and use without disease progression (3% and 4%, respectively). The totals for use before plus use without progression were therefore 10% in the CP arm and 7% in the CPB+7.5 arms.

The use of NPT after progression meant that the time of OS (unavailable at present) would not be due to the efficacy of the CPB7.5+ combination alone but due to its effect combined with the NPT used. However the comparison of the two arms would be valid, provided the NPT used in each arm was similar. Data showed that this was so and that it did not include bevacizumab for patients progressing in the CP arm. The comparison of the two arms therefore remains valid as an assessment of the efficacy of bevacizumab.

The situation is complicated by the results of the sensitivity analysis in which the PFS was analysed and compared for the time period before NPT was used. Unplanned surgery was included with the NPT used in this analysis. The results showed an increase of only 1.3 months (7.6%) from 17.1 months to 18.4 months rather than 2.3 months in the primary analysis (above). This result came about from an increase in the PFS for the CP arm from 16 months in the primary analysis to 17.1months in the sensitivity analysis, while the PFS was the same in the CPB7.5+ arm in both cases (18.3 and 18.4 months). This result suggests that the effect of bevacizumab in prolonging the PFS was achieved in the control arm, CP, when followed by NPT therapy, that is, that the positive effects of bevacizumab and NPT were similar in increasing the PFS. In the complementary analysis that was censored for NPT treatment, the 95% CI values for PFS in the CP arm was 15.6 to 18.3 months, overlapping that of 17.8 to 19.1 months for the CPB7.5+ arm. The HR in the sensitivity analysis was 0.85 (95% CI 0.73; 0.99) and the log-rank p-value = 0.0320.

The small increase in PFS of only 7.6%, the overlapping CI values for the HR, and the inappropriate use of the log-rank test to estimate the p value means that no clinically significant difference in efficacy can be accepted from the study analysis.

4. The treatment effect was not constant over time

The crossing curves observed on the Kaplan-Meier plot for progression free survival indicated that the proportional hazards assumption might not be applicable and this was tested and confirmed, casting doubt on the results for statistics that used the log-rank test (for example for p values).

5. The use of CA-125 to assess progression

The previous study rejected the use of CA-125 to assess disease progression for the reasons given previously in that section of this report. For the same reasons, the evaluator put more weight on the assessments in the present study that did not use this assessment.

6. Response rates were not independently assessed

Lack of an independent assessment compromised the reliability of this assessment in a trial because it was not blinded and assessments were carried out by the investigators. Also, the patient population assessed for response had to have measurable disease and so was a sub-population of the randomised population (36%). Extrapolation of the result to the whole population with a different disease burden is questionable.

7. Addition of bevacizumab did not improve the quality of life of patients

The results showed the same improvement in quality of life resulted from standard treatment with CP as with CP and added bevacizumab. Furthermore, addition of bevacizumab resulted in a significant increase in the side effects of the chemotherapy on QOL (see above).

Comparison of PFS in the two trials

The median PFS of 18.3 months for patients in the CPB7.5+ arm was similar to that of 18.2 months of patients in the CPB15+ arm of the previous trial (GOG-0218) but comparisons should be made with caution because of the different dose and duration of bevacizumab used and because the patient population in the present trial had earlier stage disease than those in the previous trial and so were less at risk. This also may have contributed to a shorter PFS of 12 months of patients in the CPP (control arm) of the previous trial compared to 16 months in the CP (control) arm of the present trial

Evaluator's Conclusions on Efficacy in Study BO17707

The evaluator concluded that use of bevacizumab in the CPB7.5+ combination may have resulted in a statistically significant prolongation of PFS in the primary analysis of 14% compared to standard chemotherapy (CP) when non-protocol specified antineoplastic therapy was used after disease progression, but the difference was not of clinical significance. Problems in the study include the absence of survival data and the failure to improve quality of life above that with standard therapy, as well as the issues discussed above (1-7).

Safety

Introduction

The evaluator evaluated Clinical Safety for the two trials together but not from pooled data, and will follow the sponsor's Clinical Summary, checking the safety data in each trial report. Reference will also be made to a submitted report of a trial in which bevacizumab was used to treat drug-resistant recurrent ovarian cancer.

Evaluation of Safety Parameters

Safety data collected during Study GOG-0218 were reviewed by the GOG Data Safety and Monitoring Board on an ongoing basis. Safety data collected during Study BO17707 were reviewed by an Independent Data Monitoring Committee, which met approximately every six months while patients were receiving protocol treatment and annually thereafter (until data were mature for the analysis of overall survival).

Key differences between Studies GOG-0218 and BO17707

Some key differences exist between the two studies and should be borne in mind when comparing data across the two studies, as summarized below:

- ***Patient population:*** Study GOG-0218 enrolled patients with advanced stage disease only (poorer prognosis), while Study BO17707 enrolled patients with both early and advanced stage disease.
- ***Trial design:*** Study GOG-0218 was a double-blind placebo-controlled study testing a 15 mg/kg dose of bevacizumab and with a treatment duration of 22 cycles of 3-weeks each. Study BO17707 was an open-label study testing a bevacizumab dose of 7.5 mg/kg, with a treatment duration of six or 18 cycles of 3-weeks each.
- ***CRF design***: the two studies collected safety information differently based on the design of the CRFs as summarised in Table 14 below.

Table 14. Comparison of studies GOG-0218 and BO17707

Parameter / information	GOG-0218 CRF	BO17707 CRF
onset date	toxicity form	AE form
resolved date	no	AE form
whether serious	no	AE form
dose modifications/interruptions	cycle dose drug form	AE form
treatment discontinuation	treatment completion form	AE form
hematology: – white blood cell count – absolute neutrophil count/ granulocyte count – platelet count – hemoglobin	cycle dose drug form (laboratory values) and toxicity form with NCI-CTCAE grade (nadir)	laboratory analysis form and AE form if applicable
blood chemistry	cycle dose drug form	laboratory analysis form and AE form if applicable
all deaths	treatment completion form and follow-up form	study completion form
AEs leading to death	toxicity form and NCI AdEERS	AE form and study completion form
expedited reporting of AEs	through NCI AdEERS	SAE reporting

Recording safety data: Some safety data were recorded differently in the two trials. Of special note is the difference in reporting haematological abnormalities that will be referred to later.

Expedited reporting of adverse events: The criteria for expedited reporting of adverse events (AEs) through NCI Adverse Event Expidited Reporting System (AdEERS) and as serious AEs (SAEs) also differed when comparing the criteria for reporting these events. Because of the differences, care should be taken when comparing the data for AdEERS/SAEs from the two studies.

Patient exposure to test drug

The extent of exposure to chemotherapy and bevacizumab/placebo in studies GOG-0218 and BO17707 is summarized in Table 15. Exposure to carboplatin and paclitaxel chemotherapy was comparable across both studies and all treatment arms (median 6.0 cycles for both components). In Study GOG-0218, however, several patients received more than the scheduled six cycles of carboplatin and paclitaxel: two patients received CP during Cycles 7–9, seven patients during Cycle 7 and one patient during Cycle 21.

In Study GOG-0218, the number of patients who had paclitaxel therapy replaced with docetaxel (allowed per protocol) was similar across the three treatment arms (32, 36, and 34 patients, respectively, in the CPP, CPB15, and CPB15+ arms). The median number of docetaxel cycles received was higher in the CPB15 arm (median 4.5 cycles) than in the other two study arms (median 3.0 cycles).

In Study BO17707, one patient in the CP arm switched from carboplatin to cisplatin (allowed per protocol) after receiving one cycle of carboplatin.

In Study GOG-0218, bevacizumab/placebo was to be started only at Cycle 2. The median duration and median number of cycles of bevacizumab/placebo therapy received was 7.7 months and 11.0 cycles in the CPP arm, 8.1 months and 12.0 cycles in the CPB15 arm and 9.0 months and 13.0 cycles in the CPB15+ arm. At the time of the analysis, 564 patients (93.8%) in the CPP arm, 560 patients (92.3%) in the CPB15 arm and 552 patients (90.8%) in the CPB15+ arm had received Cycle 6 or beyond of treatment. Among those patients, 103 patients (17.1%) in the CPP arm, 110 patients (18.1%) in the CPB15 arm and 152 patients (25.0%) in the CPB15+ arm went on to receive the maximum 22 cycles of study treatment.

In Study BO17707, bevacizumab was scheduled to start with Cycle 1 although it could have been omitted from the first treatment cycle if chemotherapy was started less than 28 days after surgery; the number of patients in the CPB7.5+ arm who received bevacizumab was higher at Cycle 2 than at Cycle 1 (703 patients versus 535 patients). The median duration and the median number of cycles of bevacizumab therapy in the CPB7.5+ arm were 11.6 months and 17.0 cycles, respectively. At the time of the analysis, 652 patients (85%) in the CP arm and 600 patients (80%) in the CPB7.5+ arm had started six cycles of all components of study treatment. Among those, 230 patients (31%) in the CPB7.5+ arm went on to receive all 18 cycles of bevacizumab at the time of the clinical cut-off.

Table 15. 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

Monitoring and reporting AEs

All AEs reported in the two studies were graded by the investigators for severity according to National cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 3.0, and the relationship of AEs to study treatment was described using the following categories:

(1) unrelated, (2) unlikely, (3) possibly, (4) probably, or (5) definitely. The methods of reporting and differences in the two studies were described above.

Adverse events of special interest

The following AEs were identified in both studies as adverse events of special interest (AESIs) to bevacizumab: arterial thromboembolic events; bleeding (central nervous system (CNS) and non-CNS); congestive heart failure; febrile neutropenia; fistulae and abscesses; gastrointestinal perforation; hypertension; neutropenia; proteinuria; reversible posterior leukoencephalopathy syndrome (RPLS); venous thromboembolic events; and wound-healing complications.

In Study BO17707, several of these AESIs were defined by the protocol as notable events: arterial thromboembolic events, hemorrhagic events, hypertension and proteinuria. Wound-healing complications that occurred up to 18 months after start of study treatmen, and gastrointestinal perforations and fistulae that occurred within 24 months after start of study treatment were to be reported, irrespective of severity and causal relationship, on the AE form during the periods specified. AESIs were analysed separately in both studies and are also discussed here. Notable events in Study BO17707 were included in the analysis of AESIs and are not discussed separately.

Common adverse events in the two trials

An overview of Common AEs

An overview by MedDRA system[17] organ class (SOC) is provided in Table 16, which reveals some similarities and differences between the studies. In particular, the System Organ Classes (SOCs) *Investigations*, *Metabolism and nutrition disorders*, and *Blood and lymphatic system disorders* differ because of the way laboratory abnormalities were reported as AEs in the two studies (see above).

Under the SOC *Investigations*, which refers to laboratory data, the overall number of all-grade events was significantly higher in all treatment arms in Study GOG-0218, in which NCI-CTCAE grades associated with hemoglobin, neutrophil count, platelet count, and white blood cell count were routinely collected on the toxicity form compared with Study BO17707, which had stricter criteria for reporting laboratory abnormalities as AEs (GOG-0218: range 98.8%–99.2% across treatment groups; BO17707: range 34.2%–44.4% across treatment groups).

A similar difference is apparent under the SOC *Metabolism and nutrition disorders* (GOG-0218: range 57.1%–58.7% across treatment groups; BO17707: range 16.5%–20.8% across treatment groups), which includes events associated with blood chemistry parameters; the incidence of AEs such as hypercalcemia, hyperglycemia, and hypoalbuminemia was higher in all treatment arms in Study GOG-0218 than those in Study BO17707, perhaps again reflecting the stricter criteria applied for reporting laboratory abnormalities as AEs in the latter study. Under the SOC *Blood and lymphatic system disorders*, the incidence of adverse events such as leukopenia, neutropenia, and thrombocytopenia was lower across treatment arms in Study GOG-0218 than in Study BO17707, which may reflect the instructions provided to investigators in Study BO17707 to record a single diagnosis rather than the clinical sign as the AE term (for example, anemia rather than decreased hemoglobin). Therefore, it is difficult to compare neutropenia rates, in particular, across the two studies.

Given the differences outlined above, some similarities can be seen between the safety profiles in Studies GOG-0218 and BO17707. The most common adverse events in both

[17] MedDRA or Medical Dictionary for Regulatory Activities is a clinically validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry throughout the entire regulatory process. In addition, it is the adverse event classification dictionary endorsed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The MedDRA dictionary is organized by System Organ Class (SOC).

studies occurred in the SOCs *Gastrointestinal disorders* (abdominal pain, constipation, diarrhea, 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).

Note: A number of adverse events such as alopecia, peripheral sensory neuropathy, nausea, vomiting, constipation, and myalgia are typically associated with carboplatin and/or paclitaxel chemotherapy and occurred with a similar frequency across the treatment arms within each study, mainly during the six cycles of chemotherapy. However, the following organ systems were more frequently affected in the treatment arms in which there were extended use of bevacizumab*: Eye disorders; Infections and infestations; Nervous system disorders; General disorders; Musculoskeletal and connective tissue disorders; Respiratory, Thoracic and mediastinal disorders;* and *Vascular disorders* (Table 16).

Table 16. Studies GOG-0218 and BO17707. Summary of all AEs by SOC (Safety Population).

MedDRA System Organ Class/ Overall (any grade)	GOG-0218			BO17707	
	CPP N = 601	CPB15 N = 607	CPB15+ N = 608	CP N = 763	CPB7.5+ N = 746
	n (%)	n (%)	n (%)	n (%)	n (%)
– Any adverse event –	600 (99.8)	607 (100.0)	607 (99.8)	755 (99.0)	746 (100.0)
Blood and lymphatic system disorders	103 (17.1)	106 (17.5)	113 (18.6)	307 (40.2)	303 (40.6)
Cardiac disorders	56 (9.3)	48 (7.9)	56 (9.2)	49 (6.4)	58 (7.8)
Ear and labyrinth disorders	43 (7.2)	45 (7.4)	50 (8.2)	63 (8.3)	68 (9.1)
Endocrine disorders	5 (0.8)	9 (1.5)	8 (1.3)	7 (0.9)	5 (0.7)
Eye disorders	90 (15.0)	104 (17.1)	126 (20.7)	70 (9.2)	107 (14.3)
Gastrointestinal disorders	517 (86.0)	514 (84.7)	523 (86.0)	631 (82.7)	653 (87.5)
General disorders and administration site conditions	477 (79.4)	481 (79.2)	512 (84.2)	525 (68.8)	564 (75.6)
Hepatobiliary disorders	24 (4.0)	18 (3.0)	21 (3.5)	7 (0.9)	11 (1.5)
Immune system disorders	29 (4.8)	34 (5.6)	44 (7.2)	98 (12.8)	85 (11.4)
Infections and infestations	192 (31.9)	214 (35.3)	225 (37.0)	299 (39.2)	418 (56.0)
Injury, poisoning and procedural complications	49 (8.2)	59 (9.7)	63 (10.4)	59 (7.7)	96 (12.9)
Investigations	595 (99.0)	600 (98.8)	603 (99.2)	261 (34.2)	331 (44.4)
Metabolism and nutrition disorders	343 (57.1)	350 (57.7)	357 (58.7)	126 (16.5)	155 (20.8)
Musculoskeletal and connective tissue disorders	389 (64.7)	401 (66.1)	424 (69.7)	483 (63.3)	563 (75.5)
Neoplasms benign/malignant and unspecified (incl cysts and polyps)	1 (0.2)	0 (0.0)	1 (0.2)	3 (0.4)	15 (2.0)
Nervous system disorders	472 (78.5)	475 (78.3)	496 (81.6)	589 (77.2)	623 (83.5)
Psychiatric disorders	203 (33.8)	210 (34.6)	213 (35.0)	160 (21.0)	186 (24.9)
Renal and urinary disorders	121 (20.1)	106 (17.5)	134 (22.0)	95 (12.5)	105 (14.1)
Reproductive system and breast disorders	68 (11.3)	74 (12.2)	80 (13.2)	64 (8.4)	87 (11.7)
Respiratory, thoracic and mediastinal disorders	283 (47.1)	359 (59.1)	365 (60.0)	219 (28.7)	400 (53.6)
Skin and subcutaneous tissue disorders	399 (66.4)	394 (64.9)	402 (66.1)	642 (84.1)	653 (87.5)
Social circumstance	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Surgical and medical procedures	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)	13 (1.7)
Vascular disorders	204 (33.9)	233 (38.4)	297 (48.8)	210 (27.5)	335 (44.9)

Events that occurred since start of cycle 2 and within 30 days after the last study drug and on or before the cut-off for GOG-0218 and that occurred since first drug intake and day of the safety follow-up visit for BO17707 are included in this analysis.

A summary of adverse events with an incidence ≥ 5% and 10% more than control in any bevacizumab containing treatment arm compared to the control arm

The summary is given in Table 17. Events of hypertension (32%, 25%), epistaxis (30%, 31%), diarrhea (35 to 39%), and stomatitis (14 to 24%) were more frequently reported for patients in all bevacizumab-containing arms than the corresponding control arms across both studies. Among these, AES with an incidence 10% or more greater than that of the respective control arms included hypertension (32% compared to 14%; 6% compared to 25%); epistaxis (30% compared to 9%; 31% compared to 5%); headaches (21% compared to 33%; 12% compared to 26%) in the GOG and B17707 trials respectively; and

diarrhoea (24% compared to 35% [B17707]); dysarthria (2% compared to 12% [GOG trial]); infections and infestations (39% compared to 56% [B17707]); and stomatitis (13% compared to 24% [GOG]).

The incidence of dysarthria was higher in the GOG study (CPP: 9 patients, 1.5%; CPB15:

58 patients, 9.6%; CPB15+: 72 patients, 11.8%) compared with previous studies. The majority of patients (90%) reported Grade 1 events. In Study BO17707, dysarthria was reported in only one patient in the CPB7.5+ arm (0.1%) and it was a Grade 1 event.

In Study BO17707, headache and diarrhoea were reported with ≥ 10% higher incidence in the bevacizumab arm compared with the control arm. In particular, the difference in incidence of all-grade diarrhoea between the treatment arms was higher in this study (CP: 185 patients, 24.2%; CPB7.5+: 264 patients, 35.4%) compared with previous studies. The majority of patients (90%) reported Grade ≤ 2 events.

Table 17. Studies GOG-0218 and BO17707: Summary of adverse events with ≥ 5% higher incidence in any bevacizumab arm relative to the control arm (Safety Population)

MedDRA System Organ Class Preferred Term	GOG-0218 CPP (n=601)	GOG-0218 CPB15 (n=607)	GOG-0218 CPB15+ (n=608)	BO17707 CP (n=762)	BO17707 CPB7.5+ (n=746)
- Any adverse events -	600 (99.8%)	607 (100.0%)	607 (99.8%)	755 (99.0%)	746 (100.0%)
GASTROINTESTINAL DISORDERS					
- Overall -	517 (86.0%)	514 (84.7%)	523 (86.0%)	631 (82.7%)	653 (87.5%)
ABDOMINAL PAIN	238 (39.6%)	231 (38.1%)	254 (41.8%)	171 (22.4%)	220 (29.5%)
DIARRHOEA	203 (33.8%)	238 (39.2%)	230 (37.8%)	185 (24.2%)	264 (35.4%)
NAUSEA	308 (51.2%)	319 (52.6%)	349 (57.4%)	386 (50.6%)	403 (54.0%)
STOMATITIS	80 (13.3%)	117 (19.3%)	147 (24.2%)	60 (7.9%)	106 (14.2%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS					
- Overall -	477 (79.4%)	481 (79.2%)	512 (84.2%)	525 (68.8%)	564 (75.6%)
FATIGUE	438 (72.9%)	438 (72.2%)	485 (79.8%)	338 (44.3%)	387 (51.9%)
MUCOSAL INFLAMMATION	(0.0%)	(0.0%)	(0.0%)	82 (10.7%)	141 (18.9%)
INFECTIONS AND INFESTATIONS					
- Overall -	192 (31.9%)	214 (35.3%)	225 (37.0%)	299 (39.2%)	418 (56.0%)
NASOPHARYNGITIS	(0.0%)	(0.0%)	(0.0%)	61 (8.0%)	100 (13.4%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS					
- Overall -	389 (64.7%)	401 (66.1%)	424 (69.7%)	483 (63.3%)	563 (75.5%)
ARTHRALGIA	212 (35.3%)	201 (33.1%)	244 (40.1%)	259 (33.9%)	314 (42.1%)
MUSCULAR WEAKNESS	52 (8.7%)	77 (12.7%)	87 (14.3%)	19 (2.5%)	12 (1.6%)
PAIN IN EXTREMITY	100 (16.6%)	116 (19.4%)	144 (23.7%)	94 (12.3%)	129 (17.3%)

MedDRA System Organ Class Preferred Term	GOG-0218 CPP (n=601)	GOG-0218 CPB15 (n=607)	GOG-0218 CPB15+ (n=608)	BO17707 CP (n=763)	BO17707 CPB7.5+ (n=746)
NERVOUS SYSTEM DISORDERS					
- Overall -	472 (78.5%)	475 (78.3%)	496 (81.6%)	589 (77.2%)	623 (83.5%)
DYSARTHRIA	9 (1.5%)	58 (9.6%)	72 (11.8%)	(0.0%)	1 (0.1%)
HEADACHE	126 (21.0%)	156 (25.7%)	202 (33.2%)	92 (12.1%)	196 (26.3%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS					
- Overall -	283 (47.1%)	359 (59.1%)	365 (60.0%)	219 (28.7%)	400 (53.6%)
DYSPNOEA	121 (20.1%)	170 (28.0%)	157 (25.8%)	113 (14.8%)	131 (17.6%)
EPISTAXIS	55 (9.2%)	182 (30.0%)	184 (30.3%)	39 (5.1%)	232 (31.1%)
NASAL MUCOSAL DISORDER	22 (3.7%)	45 (7.4%)	61 (10.0%)	(0.0%)	1 (0.1%)
VASCULAR DISORDERS					
- Overall -	204 (33.9%)	233 (38.4%)	297 (48.8%)	210 (27.5%)	335 (44.9%)
HYPERTENSION	81 (13.5%)	143 (23.6%)	196 (32.2%)	48 (6.3%)	183 (24.5%)

AdEERS = Adverse Event Expedited Reporting System; BV = bevacizumab; CP = carboplatin + paclitaxel; CPP = CP + up to 21 cycles of placebo; CPB15 = CP + up to 6 cycles of BV 15 mg/kg + up to 15 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.
Events were reported either on the Toxicity and Follow-Up Forms or in NCI AdEERS in Study GOG-0218 and on the Adverse Event Form in Study BO17707.
All events were graded according to NCI-CTC, Version 3.0. Maximum severity was selected for each event for each patient.
Events that occurred since start of cycle 2 and within 90 days after the last study drug and on or before the cutoff for GOG-0218 and that occurred since first drug intake and day of the safety follow-up visit for BO17707 are included in this analysis.
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Adverse events of grade 3 or more

Overall incidences of AEs of Grade 3 or more for both studies are summarised by SOC in Table 18. Grade 3 or more adverse events were reported by relatively more patients in Study GOG-0218 (range 93.0%–95.1% across treatment arms) compared with Study BO17707 (range 54.3%–64.6% across treatment arms). This result again highlights the differences between the studies in the reporting of laboratory abnormalities as adverse events and is reflected in the system organ classes as follows: *Investigations*, GOG- 88.4% to 90.3%; BO17707-7.0% to 7.3%; *Metabolism and nutrition disorders*, GOG – 13.1% to 14.3%; B17707 – 1.3% to 2.3%; and *Blood and lymphatic system disorders*, GOG – 8.3% to 9.9%; B17707 – 19.3% to 22.3%, which include events associated with laboratory parameters.

The incidence of Grade 3 or more adverse events in most other system organ classes was similar between treatment arms within studies, with the exception of *Gastrointestinal disorders* and *Vascular disorders* which had more events reported in the bevacizumab-containing treatment arms than the control arms. The most frequently reported Grade 3 or more adverse events in these systems include diarrhoea (GOG-0218: range 3.0%–3.8% across treatment groups; BO17707: range 1.8%–3.9% across treatment groups), nausea (GOG-0218: range 3.1%–4.8% across treatment groups; BO17707: range 2.8%–3.5% across treatment groups), vomiting (GOG-0218: range 2.5%–4.2% across treatment groups; BO17707: range 2.8%–3.4% across treatment groups), and hypertension (GOG-0218: range 2.0%–9.9% across treatment groups; BO17707: range 0.3%–6.0% across treatment groups).

Table 18. Studies GOG-0218 and BO17707. Summary of grade ≥3 AEs by SOC (Safety population).

MedDRA System Organ Class/ Overall (Grade ≥ 3)	GOG-0218			BO17707	
	CPP N = 601	CPB15 N = 607	CPB15+ N = 608	CP N = 763	CPB7.5+ N = 746
	n (%)	n (%)	n (%)	n (%)	n (%)
– Any adverse event –	559 (93.0)	577 (95.1)	574 (94.4)	414 (54.3)	482 (64.6)
Blood and lymphatic system disorders	50 (8.3)	51 (8.4)	60 (9.9)	147 (19.3)	166 (22.3)
Cardiac disorders	3 (0.5)	6 (1.0)	8 (1.3)	8 (1.0)	4 (0.5)
Ear and labyrinth disorders	1 (0.2)	2 (0.3)	0 (0.0)	2 (0.3)	2 (0.3)
Endocrine disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Eye disorders	4 (0.7)	2 (0.3)	3 (0.5)	2 (0.3)	2 (0.3)
Gastrointestinal disorders	82 (13.6)	99 (16.3)	95 (15.6)	96 (12.6)	120 (16.1)
General disorders and administration site conditions	48 (8.0)	57 (9.4)	75 (12.3)	43 (5.6)	65 (8.7)
Hepatobiliary disorders	3 (0.5)	2 (0.3)	5 (0.8)	2 (0.3)	5 (0.7)
Immune system disorders	6 (1.0)	6 (1.0)	7 (1.2)	30 (3.9)	12 (1.6)
Infections and infestations	47 (7.8)	46 (7.6)	55 (9.0)	27 (3.5)	50 (6.7)
Injury, poisoning and procedural complications	8 (1.3)	13 (2.1)	14 (2.3)	10 (1.3)	17 (2.3)
Investigations	531 (88.4)	548 (90.3)	538 (88.5)	56 (7.3)	52 (7.0)
Metabolism and nutrition disorders	79 (13.1)	80 (13.2)	87 (14.3)	10 (1.3)	17 (2.3)
Musculoskeletal and connective tissue disorders	30 (5.0)	48 (7.9)	51 (8.4)	36 (4.7)	49 (6.6)
Neoplasms benign/malignant and unspecified (incl cysts and polyps)	1 (0.2)	(0.0)	1 (0.2)	1 (0.1)	7 (0.9)
Nervous system disorders	48 (8.0)	61 (10.0)	76 (12.5)	70 (9.2)	88 (11.8)
Psychiatric disorders	12 (2.0)	7 (1.2)	16 (2.6)	7 (0.9)	8 (1.1)
Renal and urinary disorders	11 (1.8)	11 (1.8)	18 (3.0)	8 (1.0)	10 (1.3)
Reproductive system and breast disorders	5 (0.8)	4 (0.7)	5 (0.8)	3 (0.4)	10 (1.3)
Respiratory, thoracic and mediastinal disorders	21 (3.5)	35 (5.8)	29 (4.8)	20 (2.6)	39 (5.2)
Skin and subcutaneous tissue disorders	7 (1.2)	4 (0.7)	9 (1.5)	53 (6.9)	64 (8.6)
Social circumstance	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Surgical and medical procedures	(0.0)	(0.0)	(0.0)	1 (0.1)	2 (0.3)
Vascular disorders	45 (7.5)	65 (10.7)	93 (15.3)	27 (3.5)	76 (10.2)

Events that occurred since start of cycle 2 and within 30 days after the last study drug and on or before the cutoff for GOG-0218 and that occurred since first drug intake and day of the safety follow-up visit for BO17707 are included in this analysis.

The majority of patients in Study GOG-0218 reported Grade 4 events (Grade 3: range 26.2%–31.4% across treatment groups; Grade 4: range 60.9%–66.0% across treatment groups) whereas the majority of patients in Study BO17707 reported Grade 3 events (Grade 3: range 45.2–54.6% across treatment groups; Grade 4: range 8.1%–9.5% across treatment groups). The number of patients who experienced an adverse event leading to death (Grade 5 AEs) was low in both studies (GOG-0218: 27 patients overall; BO17707: 11 patients overall). [see next section].

Deaths

Deaths in Study GOG-0218 due to disease progression or trial treatment

The primary cause of death was categorised by the investigator on the Study GOG-0218 follow-up form as due to "this disease", "protocol treatment", "other cause", or "unknown" (see Table 19).

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 (Table 19). Overall fewer patients in the CPB15+ arm died compared with the CPB15 and CPP arms (21.5% versus 24.4% and 24.1%, respectively), due to the lower number of deaths classified as due to "this disease" (19.4% versus 22.9% and 22.5%,respectively). Ovarian cancer/ progressive disease (death due to "this disease") was the most common cause of death. 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.

Note: 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%).

Table 19. Study GOG-0218: Summary of deaths by primary cause (Safety Population).

Cause of Death	CPP (n=601)	CPB15 (n=607)	CPB15+ (n=608)
Number of deaths	145 (24.1%)	148 (24.4%)	131 (21.5%)
Due to this disease	135 (22.5%)	139 (22.9%)	118 (19.4%)
Due to protocol treatment	3 (0.5%)	6 (1.0%)	8 (1.3%)
Due to other cause	7 (1.2%)	4 (0.7%)	6 (1.0%)
Unknown	3 (0.5%)	3 (0.5%)	3 (0.5%)

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.
Multiple primary causes of death were selected in Study GOG-0218.

Source: Biostatistics(rmittal) pgm(/onco/avf/avfscs/oc_bla10/programs/t_death_cause)
Database (LOCKED) Datasets (pat)
: Generated 21AUG10 07:13 Page 1 of 1

Death due to this disease: death related to ovarian cancer/progressive disease.
Death due to protocol treatment: death related to any component of study treatment.
Death due to other cause: deaths due to cause other than protocol treatment or disease.
Unknown: no data available regarding the cause of death.

Deaths in Study GOG-0218 due to other causes

A clinical review was performed to determine the adverse event associated with the death "due to other cause" for these 17 patients. For the seven patients in the *CPP arm*, the causes of death were dehydration, septic shock, cardiac or cardiopulmonary arrest, ventricular fibrillation and anoxic brain injury, pelvic carcinomatosis with abscess, multi-organ failure, urinary tract infection and renal failure. For the four patients in the *CPB15 arm*, causes of death were intercurrent disease reported as "twisted bowel", infection, cerebrovascular accident, dehydration and cardiorespiratory arrest following a blood transfusion. For the six patients in the *CPB15+ arm*, the causes of death were cardiac or cardiopulmonary arrest attributed to overall deterioration, possible blood transfusion reaction, or unknown cause, urosepsis, neutropenia, renal failure, thrombocytopenia, myocardial infarction, abdominal and pelvic masses, ascites and evidence of carcinomatosis.

Deaths in Study B-17707

Evaluator's comment: In this section, the safety assessment in the sponsor's Clinical Summary included a revision by Roche of the causes of death in the study so it was difficult to find the number of deaths attributed by the investigators to the trial treatments. What follows is solely based on the amended figures from the study report.

Total deaths

The total number of deaths in the safety population in the CP arm (131; 17%) was higher than the number of deaths in the CPB7.5+ arm (107; 14%).

Deaths due to disease progression

A higher number of patients died as a result of disease progression (115 [15%]) in the CP arm compared with 88 [12%] in the CPB7.5+ arm).

Deaths due to causes other than disease progression

Overall, there were 35 deaths in the safety population due to causes other than progressive disease reported during the study; 16/763 (2%) in the CP arm and 19/746 (3%) in the CPB7.5+ arm. Note below that these figures were subsequently revised downwards to 5 and 4, respectively.

Deaths due to trial treatment

Two lots of data have been presented that give very different figures for the number of deaths possibly or probably related to trial treatment.

1. Original investigators' data as defined in trial protocol

In the sponsor's Trial Protocol, directions were given on how causality was to be assigned to deaths in relation to trial treatment as assessed by investigators. The results were presented in a supplementary table.

Of the 13 deaths in the CP arm, one (6.3% of deaths in this arm) died of cerebral ischemia, and was considered as probably related to the trial treatment. Of the 19 deaths due to primary causes other than disease progression in the CPB7.5+ arm, 4 (21%) were considered possibly or probably related to study drug treatment; gastrointestinal perforation on Day 92 in a 48 year old patient, cerebral hemorrhage on Day 108 in a 46 year old patient, cerebral ischaemia on Day 81 in a 69 year old patient and peritonitis on Day 424 in a 62 year old patient.

2. These data were then revised by the sponsor

The Statistical Plan of the study did not provide for any revision or additional analysis of these data nor was any included in *the Trial Protocol.* The protocol does include a section entitled "*Analyses for Regulatory Submissions"* that reads

"Further analyses to be performed by F. Hoffmann-La Roche for inclusion in submissions to regulatory authorities will include analysis of the efficacy outcome measures; progression free survival, overall survival, objective response rate and duration of response on the per protocol population. The per protocol population (PP) consists of those patients in the intention-to-treat (ITT) population who received at least 3 cycles of study treatment and patients who terminated treatment before 3 cycles because of progression or death and adhered to the protocol. Patients included in this analysis population should have had at least one tumour assessment during treatment and no major protocol violation."

There was no mention of an additional analysis of data on patients' deaths.

The study report, in presenting the method of safety assessment, states that:

"For the summary tables of 'Deaths by Cause of Death (PD versus Other)', a clinical review of the list of MedDRA terms of primary death causes prior to database closure was performed in order to specify which terms referred to PD".

It is not clear if this refers to the revision of the causes of death or how it was done without bias. The report later states that

"An additional analysis summarizing the underlying cause of death and relationship to trial treatment is shown on page 1504" without further comment.

The sponsor's Clinical Summary presented the revised data as follows:

"After further clarification from the investigator and additional medical review, the primary death causes for those patients initially classified as death from other causes could be reclassified as being related or unrelated to disease progression, as outlined in the following: Of the 16 patients in the CP arm who died from other causes, 11 deaths were related to disease progression (the primary causes of death were cardiac failure, intestinal obstruction, respiratory failure, small intestinal obstruction, embolism, aspiration, cerebrovascular accident, intestinal perforation, and metastatic breast cancer) and five deaths were not related to disease progression (the primary causes of death were cranial nerve disorder, pulmonary embolism, cerebral ischemia, renal failure, and gastrointestinal hemorrhage). Of the 19 patients in the CPB7.5+ arm who died from other causes, 15 deaths were related to disease progression (the primary causes of death were small intestine obstruction, embolism which was amended to thrombosis, gastrointestinal hemorrhage, duodenal obstruction, pneumonia, cardiac failure, intestinal obstruction, respiratory failure, peritonitis, ileus, pleural effusion, and acute renal failure) and four deaths were unrelated to disease progression (the primary causes of death were cerebral ischemia, cerebral hemorrhage, gastrointestinal perforation, and pancreatic carcinoma)."

Note: The 16 patients in the CP arm who were originally classed as dying of causes other than disease progression by the investigators have now been reduced to 5 by the revision, and the 19 in the CPB7.5+ arm has been reduced to 4. The number of deaths that were classed as possibly or probably related to trial treatment was unchanged; one in the CP arm, and 4 in the CPB7.5+ arms.

Evaluator's comment: It is of concern when data on the cause of death undergoes revision in an unblinded trial by reviewers who were not independent. However, in this case the changes were in the category of "death from other causes". Eleven (11) of 16 and 15 of 19 were reclassified in the review as due to disease progression. The number of deaths related to trial treatment remained unchanged as one in the CP arm and 4 in the CPB7.5+arm. The percentage of deaths from drug treatment in the CP arm then was 1 of 763 (0.13%) patients randomised to that treatment; 1 of 131 (0.76%) deaths from all causes; and 1 of 5 (20%) deaths from other than disease progression. In the CPB7.5+ arm, the figures were 4 of 746 (0.54%); 4 of 107 (3.74%); and 4 of 4 (100%). The Australian PI for Avastin does not give an overall figure for deaths caused by bevacizumab (incidence for gastrointestinal (GI) perforation and Thromboembolic events are given). The death rate from bevacizumab treatment in breast cancer has been stated by the FDA [18] as ranging from 0.8 to 1.2% (presumably this percentage is of the total deaths on study).

Deaths from AEs: Some AEs were associated with death of the patient.

In Study GOG-0218, 27 patients were reported either on the toxicity form or in NCI AdEERS as having an adverse event leading to death. Table 20 summarises the adverse events leading to death. Deaths due to disease progression, when reported as an adverse event by the investigator, were included in this analysis. Multiple Grade 5 AEs were reported for each of 11 patients. 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, versus 4 patients in the CPP arm). These adverse events included 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 that died after Cycle 7 of treatment, all other deaths from adverse events occurred during the first six cycles of therapy.

[18]FDA Center for Drug Evaluation and Research: Regulatory Decision to Withdraw Avastin (bevacizumab) Firstline Metastatic Breast Cancer Indication. Page 6, Item 9, Conclusions. http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM237171.pdf. Accessed 19 May 2011.

Table 20. Study GOG-0218. Summary of AEs leading to death. (Safety population).

Grade 5 AE – preferred term	CPP N = 601	CPB15 N = 607	CPB15+ N = 608
	n (%)	n (%)	n (%)
– Any adverse event –	4 (0.7)	9 (1.5)	14 (2.3)
Death	2 (0.3)	1 (0.2)	4 (0.7)
Disease progression	1 (0.2)	2 (0.3)	4 (0.7)
Embolism	(0.0)	(0.0)	1 (0.2)
Enterocolitis infectious	1 (0.2)	(0.0)	(0.0)
Gastrointestinal necrosis	(0.0)	1 (0.2)	(0.0)
Hemorrhage intracranial	(0.0)	(0.0)	1 (0.2)
Infection	(0.0)	1 (0.2)	(0.0)
Large intestine perforation	(0.0)	4 (0.7)	2 (0.3)
Lymphopenia	1 (0.2)	(0.0)	(0.0)
Multi-organ failure	1 (0.2)	(0.0)	(0.0)
Neutropenia	(0.0)	1 (0.2)	3 (0.5)
Opportunistic infection	1 (0.2)	(0.0)	(0.0)
Small intestinal perforation	(0.0)	(0.0)	1 (0.2)
Sudden death	(0.0)	1 (0.2)	2 (0.3)
Urinary tract infection	(0.0)	(0.0)	3 (0.5)
Visceral arterial ischemia	(0.0)	1 (0.2)	(0.0)

Events were reported either on CRF or in NCI AdEERS and graded according to NCI-CTCAE, Version 3.0.
Event categories are not mutually exclusive; patients may have experienced more than one event. Maximum severity was selected for each event for each patient. Only those adverse events that occurred within 30 days after the last study drug and on or before the cut-off date are included in this analysis.

In Study BO17707, seven patients in the CP arm and four patients in the CPB7.5+ arm were reported on the AE case report form (CRF) page as having an AE leading to death (Table 21). 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 AE of abdominal pain but the cause of death was recorded as gastrointestinal perforation on the study completion form.

Table 21. Study BO17707: Summary of AEs leading to death. (Safety Population).

Body System/ Adverse Event	CP N = 763 No. (%)	CPB7.5+ N = 746 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	7 (0.9)	4 (0.5)
Total Number of AEs	7	4
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	2 (0.3)	2 (0.3)
ABDOMINAL PAIN	-	1 (0.1)
DUODENAL OBSTRUCTION	-	1 (0.1)
GASTROINTESTINAL HAEMORRHAGE	1 (0.1)	-
INTESTINAL OBSTRUCTION	1 (0.1)	-
Total Number of AEs	2	2
NERVOUS SYSTEM DISORDERS		
Total Pts With at Least one AE	2 (0.3)	1 (0.1)
CEREBRAL HAEMORRHAGE	-	1 (0.1)
CEREBRAL ISCHAEMIA	1 (0.1)	-
CRANIAL NERVE DISORDER	1 (0.1)	-
Total Number of AEs	2	1
CARDIAC DISORDERS		
Total Pts With at Least one AE	2 (0.3)	-
CARDIAC FAILURE	2 (0.3)	-
Total Number of AEs	2	-
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total Pts With at Least one AE	1 (0.1)	-
DISEASE PROGRESSION	1 (0.1)	-
Total Number of AEs	1	-
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
Total Pts With at Least one AE	-	1 (0.1)
NEOPLASM MALIGNANT	-	1 (0.1)
Total Number of AEs	-	1

Investigator text for Adverse Events encoded using MedDRA version 13.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
AE onset between time of very first drug intake and day of the safety follow-up visit.
AE11 28JUL2010:14:57:50 (1 of 1)

Serious Adverse Events (SAEs) other than death and significant Adverse Events

SAEs

Serious adverse events were subject to expedited reporting in both studies; AEs reported to NCI AdEERS in Study GOG-0218 and serious AEs in Study BO17707. The events that required expedited reporting to NCI AdEERS were not the same as those defined according to standard SAE criteria but there was some overlap between the two.

The incidence of all-grade adverse events reported to NCI AdEERS or as SAEs was slightly higher in all bevacizumab-containing treatment arms compared with the corresponding control arms. Besides those SOCs comprising AEs associated with laboratory parameters (such as *Investigations*, *Metabolism and nutrition disorders*, and *Blood and lymphatic system disorders*), which are difficult to compare across studies due to differences in data collection and AE reporting, the most common types of AEs reported to NCI 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 AE that was reported to NCI 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%). The incidence of Grade 3/4 adverse events reported to NCI AdEERS was comparable across the three treatment arms, while the incidence of Grade 5 events (death) reported to NCI AdEERS was higher in both bevacizumab-containing treatment

arms than the CPP arm (CPP: 3 patients, 0.5%; CBP15: 6 patients, 1.0%; CPB15+: 14 patients, 2.3%).

In Study BO17707, several adverse events reported as SAEs occurred with ≥ 1% higher incidence in the CPB7.5+ arm relative to the CP arm: these events were abdominal pain, hypertension, vomiting, constipation, embolism, pulmonary embolism and wound complication. The incidence of Grade 3/4 serious adverse events was comparable across the treatment arms. With the exception of one patient in the CP arm who had an adverse event of disease progression leading to death, all other Grade 5 AEs were reported as SAEs (CP: 6 patients, 0.8%; CPB7.5+:4 patients, 0.5%).

Adverse Events leading to premature discontinuation of trial treatment

In Study GOG-0218, adverse events leading to treatment discontinuation were not collected on the toxicity form; however, this information was captured on the treatment completion form as treatment discontinued due to an AE, side effects or complications. The *component* of study treatment was not identified. 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%). 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.

Adverse Events by treatment period

Adverse events in both studies were analysed according to the treatment phase in which they occurred; during chemotherapy or after chemotherapy. In Study GOG-0218, more patients reported Grade ≥ 3 adverse events during the chemotherapy phase (CPP: 551 patients, 91.7%; CPB15: 572 patients, 94.2%; CPB15+: 566 patients: 93.1%) compared with after the chemotherapy phase (CPP: 112 patients, 18.6%; CPB15+: 102 patients, 16.8%; CPB15+: 150 patients, 24.7%). The proportion of patients in the long-duration bevacizumab arm reporting AEs during the post-chemotherapy phase was higher compared with the other treatment arms. More Grade 5 adverse events (deaths) were reported from Cycle 2 up to the start of Cycle 7 (CPP: 4 patients, 0.7%; CPB15: 9 patients, 1.5%; CPB15+: 12 patients, 2.0%) than from Cycle 7 onwards, during which period two Grade 5 events (deaths) were reported for two patients in the CPB15+ arm.

In Study BO17707, more Grade ≥ 3 AEs were reported during the chemotherapy phase (CP: 365 patients, 47.8%; CPB7.5+: 398 patients, 53.4%) than after the chemotherapy phase (CP: 115 patients, 15.1%; CPB7.5+: 225 patients, 30.2%).

Adverse Events of Special Interest (AESIs)

On the basis of previous clinical trials with bevacizumab, a number of adverse events have been identified as being of special interest. The incidence of these is summarised the in the following table, based on a table in the sponsor's *Summary of Clinical Safety*.

Table 22. AEs (all grades) of special interest. Studies GOG-0218 and BO17707.

	CPP	CPB15	CPB15+
All	97.3%	97.5	97.2
TE event	2.3	3.1	3.1
Bleeding (CNS)	0	0	0.5
Bleeding (non-CNS)	16.0	35.6	36.7
CHF	0	0	0.5
Febrile Neutropenia	3.5	5.1	4.4
Fistula/Abscess	1.2	0.8	2.0
GI Perforation	0.3	1.8	2.0
Hypertension	13.5	23.6	32.2
Neutropenia	95.7	95.2	95.4
Proteinuria	6.5	5.3	8.4
RPLS	0	0.2	0
Venous TE event	4.0	3.5	4.1
Wound healing complication	4.5	4.8	3.6

TE=Thromboembolic event

The following is a qualitative summary.

AESIs associated with the administration of bevacizumab

The above table shows that of the 12 AESIs, 6 were of two-fold or greater frequency in the bevacizumab arms than in the control arms of both studies, while others were increased to a lesser extent.

Increase of incidence of more than two-fold in bevacizumab-containing arms compared to that of control

These were as follows: thromboembolic (TE) event 2.2x B17707; CNS bleeding in extended use arms of both trials (>2fold); non-CNS bleeding 2.3x GOG; 3.5x B17707; GI perforation 6.6x GOG; 3.3x B17707; hypertension 2.4x GOG; 4.0x B17707; proteinuria 2.0x B17707; wound healing 2.9x B17707.

Evaluator's comment: The absolute value of the incidence of AESIs was not higher in the B17707 trial compared to the GOG trial, except for Venous TE events, (see below). However, the increase over the control was greater (see above) and seems to result from a lower incidence of AEs in the control group in B17707 than in the GOG study. The reason for this lower incidence is unexplained, although one factor might be that the patient population in the BO17707 study did not have as advanced disease as those in the GOG trial. Another reason could be a difference in medical practice in the US trial (GOG) and the mainly European trial (BO17707) in assessing and reporting AEs.

When did the AESIs occur?

Given that most AESIs were related to treatment with bevacizumab, an important question is whether they occurred during or after the chemotherapy phase of treatment. The

incidence of the events was higher as follows ("after chemotherapy" refers to the period of continuing treatment with bevacizumab):

1. Arterial thromboembolic events: both trial; after chemotherapy.
2. Bleeding (CNS and non-CNS): GOG- Cycle 2 to 7; BO17707- not stated
3. Congestive heart failure: GOG- Cycle 2 to 7; BO17707- not stated
4. Febrile neutropenia: GOG- Cycle 1 to 7; BO17707- during chemotherapy
5. Fistulae and abscesses: GOG- Cycle 2 to 7; BO17707- during chemotherapy
6. Gastrointestinal perforation: GOG-prior to Cycle 7; BO17707- after chemotherapy
7. Hypertension: GOG- Cycle 2 to 7 but higher afterwards; BO17707- higher than control both during and after chemotherapy
8. Neutropenia: GOG- Cycle 1 to 7; BO17707- during chemotherapy
9. Proteinuria: GOG- after chemotherapy; BO17707- after chemotherapy
10. Reversible posterior leukoencephalopathy syndrome (RPLS): GOG-one case between Cycles 2 to 7; BO17707- no cases
11. Venous thromboembolic events: GOG- Cycle 1 to 7; BO17707- during chemotherapy
12. Wound-healing complications: GOG- no increase; BO17707-during chemotherapy

Conclusions

Although some results from each trial differed, the majority of AESIs occurred during the chemotherapy phase of treatment, that is, when bevacizumab was administered in combination with carboplatin and paclitaxel.

The only AESIs that occurred more frequency after chemotherapy compared to before was proteinuria which was of lesser clinical concern and gastrointestinal perforation in Study BO17707 that was of greater concern (see below).

Which AESIs caused death?

The AESIs reported to cause death, a Grade 5 event, with their incidence were as follows:

- Arterial TE: GOG – 0 CPP; 1 CPB15; 1CPB15+. BO17707 - 1 in CP and 2 in CPB7.5+
- Bleeding: GOG - 1 (CNS) in CPB15+ arm. BO17707 – 1(non-CNS) in CP arm, 1(CNS) in CPB7.5+ arm.
- Congestive heart failure (CHF): GOG- 0; BO17707 – 2 in CP arm
- Febrile Neutropenia: GOG – 0. BO17707 – 0
- Fistulae and Abscesses: GOG – 0. BO17707 - 0
- GI Perforation: GOG – 0 in CPP; 4 in CPB15; 2 CPB15+. BO17707 – 1 in CPB7.5+
- Hypertension: GOG – 0. BO17707 – 0
- Neutropenia: GOG – 0 in CPP; 1 in CPB15; 3 in CPB15+. BO17707 - 0
- Proteinuria: GOG – 0. BO17707 - 0
- RPLS: GOG - 0. BO17707 – 0
- Venous TE Events: GOG – 0. BO17707 - 0

Conclusions about the risk of treatment deaths from bevacizumab

To consider the risk of death further, the figures that follow in brackets for the AESIs give the highest figure for the incidence of occurrence of the AESI and the incidence of death

for each, expressed as a percentage of deaths, the denominator being the total patient population treated, for example, 608 patients in the CPB15+ arm of the GOG study. The figures for the number of deaths are taken from sponsor's Summary of Clinical Safety.

The incidence figures/death rates are as follows: arterial thromboembolic events (3.5%/0.3%) , bleeding (0.5%/0.1%), GI perforation (2.0%/0.7%) and neutropenia (95.7%/0.5%). In these cases, bevacizumab treatment in whole or in part, resulted in patients' deaths.

Some infrequent AESIs such as GI perforation were much more lethal than more frequent events such as neutropenia. Of the 23 patients in the two bevacizumab arms of the GOG trial with GI perforation, 6 (26%) died, whereas of the 1158 patients with an AESI of neutropenia only 4 (0.3%) died. For comparison, the corresponding death rates (taken as highest reported in the two studies) for the AESIs that cause death were: arterial TE events; 2 of 26 (7.7%) [CPB7.5+]; and CNS bleeding – 1 of 3 (33.3%)[each of CPB15+ and CPB7.5+].

Clinical laboratory evaluation

In Study GOG-0218, pretreatment hematology and chemistry laboratory values were collected on the CRF page of drug cycle and dose. As these values were collected at local laboratories and normal ranges were not recorded on the CRF, these measurements were not analysed in the CSR. NCI-CTCAE grades associated with white blood cell counts, absolute neutrophil counts /granulocyte counts, platelet counts and hemoglobin (the lowest point (nadir)) collected on the GOG-0218 toxicity form at each cycle were assigned MedDRA preferred terms and were analysed with adverse events.

For study BO17707, the CSR presented results of analyses of laboratory test parameters (such as shifts from baseline and marked laboratory test value abnormalities). 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 hematologic 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.

Age, race and clinical safety

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.

Age, AESIs and death

AESIs: 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 (Study GOG-0218: CPP: 90.6% vs 88.0%; CPB15: 93.6% versus 87.2%; CPB15+: 91.3% versus 89.4%; Study BO17707: CP: 22.7% versus 19.7%; CPB7.5+: 35.9% versus 31%). There were no events of CNS bleeding in the older patient subgroup.

In Study GOG-0218, the generally higher incidence of Grade ≥ 3 AESIs among bevacizumab-treated patients compared with patients in the CPP arm was not more pronounced for one age subgroup than the other, with the 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 (CPP:4.2%; CPB15: 7.9%; CPB15+: 13.7%) compared with patients under 65 years old (CPP: 1.0%; CPB15: 4.4%; CPB15+: 8.2%).

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 (CP: 0.0%; CPB7.5+: 9.9%) than the < 65 year age group (CP: 0.4%; 5.0%). In the older age group, a higher proportion of patients in the CP arm reported neutropenia than the bevacizumab treatment arm (CP: 12.4%; CPB7.5+: 9.4%).

Deaths

In Study GOG-0218, the proportion of patients who died in the ≥ 65 year age group (overall 144 patients, 25.0%) was higher than that in the < 65 age group (overall 280 patients, 22.6%). There were no striking differences in the primary causes of deaths between the two age subgroups.

In Study BO17707, the proportion of patients who died in the ≥ 65 year age group (overall 82 patients, 21.9%) was higher than that in the < 65 year group (overall 156 patients, 13.8%). There were no striking differences in the primary causes of deaths between the two age subgroups.

Race, AESIs and death

Given the small numbers of patients in the subgroup of non-White patients (GOG-0218: 234 patients, 12.9% overall; BO17707: 61 patients, 4.0% overall), any analyses based on this subgroup should be interpreted with caution.

AESIs

Overall, 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.

Deaths

Summaries of deaths due to primary cause by race (White, non-White) for the two studies were given in the study report.

In Study GOG-0218, a lower proportion of non-White patients (39 patients, 16.7%) died compared with white patients (385 patients, 24.3%). In Study BO17707, bearing in mind the low numbers of patients in the non-White subgroup, the proportions of deaths among non-White patients (12 patients, 19.7%) and White patients (226 patients, 15.6%) were comparable.

Stage of disease and safety

The safety profiles of patients in Study BO17707 with FIGO Stage I and II disease (CP: 144 patients; CPB7.5+: 134 patients) were compared to those of the overall safety population (CP: 763 patients, CPB7.5+: 746 patients). The proportion of patients with FIGO Stage I and II disease with AEs of any grade was similar to that in the overall safety population, although the proportion of patients with Grade 3 AEs was slightly lower across both arms in the Stage I and II subset than the overall safety population (CP: 50.7%; CPB7.5+: 58.2% Stage I and II; versus CP: 54.3%; CPB7.5+: 64.6% overall).

AESIs

The proportions of patients within treatment arms with AESIs of any grade and of Grade ≥ 3 AESIs were similar between the subgroup and the overall analysis population. A comparison of the individual AESIs revealed no reports of gastrointestinal perforations among patients with early-stage disease.

Deaths

There were no deaths due to causes other than disease progression among patients with early-stage disease.

Other safety issues

There was no new information relating to bevacizumab with respect to other issues in the PI such as *Extrinsic Factors, Drug Interactions, Use in Pregnancy and Lactation, Overdose, Drug Abuse, Withdrawal and Rebound, Effects on Ability to Drive or Operate Machinery* or *Impairment of Mental Ability*.

Safety results from phase II Study AVF2949g

In this section, the safety results of Study AVF2949g are presented. The trial was a multicenter, single-arm, Phase II trial of bevacizumab in subjects with platinum-resistant epithelial carcinoma of the ovary or primary peritoneal carcinoma in whom subsequent doxil or topotecan therapy had failed. Treatment and the patient population differed from those in the two trials presented above. Bevacizumab was only administered as a single agent. Patients were to have progressive or recurrent disease after treatment first with a platinum-drug combination, then, if platinum-resistant, with either doxil or topotecan, and further progression or recurrence. Patients were to have received no more than three treatment regimens. The study was conducted at 14 investigative sites in the United States and was planned to take place from 26 January 2005 to 7 May 2006. However, because of safety concerns the trial closed early and patient recruitment stopped on 23 September 2005.

The treatment requested in the present application is for first-line combination chemotherapy with bevacizumab, whereas in Study AVF2949g the treatment tested was after two or more other chemotherapy combinations. Efficacy in the study is therefore not relevant to the present application and is not evaluated here.

Design

This was an open-label, single-arm, two-stage, Phase II study (see above) Subjects were followed for adverse events until the termination visit, which occurred 30–40 days after discontinuation from the study and for survival every 4 months until death, loss to follow-up, termination of the study by Genentech or withdrawal of consent from survival follow-up.

Number of subjects (Planned and Analysed)

A two-stage design was employed. Thirty-five subjects were to be enrolled in the first stage of the study. If 2 or more subjects achieved an objective response (confirmed complete response or partial response) in the first stage, an additional 85 subjects were to be enrolled in the second stage. By 8 August 2005, two objective responses had been observed and enrolment continued into the second stage. The study was closed to further enrolment on 23 September 2005 after a higher-than-expected rate of GI perforation events was reported. Forty-four subjects had been enrolled.

Test product, dose, mode and duration of administration

Bevacizumab was administered at a dose of 15 mg/kg once every 3 weeks by IV infusion. Subjects could receive bevacizumab for up to 102 weeks.

Safety

Subjects who received any amount of study treatment were included in the safety analyses. Safety was assessed through summaries of adverse events, including serious adverse events and adverse events leading to discontinuation of bevacizumab.

Safety assessment

Forty-four patients received a median of 5 doses (range 2-16) of bevacizmab.

Adverse events

AEs - overall and severe

Adverse events of any grade that occurred in 10% or more of subjects are summarized in Table 23. All subjects had at least one adverse event reported. Seventeen of 44 subjects (38.6%) had a Grade 3 event, 5 (11.4%) had a Grade 4 event, and 3 (6.8%) had a Grade 5 event reported.

Table 23. AEs occurring in ≥10% of subjects. Treated subjects.

	No. (%) of Subjects (n=44)	
	Any Grade	Grades 3–5
Gastrointestinal disorders		
Diarrhea	15 (34.1%)	1 (2.3%)
Nausea	15 (34.1%)	1 (2.3%)
Abdominal pain	13 (29.5%)	2 (4.5%)
Vomiting	11 (25.0%)	1 (2.3%)
Abdominal digestion	9 (20.5%)	2 (4.5%)
Constipation	7 (15.9%)	0 (0.0%)
General disorders		
Fatigue	14 (31.8%)	2 (4.5%)
Pyrexia	8 (18.2%)	1 (2.3%)
Infections and infestations		
Urinary tract infection	6 (13.6%)	1 (2.3%)
Investigations		
Weight decreased	5 (11.4%)	0 (0.0%)
Metabolism and nutrition disorders		
Dehydration	5 (11.4%)	1 (2.3%)
Musculoskeletal/connective tissue		
Arthralgia	12 (27.3%)	0 (0.0%)
Nervous system disorders		
Headache	13 (29.5%)	0 (0.0%)
Dizziness	7 (15.9%)	0 (0.0%)
Psychiatric disorders		
Anxiety	5 (11.4%)	0 (0.0%)
Renal and urinary disorders		
Proteinuria	7 (15.9%)	0 (0.0%)
Respiratory, thoracic, and mediastinal		
Dyspnoea	7 (15.9%)	2 (4.5%)
Dysphonia	5 (11.4%)	0 (0.0%)
Skin and subcutaneous tissue		
Rash	6 (13.6%)	0 (0.0%)
Vascular disorders		
Hypertension	13 (29.5%)	4 (9.1%)

Note: Adverse events with a common preferred term that occurred in 5 or more subjects are presented in this table.

Deaths

Twenty-one of 44 subjects (47.7%) died because of disease progression. There were 4 deaths attributed to adverse events in this study: bowel obstruction related to metastatic

disease, cerebrovascular ischemia, intestinal perforation, and sepsis from an abdominal fistula.

Deaths (Grade 5 events) that were attributed to bevacizumab treatment were reported for 3 subjects (6.8%): one from myocardial infarction and cerebrovascular ischemia, one from intestinal perforation and a third from convulsion and a hypertensive encephalopathy event.

Other serious events

Serious adverse events occurred in 18 of 44 subjects (40.9%). Perforation and obstruction of the GI tract and arterial TE events were the most commonly reported serious adverse events.

Adverse Events of Special Interest (AESIs)

As in the previous studies, AESIs were selected from previous bevacizumab studies. The AESIs and their incidence included GI perforation (5/44, 11.4%), arterial (3/44, 6.8%) and venous (1/44, 2.3%) TE events, bleeding (9/44, 20.5%), wound-healing complications (1/44, 2.3%), hypertension (13/44, 29.5%), proteinuria (8/44, 18.2%) and CHF (1/44, 2.3%). An AESI in this study that was not in the two previous studies was GI obstruction (5/44, 11.4%). Not included were fistula/abscess, neutropenia, febrile neutropenia, and reversible posterior leukoencephalopathy syndrome.

Evaluator's comment: Compared to the highest incidences of AESIs in the pivotal study, GOG-0218, the incidence of AESIs in the present study was higher, except for bleeding, hypertension and wound healing. The incidence of GI perforation (11.4%) was markedly higher than that (2.0%) in the CPB15+ arm of the GOG trial. Since 5 patients developed this complication and one died (this event was attributed to bevacizumab treatment) the trial was stopped. A further review of this event was therefore performed.

Gastro-intestinal perforation

The review showed that the 5 subjects who developed GI perforations all had evidence of bowel involvement with tumor at baseline, had received three prior chemotherapy regimens before study entry and developed perforations within 51–178 days after initiating bevacizumab therapy. Based on radiological data, the presence of bowel obstruction and bowel wall thickening at baseline appear to be the factors most strongly associated with the greatest risk of GI perforation in this study population. The presence of tumor involvement of the GI tract was common in this study population but did not appear to increase the risk of developing GI perforation as much as the presence of bowel obstruction, bowel wall thickening, or colon involvement. It is also worth noting that 5 of 21 subjects with three prior chemotherapy regimens (23.8%) had GI perforations compared with 0 of 23 subjects with two prior regimens.

Evaluator's comment: In the GOG study, the highest incidence of GI perforation was 2% of patients with 0.7% deaths, while in the AVF study the figures were 11.4% and 2.3%, respectively. The reason for the difference is not clear but one factor may have been that no patients in the AVF study had debulking surgery prior to bevacizumab treatment and so may have had more extensive disease, although they were initially staged as Stage III and IV as were those in the GOG trial. The patients in the AVF trial may therefore have been at higher risk of bowel involvement from tumour. Although the data shows such involvement did not by itself confer greater risk, perforation may have been associated with tumor response and resulting bowel disruption. The AVF trial did not report if the 5 patients who died with GI perforation showed evidence of a tumour response to bevacizumab treatment before their death. Beyond the caution noted for bowel involvement, the safety data from this trial are difficult to extrapolate to the treatment of previously untreated patients with smaller tumour burdens and who are treated with combination therapy plus bevacizumab rather than bevacizumab as a single agent.

Evaluator's Conclusions on Overall Safety

In the following conclusions, the evaluator took into account the differences in the three studies (GOG-0218, BO17707, and AVF) especially in their methods of reporting adverse events which made some comparisons difficult. In addition, the patient population in the three studies differed with respect to the stage of disease and the duration and doses of bevacizumab used. The main emphasis therefore is on data from Study GOG-0218, with supplementary results from the more problematic Study BO17707 and the less relevant Study AVF.

Summary

1. Hypertension, epistaxis, headaches, diarrhoea, dysarthria, infections/infestations and stomatitis of all grades of severity occurred in patients treated in all bevacizumab-containing arms at incidences 10% or greater than in the corresponding control arms of one or both studies (GOG, BO17707).
2. Of severe AEs (Grade 3 or more), those affecting the GI and vascular systems were more common with treatments that included bevacizumab. Of these the most frequent were diarrhoea (3.9%), nausea (4.8%), vomiting (4.2%), and hypertension (9.9%).
3. Deaths due to drug treatment were more frequent in the bevacizumab arm (CPB15+, 1.3%) than in the control arm (CPP, 0.5%) of the GOG-0218 trial. The higher death rate with bevacizumab was confirmed in the BO17707 trial (0.54% compared to 0.13%, equivalent to 1 death and 4 deaths in the CP and CPB7.5+ arms respectively). The causes of death in this trial appear to have been revised after the fact (post hoc) by the sponsor.
4. Serious AEs with an incidence of 1% or more were GI perforations in GOG-0218 (CPP, 0%; CPB15 1.2%, n=7; CPB15+ 1.0%, n=6), abdominal pain, hypertension, vomiting, constipation, embolism, pulmonary embolism and wound complication in B17707.
5. The AEs that lead to patients' deaths were more frequent in the CPB15+ (n=14) and the CPB15 (n=9) arms of the GOG trial than in the CPP arm (n=4). This differed from the results in Study BO17707, in which 7 patients died from AEs in the CP arm and 4 in the CPB7.5+ arm but the causes of death in this study, as stated above, had been revised and differed from those of the investigators. Three deaths (6.8%) were attributed to bevacizumab in Study AVF and the study was stopped for this reason. Another reason was the high incidence of GI perforation (11.4%; 5 of 44 patients). The high incidence of this adverse event may have been due to patients having more advanced with a greater frequency of bowel involvement.
6. Twelve adverse events previously associated with bevacizumab (AESIs), were assessed in the two studies. Six of these were two-fold or more frequent in the bevacizumab arms of Studies GOG-0218 and BO17707 compared to the control arms; thromboembolic events, bleeding (CNS and non-CNS), GI perforation, hypertension, proteinuria.
7. Most AESIs occurred during chemotherapy. Proteinuria and GI perforation (Study BO17707) occurred after chemotherapy, during continuing therapy with bevacizumab.
8. Some AESIs such as neutropenia were of high frequency but low mortality, while other such as bleeding and GI perforation were of lower frequency and high mortality. Of 1158 patients with neutropenia, 4 (0.3%) died, whereas of 6 patients with bleeding, 2 (33%) died. Of 23 patients with GI perforation, 6 (26%) died. Moreover, in previously treated patients (Study AVF) the incidence of GI perforation was 11.4% and caused the trial to be stopped.

9. A higher proportion of patients in the bevacizumab-containing treatment arms of Study GOG –0218 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 B17707, the figures for patients discontinuing treatment were CP: 68 patients, 8.9%; CPB7.5+: 164 patients, 22.0%.

Conclusions

Bevacizumab increased the incidence and severity of adverse events when used to treat patients suffering from ovarian cancer in combination with standard chemotherapy and when continued as a single agent. Many of these adverse events were specifically associated with treatment with bevacizumab, as shown by previous studies. A number of such events contributed to the deaths seen in the bevacizumab arms of the three trials. As well, patients discontinued bevacizumab treatment more frequently than standard treatment. To be justifiable, such toxicity would require a significant therapeutic benefit, convincingly demonstrated.

List of questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

Efficacy

The sponsor was asked to confirm that the formulation of bevacizumab used in Study GOG-0218 was the same as that marketed in Australia, noting that in the study it was a protocol violation to use commercially available Avastin.

Clinical summary and conclusions

Pharmacokinetics

The pharmacokinetics of bevacizumab have been well characterised across a variety of cancer indications, and tumor type has not been shown to alter its pharmacokinetics. The PK parameters in tumor types other than ovarian cancer are consistent with those in the draft PI. The effect of ascites on the PK of bevacizumab was not discussed in the application and the sponsor's response that any effect was not clinically relevant is noted.

The population PK analysis provided in the application gave results consistent with the PK parameters in the Australian PI, except that the PI did not mention the effect of body weight and gender on these parameters, as shown in the analysis. The predictions of the model were tested and found consistent with the PK parameters determined in a study of bevacizumab in patients with metastatic renal cancer.

Clinical efficacy

In the main Study GOG-0218 and the supporting Study B17707, clinical efficacy was primarily assessed by comparing the effect on PFS of treatment with bevacizumab plus standard therapy with that of standard therapy alone. The measurement and analysis of PFS complied with regulatory guidelines in the GOG study but the B17707 study had issues of concern. In both studies, as required, OS was evaluated as a secondary objective.

The GOG study was well designed, executed and the data well analysed. The interpretation of the analyses, however, lacked balance when considering possible patient risks and benefits. The study showed that adding bevacizumab at the study dose to the standard treatment of carboplatin and paclitaxel for an extended period of 22 cycles in total,

increased PFS by 6.2 months, a significant period, without improving the patients' quality of life in a clinically significant way above that seen with standard chemotherapy. The increase in PFS occurred whether or not the patients also received non-protocol treatment during the study. The high percentage of protocol violations (22.5%) is of concern but would not affect the comparison among the treatment arms but would change the responding population since it differed from that intended by the inclusion and exclusion criteria. No detrimental effect on overall survival was seen, and to date, no statistically or clinically significant increase has been found in the OS of patients treated with CPB15+ compared to the standard treatment with CPP.

The B17707 study had a number of design and procedural problems. The use of bevacizumab in the CPB7.5+ combination resulted in a statistically significant prolongation of PFS in the primary analysis by 14% (from 16 to 18.3 months) compared to standard chemotherapy (CP) when non-protocol specified antineoplastic therapy was used after disease progression. This increase in PFS reduced to 7.6% (from 17.1 to 18.4 months) for the period before non-protocol treatment was used and to 6.7% (from 17.8 to 19 months) in the "restricted time" analysis. The increase in PFS therefore was not of clinical significance, given its small value and other problems in the study, including the absence of survival data and the failure to improve quality of life above that with standard therapy, as well as other issues discussed above.

Safety

Bevacizumab increased the incidence and severity of adverse events when used to treat patients suffering from ovarian cancer in combination with standard chemotherapy and continued as a single agent. Many of these were specific to the use of bevacizumab, as shown by previous studies. A number of such events contributed to the deaths seen in the bevacizumab arms of the three trials. As well, patients discontinued bevacizamub treatment more frequently than standard treatment. To be justifiable, such toxicity requires a significant therapeutic benefit to be convincingly demonstrated.

Benefit risk assessment

Benefits

This assessment of patient benefit is based mainly on the pivotal Study GOG-0218. In this study, extended use of bevacizumab combined as described with standard chemotherapy, increased in a statistically significant manner the patients' period of progression free survival (PFS) by 6.2 months, from 12 months with standard therapy, CPP, to 18.2 months with CPB15+.

The endpoint of PFS is intended as a surrogate marker for patient benefit, with the expectation that a significant increase in PFS would be accompanied by an increase in overall survival and quality of life. An extension of PFS in itself does not necessarily indicate a benefit to the patient and the acceptance of PFS as a surrogate endpoint by regulatory authorities does not remove the requirement to demonstrate such a benefit.

In the GOG study, an increase in PFS was not seen with the combination of 5 cycles of bevacizumab with 6 cycles of standard chemotherapy (CPB15), so the longer treatment period with bevacizumab (CPB15+) was required to produce the increase in PFS. The time course of a patient in this study shows that the additional time of treatment with bevacizumab reduced the "well-time" when the patient had neither treatment nor disease progression.

In the CPP arm, the treatment period (standard chemotherapy) was 4.5 months and progression occurred 7.5 months after treatment stopped (PFS 12 months). The patient

therefore had 7.5 months free of both treatment and disease before death occurred 27.4 months after progression (median survival, 39.4 months).

In the CPB15+ arm, the extended treatment period was 16.5 months (66weeks, 22 cycles, one treatment every 3 weeks) and progression occurred 1.7 months after treatment stopped (PFS 18.2 months). The patient therefore had only 1.7 months free of both treatment and disease before death occurred 25.2 months after progression (median survival 43.4 months).

The comparison shows that with the addition of bevacizumab to standard treatment, the patient accepts 16.5 months of difficult treatment rather than 4.5 months, in return for only 1.7 months free of both treatment and disease compared to 7.5 months with standard treatment, and still dies at the same time with no significant improvement in the quality of life.

The supporting Study B17707 also showed an increase in PFS, the primary endpoint, in this case by 2.3 months from 16 months with standard CP treatment to 18.3 months with CPB7.5+ treatment. The increase in PFS was small (14%), and the statistical significance doubtful because the treatment effect was not constant throughout the trial period. As well the trial had a number of problems; it was unblinded and had no independent review of assessments of progressive disease; 40% of patients withdrew from treatment with bevacizumab during the 12 weeks of treatment with bevacizumab alone; after disease progression, a variety of non-protocol treatments were used so any difference in survival times could not be attributed to bevacizumab alone but to bevacizumab plus non-protocol therapy; causes of death were revised in a manner not defined by the trial protocol; and the quality of life measures showed a negative impact of the bevacizumab combination compared to that of standard chemotherapy.

The evaluator concluded that although the increase in PFS was statistically significant in the GOG and questionably so in the BO17707 trial, the increase did not confer a worthwhile clinical benefit on the patients so treated.

Risks

Two main risks need to be considered; the first is that the statistically significant increase in PFS in the GOG trial may not result in an accompanying increase in OS and QOL; the second is whether the adverse effects, including death, as documented in the three trials from adding bevacizumab to standard therapy are acceptable given the small benefit if any from the treatment.

The risk of accepting PFS without a demonstrated increase in OS or QOL

The Australian Product Information shows that Avastin increased the PFS of patients with various cancers that are approved indications, including metastatic colorectal cancer (mCRC), non-small cell lung cancer (NSCLC), metastatic breast cancer (mBC), and metastatic renal cell cancer (mRCC). Glioblastoma is also an approved indication, but no effect on PFS was assessed in the related trial.

In the case of *mCRC*, increases of from 18% to 88% in the PFS in three trials were accompanied by increases in OS of 30% and 67% in two trials and no increase in the third. For *NSCLC*, the 20% increase in PFS was accompanied by a 30% increase in OS. For *mRCC*, the increase of 88% in the PFS was not accompanied by any increase in OS.

The case of *mBC* is more complicated. The Australian PI gives the results of trial E2100 that demonstrated an increase in the PFS by 5.5 months with no increase in the OS. This result was not confirmed in two subsequent trials, the AVDO and the RIBBON1 trials, in which the PFS was only increased by 0.9 and 1.2 months, respectively, with no increase in OS. The FDA is currently proposing to withdraw this indication for Avastin[18].

Conclusion

Of the four approved indications (with the exception of gliobalstoma) for Avastin, two cases that showed an increase in PFS did not demonstrated any increase in the OS. The evaluator concluded therefore that there is a significant risk in assuming an increase in PFS means an increase in patient benefit as shown by improved survival or QOL after treatment. Such an improvement in survival may occur in the present GOG trial but will require fully mature data to show it convincingly.

Treatment with bevacizumab increases toxicity to a significant extent

All three studies showed a significant increase in the number, severity and seriousness of the adverse events when bevacizumab was added to standard therapy. This included a significant risk of death from the drug-specific event of GI perforation and of bleeding, events of low incidence but high mortality, as discussed in the *Safety* section of this evaluation. The third trial, AVF, was stopped early because of concern about GI related AEs, including GI-perforation. The increased toxicity of bevacizumab combination therapy was detailed in a previous section of this evaluation and will not be repeated here.

In both Studies GOG and BO17707, more patients discontinued treatment in the bevacizumab-containing arms compared to control because of an adverse event, side effect or complication, again indicating the toxicity of the treatment. In Study BO17707, around half of all patients who discontinued bevacizumab (16% of the treated patient population) did so during the six cycles when bevacizumab was administered concurrently with chemotherapy. The remainder discontinued bevacizumab during the 12 additional cycles when bevacizumab was administered alone.

The toxicity of bevacizuamb was also demonstrated by the QOL assessment in Study BO17707 in which patients in the bevacizumab containing arm had higher scores for symptoms and side effects of treatment than in the control arm, noting that the dose of bevacizumab in this trial was half that requested in the present application and was administered for a shorter time.

Conclusion

Compared to standard treatment, the combination with bevacizumab is significantly more toxic and less well tolerated by patients.

Balance and conclusions

Considering the small clinical benefit, if any, of the demonstrated increase in the PFS of patients treated with the bevacizumab-containing combination, the lack of a significant improvement in their QOL, the absence of mature survival data, and the toxicity of the treatment, the evaluator concluded that this use of the bevacizumab-containing combination cannot be recommended at this time. If and when a significant improvement in OS is demonstrated, the question could be reconsidered.

Recommended conditions for registration

Avastin should not be registered for the requested indication until mature survival data have been provided to show a benefit to the patients treated. The reasons for this recommendation are given above.

In the event that this recommendation is not accepted and registration proceeds, the evaluator would make a further recommendation that the indication requested be modified to refer to only the patient population treated in the GOG study (untreated FIGO Stage III disease with any gross residual disease and FIGO Stage IV epithelial ovarian, primary peritoneal or fallopian tube cancer) because the broader patient population (high risk early FIGO Stage I or IIa clear cell or Grade 3 carcinoma, and FIGO Stage IIb or greater) in Study B17707 showed no significant clinical benefit.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing safety Concerns which are shown at Table 24.

Table 24. Ongoing safety concerns

Important identified risks	• bleeding / haemorrhage • pulmonary haemorrhage • arterial thromboembolic events (ATE) • hypertension • proteinuria • congestive heart failure (CHF) • wound healing complications • gastrointestinal perforations • reversible posterior leukencephalopathy syndrome • neutropenia • venous thromboembolic events (VTE) • fistula • thrombotic microangiopathy (TMA) • pulmonary hypertension
Important potential risks	• embryo-fetal development disturbance • physeal dysplasia • peripheral sensory neuropathy • ovarian failure • cardiac disorders (excluding CHF and ATE)
Newly identified safety concerns	• hypersensitivity and infusion reactions • ONJ
Important missing information	• safety profile of the different treatment combinations in patients with non-squamous NSCLC • long term use in paediatric patients • patients with renal impairment • patients with hepatic impairment

OPR evaluator comment:

Hypersensitivity/infusion reactions and ONJ have been added to this RMP version (9.0) as newly identified safety concerns.

Hypersensitivity/infusion reactions

The sponsor searched their clinical trials and safety databases and detected 273 case reports relating to hypersensitivity reactions. While the majority of cases were confounded by concomitant chemotherapy, there were 4 individual case reports for which the use of Avastin as a single agent could be confirmed as well as cases of positive rechallenges. The *Precautions* section and *Post-marketing experience* subsection of the PI were subsequently updated.

ONJ

The sponsor identified 55 case reports of ONJ from their database search. Of these, 43 were confounded by concomitant chemotherapy and concomitant bisphosphonate treatment was described in 31. In another 12 cases there were underlying medical conditions providing alternative explanations. The 55 ONJ cases would yield a reporting rate of less than 1 to 10,000. Taking into account the risk of ONJ in patients with cancer treated with high doses of intravenous bisphosphonates, a causative role of Avastin is uncertain. The *Post-marketing experience* subsection of the PI has since been updated to include a statement about the observed cases of ONJ in Avastin treated patients and the possible association with prior or concomitant bisphosphonates.

CNS metastases contraindication

The contraindication for use in patients with central nervous system (CNS) metastases has been removed from the Australian PI following the submission in 2009 of a drug safety report on the available safety information in patients with brain metastases, treated with Avastin. The detailed review of the documentation did not suggest that patients with brain metastases would be at a prohibitively greater risk of tumour-associated haemorrhage when treated with Avastin. Therefore it was not considered justified to continue withholding a potentially beneficial treatment from these patients. The *Precautions* section of the PI was updated regarding CNS bleeding and CNS metastases.

Conjunctival haemorrhage

The widespread off-label use of Avastin for AMD in the US appears to be related to cost[19] (Lucentis approximately US$2000 per dose compared to US$50 for Avastin[20]). It is likely that this type of off-label use in Australia is mitigated by the subsidised cost of Lucentis under the Pharmaceutical Benefits Scheme (PBS) on authority prescription for subfoveal choroidal neovascularisation due to AMD, as diagnosed by fluorescein angiography.

The sponsor has provided an overview of results from a recently completed Medicare claims database study performed at John Hopkins University in collaboration with Roche and Genentech and it viewed together with a previously published Medicare claims study suggest an increased risk for ocular inflammation, cataract requiring surgery, haemorrhagic stroke and all-cause mortality when off-label Avastin is used in patients being treated for wet AMD as compared to ranibizumab. A statistically significant increased risk was demonstrated in ocular inflammation (adjusted HR 1.82; 99% CI 1.20, 2.76), cataract requiring surgery (adjusted HR: 1.11; 99% CI: 1.01-1.23), haemorrhagic stroke (adjusted HR: 1.57; 99% CI: 1.04-2.37), and all-cause mortality (adjusted HR 1.11; 99% CI: 1.01-1.23) for patients with wet AMD being treated with off-label intravitreal Avastin as compared to ranibizumab. Other endpoints, such as myocardial infarction and ischaemic stroke did not find a significant differential risk between the two therapies. While there are important limitations to retrospective, observational claims studies, these findings are significant. The sponsor states that as part of the ongoing application for Avastin treatment of recurrent ovarian cancer the sponsor has proposed updates to the Avastin PI to describe the increased risk of ocular inflammation, cataract requiring surgery, haemorrhagic stroke and all-cause mortality when off-label intravitreal Avastin is used as compared to ranibizumab in patients being treated for wet AMD. Systemic adverse events associated with unapproved, off-label intravitreal use have been identified as a "*newly identified risk*" in the updated version of the Australian RMP (version 2.0, dated

[19]Brechner RJ, Rosenfeld PJ, Babish JD, Caplan S. Pharmacotherapy for neovascular age-related macular degeneration: an analysis of the 100% 2008 Medicare fee for- service Part B claims file. Am J Ophthalmol 2011;151:887-95.

[20]Rosenfeld PJ. Bevacizumab versus Ranibizumab for AMD. NEJM 2011;364:1966-67

September 2011). The sponsor states that this RMP and the PI update are to be submitted to the TGA.

Left Ventricular Ejection Fraction (LVEF) and CHF events

In the Australian-RMP Addendum the sponsor states that there was discontinuation of clinical trial enrolment for the Phase III study BO20603 / AVF4065g (MAIN study) in previously untreated patients with CD20-positive diffuse large B-cell lymphoma and that the results of the MAIN study analyses, indicated as ongoing at the time of European Union-RMP publication, would be incorporated into the next Avastin PSUR (due April 2011). This PSUR has since been submitted with additional safety analysis of MAIN data showing:

- An increased LVEF/CHF rate (all grades) in patients treated with Avastin as compared to the control arm (both included doxorubicin and R-CHOP) (14.6% versus 6.3%, 16.1% versus 6.1% for LVEF and CHF, respectively).
- A CHF event rate (all grades and Grades ≥3) for Avastin in combination with doxorubicin and R-CHOP that is higher than for Avastin used in combination with doxorubicin in solid tumours.

Proteinuria

A recent meta-analysis[13] reported on the incidence of high grade proteinuria. This analysis plus the sponsor's clinical trial pooled analysis suggests that a dose dependent relationship not only exists for Grade 1 proteinuria, as is currently mentioned in the PI, but also for high grade proteinuria.

OPR evaluator comments:

The clinical evaluation report does not appear to have identified any new safety signals although the evaluator's comments regarding the greater toxicity of Avastin compared to standard treatment was noted. The Ongoing Safety Concerns as specified by the sponsor are considered acceptable with the addition of ocular and systemic toxicity from off-label intravireal use.

Pharmacovigilance Plan

In the Australian-RMP Addendum Version 1.0, the sponsor states that the pharmacovigilance (PhV) activities are as per the European Union-RMP.

Routine PhV[21] was proposed for the following safety concerns:

- Important identified risks
  - Reversible posterior leukencephalopathy syndrome
  - Neutropaenia
  - VTE
  - Thrombotic microangiopathy
  - Pulmonary hypertension

[21] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

- Important potential risks
  - Embryo-foetal developmental disturbance
  - Peripheral sensory neuropathy
- Newly identified safety concerns
  - Hypersensitivity/infusion reactions
- Important missing information
  - Patients with renal/hepatic impairment

Targeted follow-up using a guided questionnaire was identified for the following safety concerns:

- Important identified risks
  - Pulmonary haemorrhage
  - Arterial thromboembolic event (ATE)
  - CHF
  - Gastrointestinal perforations
- Newly identified safety concerns
  - ONJ
- Important missing information
  - Safety profile of the different treatment combinations in patients with non-squamous NSCLC .

Ongoing clinical trials

The main objective of the prospective safety data collection in the ongoing Phase II/III trials (identified in various sections of the PhV plan) is to continue to assess the magnitude of the risk and potential risk factors for the specified safety concerns. For studies contributing to the monitoring of haemorrhage, the objectives also include the evaluation of bleeding in patients on anticoagulation therapy. An additional objective for studies informing the risk of ATE is a benefit-risk assessment for the use of low dose aspirin in patients at an increased risk of experiencing ATE. Data collection also aims to examine the reversibility of hypertension after Avastin discontinuation, the safety of resuming Avastin after gastrointestinal fistulae formation and to explore the possible pathophysiological mechanisms of CHF.

Pos authorisation studies

There are seven post authorisation studies identified by the sponsor (*Post-authorisation safety studies*) and two planned studies (*Detailed action plan for specific safety concerns*). Of these, two studies are reported as completed (AVF2941n & MO19390) and therefore the study protocols provided have not been evaluated with this submission. The safety results of these completed studies have been discussed in the *Safety specifications* section of the RMP and as such are not considered part of the PhV plan and the RMP should be updated to reflect this. Another study (MO18024 – First BEAT) is described in the PhV plan but there is no mention on the study status. As safety data analysis from this study has been included in *Safety specifications* section, it is presumed that this study has been completed and analysed. The overview of post authorisation studies below has been obtained from information contained in the PhV plan and Annexes 3 and 9.

Biomarker sampling

To be prepared for exploratory investigation of unexpected safety findings, the sponsor has introduced a precautionary biomarker sampling strategy has been adopted across the

Avastin development program. As of May 2006, precautionary deoxyribonucleic acid (DNA) sampling has been instituted in the following trials: BO17920, BO17704, BO17706, BO17934, BO17705, BO17708 and BO20231. Precautionary ribonucleic acid (RNA)/protein sampling via the Biomarker Sampling Repository has been instituted in BO17934, BO20231, BO17920, BO17708 and BO17706. In addition to this safety-oriented approach, precautionary tumour sampling has been instituted or is planned for the following trials: BO17920, BO17708 BO20231 and BO21990. It is expected that these samples may be utilised for correlative studies and translational research.

OPR evaluator comment:

General considerations

There were several inconsistencies with regard to the status and milestone for reporting of studies identified in the PhV plan. This made the evaluation difficult and required frequent navigation throughout the document and annexes to try to establish study status and their relevance to pharmacovigilance. In the sponsor's response to request for information dated 30 September 2011, the sponsor provided a commitment that the inconsistencies identified will be amended in the Australian RMP version 2.0 to be submitted with another current TGA application.

The inconsistencies can be summarised into three broad categories:

- Studies that have been reported in some sections of the RMP as having been completed, and are therefore no longer considered part of the PhV plan but continue to be listed as proposed PhV activities:
  - AVF3729g; listed as a PhV activity for the haemorrhage and pulmonary haemorrhage safety concerns in Section 5 *Summary of the EU Risk Management Plan* and identified as ongoing in Section 2.7 *Summary of outstanding actions including milestones;* however, in Section 1.5.2.2.6 *Risk groups or risk factors* the outcomes of this analysis are described suggesting that AVF3729g has been completed.
  - BO19734 (AVASQ) and AVF3744g (BRIDGE); these 2 open-label safety studies in patients with squamous NSCLC are identified as PhV activities for the risk of haemorrhage in Section 5 *Summary of the EU Risk Management Plan*. The BRIDGE study is listed as ongoing in Section 2.7 *Summary of outstanding actions*, including milestones but as completed in Section 2.5 *Overview of study protocols for the PhV plan*, Section 1.3.16 Patients with predominantly squamous cell NSCLC and in Annex 3 *Ongoing and completed clinical trial programme*. The AVASQ study was prematurely terminated in 2007 due to a second patient experiencing pulmonary haemorrhage
  - BO17708 (AVADO) and AVF3752g (PASSPORT); identified as a PhV activities for the risk of haemorrhage in Section 2.4 *Detailed action plan for the specific safety concerns*, however, these studies have been completed and the data updated in the RMP *Safety specifications* section.
  - MO18024 (First BEAT); described in Section 2.2 *Post-authorisation safety studies* but there is no mention on the study status. As safety data analysis from this study has been included in the *Safety specifications* section, it is assumed that this study has been completed and analysed.
- No milestones for the reporting have been provided for some ongoing studies:
  - AVF3671g (ATLAS)
  - E5105

- Information from studies that should be included in the RMP:
  - In Section 2.4 (*Detailed action plan for the specific safety concerns*) the milestone for reporting of Study AVF4223g (QTc) is stated as fourth quarter of 2010 however this postmarket commitment is dependent on data from cardiac monitoring in Study BO17920 (milestone for reporting fourth quarter of 2011). It is noted from a search of the ClinicalTrials.gov website that this study has now been withdrawn.
  - In Section 2.4 (*Detailed action plan for the specific safety concerns*) Study AVG3726g is identified as a completed with respect to the pulmonary haemorrhage safety concern. Reference is made to Sections 1.5.2.2.6 and 1.3.15 for further information, however, there appears to be no mention of the results of the safety analysis from this study in these sections or anywhere else in the RMP.

Appropriateness of planned actions: Ongoing studies

For the indications of ovarian, fallopian tube or primary peritoneal cancers for which approval is being sought, one ongoing Study AVF4095g (OCEANS) will evaluate the incidence of gastrointestinal perforation in patients with platinum-sensitive recurrent cancer. A previous study (AVF2949g) was prematurely terminated as a result of an observed gastrointestinal (GI) perforation rate of 11% in a small study of 44 patients with highly refractory platinum-resistant ovarian cancer. There is limited data on the incidence of GI perforation among first-line ovarian cancer patients. In a retrospective cohort study[22] of women with recurrent ovarian cancer, the overall frequency of gastrointestinal perforation and/or fistula among patients treated only with standard chemotherapy was 6.5%, which equates to just over 19 per 292 patients. It is possible that this study will be able to detect an increased rate of gastrointestinal perforations above the background rate.

Considering the large number of patients currently enrolled in clinical trials and post-marketing studies for the product and the estimated background rates of the respective identified and potential safety concerns (see Table 25), it is possible that these studies will detect rates above the expected rate. The ongoing studies identified in this evaluation are considered acceptable to continue to characterise and monitor the risks.

[22] Sfakianos GP, Numnum TM, Halverson CB, Panjeti D, Kendrick JE, Straughn JM. The risk of gastrointestinal perforation and/or fistula in patients with recurrent ovarian cancer receiving bevacizumab compared to standard chemotherapy: a retrospective cohort study. Gynecol Oncol. 2009;114:424-6.

Table 25. Ongoing safety concerns: Background rates in cancer patients.

Safety Concern	Background rate (% or /100 PY)	Background population
Haemorrhage	3.9-11.3. /100 PY	Lung, colorectal and any cancer
Pulmonary haemorrhage	0.18-1.0%	Chemotherapy treated NSCLC
ATE: CVA	0.4-1.4/100 PY	Lung, colorectal, ovarian, renal and any cancer
ATE: MI	0.8-4.0/100 PY	Lung, colorectal, ovarian, renal and any cancer
Hypertension (HT)	1-8%	≥ grade 3 HT in advanced cancer
Proteinuria	0.02%	Grade 3 or 4 proteinuria in metastatic colorectal cancer
CHF	2.8-8. %/100 PY	New CHF in all cancer
Wound healing complications	4-11%	Cancer patients
GIT perforation/fistula	6.5%	Ovarian cancer
Fistula	3.7%	Metastatic colorectal cancer
RPLS	unknown	
Neutropenia	Wide range 0-97%	Chemotherapy
VTE: DVT	0.6-0.7/100 PY	New DVT in all cancer
VTE: PE	0.35-0.4/100 PY	New PE in all cancer
TMA	unclear	
Pulmonary hypertension	Unknown incidence in cancer patients	
Physeal dysplasia	Unknown	
Peripheral sensory neuropathy	3.4-21.8%	Cancer patients
Ovarian failure	22-61% (≤ 40 years) 61-97% (> 40 years)	Breast cancer

With respect to ovarian, fallopian tube and primary peritoneal cancers, a search of the ClinicalTrials.gov database for Avastin studies (search parameters: studies by the sponsor; Phase III/IV; safety outcome measures)[23] identified two studies for which safety outcomes were being measured but that could not been located in the RMP:

1. MO22923 (ROSIA)
2. MO22224 (AURELIA)

The following follow-up information, dated 30 September 2011, was obtained from the sponsor regarding these studies and the sponsor has committed to including them in the next version of the EU-RMP.

Appropriateness of planned actions: planned studies

Pooled data form blinded and unblinded trials shows 2% (95% CI: 1.4-2.5) of patients treated with Avastin having at least 1 wound healing complication event. Complications of wound healing have been estimated as occurring in between 4 - 11 % of cancer patients. This equates to between 3.2 to 8.8 events per 80 patients. It is possible that Study MO18725 will be able to detect an increased rate of wound healing complications over the background rate.

[23] US National Institue of Health. Clinical trials database. http://clinicaltrials.gov/ct2/results?flds=Xe&flds=a&flds=b&flds=c&flds=f&flds=g&flds=i&flds=j&flds=k&flds=l&flds=n&flds=t&term=bevacizumab&cond=ovarian+cancer&phase=23&fund=2&show_flds=Y [cited 13 June 2011]

Safety analyses that have reached the milestone for reporting

With respect to the haemorrhage (including bleeding in patients with CNS metastases) safety concern, the results from OSI3364g (BeTa Lung) and AVF3995g (SALUTE) are reported as being expected by first quarter of 2011. Follow-up information obtained from the sponsor is that the results of these studies have been included in an updated EU-RMP to be included in the Australian RMP version 2.0 to be submitted to the TGA. Also reported as expected by first quarter of 2011 is the safety data analysis for NSABP-C08 and the cardiac monitoring analysis of Study BO20231 (AVEREL). Updated information obtained from the sponsor identifies the results of Study NSABP-C08 as being currently under review with completion expected by the fourth quarter of 2011 and the final study report for B020231 expected by the fourth quarter of 2012. While the safety data from the completed AVF3693g (RIBBON-2) trial has been included in the RMP *Safety specifications* section, an analysis of bleeding in patients with CNS metastases could not be found. The sponsor has clarified that this analysis has been included in the current EU-RMP to be included in the Australian RMP version 2.0 that will be submitted to the TGA.

Appropriateness of biomarker sampling

With regard to the planned biomarker sampling, these analyses can only be done in the subpopulation of patients who give consent. Furthermore, these analyses are exploratory in nature and potential results will have to be confirmed in independent studies.

Risk minimisation activities

The sponsor proposed routine risk minimisation[24] for all of the ongoing safety concerns by way of the proposed product information document.

OPR evaluator comment:

The prescribing of Avastin in Australia for the treatment of malignant disease will be primarily by specialist Oncologists. The safety concerns identified for Avastin are reflective of the range of side effects that are known to occur with other chemotherapeutic drugs. Given that the main side effects that may encountered with Avastin reflect Oncologists' expertise in prescribing and monitoring the safety of a wide range of chemotherapeutic drugs, routine risk minimisation was considered adequate.

Summary of recommendations

- The implementation of Risk Management Plan included in the submission, that identified as the European Union-RMP version 9.0 and dated 18 November 2010, and the Australian-RMP addendum version 1.0 dated 25 February 2011, and any subsequent updated versions, be implemented as a condition of registration, and:
- The sponsor proposed to submit an updated European Union -RMP in the Australian RMP version 2.0 and a safety related PI change (adverse reactions associated off-label intravitreal use. The updated RMP should address several inconsistencies identified in the RMP version submitted with the current application which were raised by the evaluator. It was recommended to the Delegate that the aforementioned updated RMP should be submitted to the OPR in a timely manner.

[24] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The evaluator has recommended rejection of the application on the grounds of an unfavourable risk-benefit balance.

Pharmacokinetics (PK)

The current submission did not contain any data on the PK of bevacizumab in the ovarian cancer population. The sponsor argued that the PK of the drug were consistent across the various tumour types previously evaluated and that therefore they were unlikely to be altered in ovarian cancer. The evaluator has raised the issue of whether the PK of the drug are altered in patients with ascites. No PK data are available to address this question and the evaluator has recommended that a statement to this effect should be added to the PI.

The submission included a population PK analysis which compared the PK of the drug in renal cell carcinoma patients with other tumour types. No significant differences in PK were identified between the two groups.

Efficacy

Evidence for efficacy in the new population comes from two randomised, controlled Phase III studies; Study GOG-0218 and Study BO17707 (the ICON-7 study).

The *GOG-0218 study* was randomised, double-blind, placebo-controlled with a parallel groups (x3) design. Patients enrolled had previously untreated, histologically diagnosed, epithelial ovarian, primary peritoneal or fallopian tube cancer, after initial abdominal surgery for diagnosis, staging and cytoreduction. Patients could have either:

- FIGO Stage III disease with macroscopic or palpable residual disease (that is, IIIB or IIIC); or:
- FIGO Stage IV disease.

The FIGO staging system is illustrated in Table 26.

Table 26. FIGO staging system

American Joint Committee on Cancer (AJCC)
TNM and FIGO Staging System for Ovarian and Primary Peritoneal Cancer (7th ed., 2010)

Primary Tumor (T)

TNM	FIGO	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor limited to ovaries (one or both)
T1a	IA	Tumor limited to one ovary; capsule intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings
T1b	IB	Tumor limited to both ovaries; capsules intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings
T1c	IC	Tumor limited to one or both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings
T2	II	Tumor involves one or both ovaries with pelvic extension
T2a	IIA	Extension and/or implants on uterus and/or tube(s). No malignant cells in ascites or peritoneal washings
T2b	IIB	Extension to and/or implants on other pelvic tissues. No malignant cells in ascites or peritoneal washings
T2c	IIC	Pelvic extension and/or implants (T2a or T2b) with malignant cells in ascites or peritoneal washings
T3	III	Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis
T3a	IIIA	Microscopic peritoneal metastasis beyond pelvis (no macroscopic tumor)
T3b	IIIB	Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension
T3c	IIIC	Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis

Regional Lymph Nodes (N)

NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC	Regional lymph node metastasis

Distant Metastasis (M)

M0		No distant metastasis
M1	IV	Distant metastasis (excludes peritoneal metastasis)

Note: Liver capsule metastasis is T3/Stage III; liver parenchymal metastasis, M1/Stage IV. Pleural effusion must have positive cytology for M1/Stage IV.

All patients were treated with 6 cycles of:

- Paclitaxel 175 mg/m2 q 21 days; and
- Carboplatin AUC = 6.0 q 21 days.

Patients were randomised (1:1:1) to receive:

- Placebo
- Bevacizumab 15 mg/kg q 21 days for Cycles 2 to **6** (total = 5 cycles or **15** weeks); or
- Bevacizumab 15 mg/kg q 21 days for Cycles 2 to **22** (total = 21 cycles or **63** weeks).

The primary endpoint was PFS. The two bevacizumab arms received identical treatment for Cycles 1 – 6. Therefore, the two arms were pooled for PFS events occurring during these cycles. Secondary endpoints were overall survival, response rates and quality of life measures.

A total of 1873 subjects were enrolled. Results for the primary endpoint are shown in the clinical evaluation report (CER). Compared to the placebo arm (CPP), the long-term bevacizumab arm (CPB15+) was associated with a significant increase in PFS (HR = 0.64; 95% CI: 0.54 – 0.77; $p < 0.0001$). Median PFS was increased by 6.2 months (18.2 versus 12.0 months). The Kaplan-Meier curved for PFS is shown in the CER. The short term bevacizumab arm (CPB15) was *not* associated with any benefit compared to placebo.

There was no improvement in overall survival although the survival data were not mature with only 36% of patients having died. There was no improvement in overall response rate and no clinically significant benefits in terms of improved quality of life.

Study BO17707 was a randomised, open study with a parallel groups (x2) design. Patients had previously untreated, histologically diagnosed, epithelial ovarian, primary peritoneal or fallopian tube cancer. Patients could have:

- FIGO Stage I or IIa disease provided that it had poorly differentiated (Grade 3) histology; or:
- FIGO stages IIb, III or IV disease.

All patients were treated with 6 cycles of:

- Paclitaxel 175 mg/m2 q 21 days; and
- Carboplatin AUC = 6.0 q 21 days.

Patients were randomised (1:1) to receive:

- No additional treatment; or
- Bevacizumab 7.5 mg/kg q 21 days for a total of 18 cycles (or 54 weeks).

The primary endpoint was PFS. Secondary endpoints included response rates, overall survival and quality of life. Assessments regarding response or progression of disease were made by the investigators who were not blinded to treatment allocation.

A total of 1528 subjects were enrolled. Results are shown in the CER. Treatment with bevacizumab was associated with a significant improvement in PFS (HR=0.79; 95% CI: 0.68 – 0.91; p = 0.0010). Median PFS was increased by 2.3 months (18.3 versus 16.0 months). The Kaplan-Meier curved for PFS is shown in the CER.

Overall response rate was also improved (62% versus 42%). There was no improvement in overall survival although the survival data were not mature with only 24% of patients having died. There were no notable differences in quality of life between the two treatment arms, although bevacizumab treatment was associated with a reduction in one scale measuring 'chemotherapy side effects'.

Safety

The total number of patients exposed to bevacizumab in the two Phase III studies was approximately 1960. Of these, approximately 1350 were treated in the long term bevacizumab arms. Median duration of bevacizumab treatment in the long term bevacizumab arms was 9.0 months in Study GOG-0218 and 11.6 months in Study BO17707.

Overall toxicity in terms of the incidence of adverse events etc is summarised in Table 27.

Table 27. Incidence of adverse events

	GOG-0218			BO17707	
	CP-P (n=601)	CP-Bev15 (n=607)	CP-Bev15+ (n=608)	CP (n=763)	CP-Bev7.5+ (n=746)
AEs	99.8 %	100 %	99.8 %	99.0 %	100 %
AEs ≥ Grade 3	93.0 %	95.1 %	94.4 %	54.3 %	64.6 %
Serious AEs	21.3 %	23.7 %	25.8 %	23.5 %	37.7 %
Withdrawals due to AEs	9.7 %	13.7 %	16.4 %	8.9 %	22.0 %
Fatal AEs	4	9	14	7	4
Related Fatal AEs	3	6	8	1	4
Overall deaths	145	148	131	131	107

CP = carboplatin + paclitaxel; P = placebo; Bev = bevacizumab; + = long term treatment; AEs = adverse events.

In Study BO17707, long term bevacizumab treatment was associated with a 10% increase in Grade III or higher adverse events, a 15% increase in serious adverse events and a 13% increase in withdrawals due to adverse events. In Study GOG-0218, the differences between treatment groups were less marked, even though the dose of bevacizumab used in this study was higher. In both trials there was a small increase in the incidence of treatment-related fatal adverse events. However, the incidence of death due to any cause was lower in the long term bevacizumab treatment arms.

The pattern of individual adverse events associated with bevacizumab treatment was consistent with that previously documented in other tumour types. Toxicities increased in the bevacizumab-treated arms included the following:

- Hypertension;
- Bleeding events;
- Arterial and venous thromboembolic events;
- Congestive heart failure;
- Wound healing complications;
- GIT toxicity – GIT perforation, fistulae, diarrhoea, stomatitis;
- Proteinuria.

No new safety issues specific to the new indication were identified.

Risk management plan

The proposed RMP submitted with the application has been found to be acceptable by the TGA's Office of Product Review.

Risk-benefit analysis

Delegate considerations

Balance of benefits and risks

The clinical evaluator recommended rejection of the application, having concluded that the efficacy benefit was not clinically significant and was outweighed by the toxicity of the drug. The evaluator considered that a decision to reject could be reconsidered if a benefit in overall survival was demonstrated with longer follow up in the two Phase III studies. *In the pre-Advisory Committee on Prescription Medicines (ACPM) response, the sponsor is requested to provide a summary of any updated data on overall survival.*

The GOG-0218 study demonstrated a statistically significant benefit in terms of PFS. The risk of PFS events was reduced by 36% and median PFS was increased by 6.2 months but the evaluator did not consider this to be *clinically* significant. The TGA has in recent years approved many applications for anticancer agents with a smaller increase in PFS. For example, approval for the existing indications of bevacizumab was based on comparable or smaller effects on PFS. The Delegate therefore considered that the PFS benefit shown in the GOG-0218 study is clinically significant.

The efficacy benefit in BO17707 was less impressive, with the risk of PFS events being reduced by 21% and median PFS being increased by only 2.3 months. This study enrolled patients with earlier stage disease, used a lower dose of bevacizumab and assessment of efficacy was not conducted in a blinded manner. The evaluator recommended that if the application was approved, the indication should be limited to be consistent with the population enrolled in the GOG-0218 study. The Delegate agreed with this recommendation.

The evaluator also considered that a survival benefit should be demonstrated before approval was granted. The following points are brought to the Committee's attention:

- PFS is a surrogate endpoint for overall survival. The TGA has adopted the EU guideline[25] on anticancer agents as an appropriate set of requirements for regulatory approval of new agents or indications. According to this guideline, PFS is an acceptable endpoint for Phase III trials and for regulatory approval.
- In accordance with this guideline, the ACPM has recommended approval, and the TGA has approved, many agents that have demonstrated a benefit in terms of PFS without having demonstrated an overall survival benefit.
- The current registrations for bevacizumab in renal cell cancer, breast cancer and some colorectal cancer combinations have been approved on the basis of a benefit in terms of PFS without having demonstrated an overall survival benefit.
- In the two Phase III studies, bevacizumab was studied in the first-line setting. Following disease progression, it is likely that patients will receive further lines of therapy outside the trial, and that these subsequent therapies will not be balanced across treatment arms. For example, patients assigned to the non-bevacizumab arms in the trials may receive bevacizumab as part of second line therapy. Any effect of

[25] CPMP/EWP/205/95/Rev.3/Corr. Guideline on the evaluation of anticancer medicinal products in man. http://www.tga.gov.au/pdf/euguide/ewp020595enrev3.pdf

bevacizumab on overall survival may therefore be obscured by subsequent therapies received.

For these reasons the Delegate did not consider that it is necessary for a benefit in terms of overall survival to be demonstrated to obtain approval.

The safety profile of bevacizumab in the new indication appears comparable to that seen in other malignancies. There were no new safety issues raised.

Overall the Delegate considered that the efficacy benefit demonstrated in the GOG-0218 study is clinically significant and is comparable to that seen with the drug when used in the currently approved indications. In the Delegate's view the toxicity of the drug does not outweigh the efficacy benefit and the Delegate therefore proposed to approve the application for the following indication:

> *"In combination with carboplatin and paclitaxel for the first line treatment of patients with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer."*

The Delegate proposed to approve the application with the modified indication outlined above. The advice of the Committee was requested.

Response from sponsor

Comment on the delegate's proposed action:

Roche Products Pty Limited agreed with the Delegate's proposed action to approve the application with the modified indication below:

> *Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer*
>
> *Avastin (bevacizumab) in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.*

Comment on the delegates overview

The sponsor wished to highlight the following errors in the Delegates Overview

(BO17707 summary):

"Study BO17707 ... Patients had previously untreated, histologically diagnosed, epithelial ovarian, primary peritoneal or fallopian tube cancer. Patients could have:

- FIGO Stage I or IIa disease provided that it had poorly differentiated (grade 3) or clear cell histology; or:
- FIGO stages Ilb, III or IV disease."

and proposes the following revisions to the Adverse Events table (Table 28) of the Delegates Overview, for clarification;

1. Change the label from "Related fatal AEs" to "Death due to protocol treatment".
2. Add footnote to BO11707 data that states these were "investigator assessed as possible, probable or definite related" and
3. The correct numbers for BO11707 should be 1 and 5 (instead of 4).

Comment in response to delegate's specific requests

The Delegate requested the sponsor *provide a summary of any updated data on overall survival*. An updated OS analysis is available (submitted to the European Medicines Agency (EMA) in Response to Questions, May 2011) and the details are described below. At the time of the updated OS analyses, for Study GOG-0218, overall 36% of the patients

randomised had died after an additional 10-month follow-up (since the original CSR analysis performed at the time of final PFS analysis). For Study BO17707, overall 24% of patient randomised had died after an additional 9 month follow-up (since the original CSR analysis performed at the time of final PFS analysis).

Study GOG-0218 -Updated Overall Survival Analysis

Consistent with the original CSR analysis, no detrimental effect on OS was seen in the updated analysis when comparing the CPB15+ arm with the CPP arm (see Table 28 below). The median survival times were 43.4 months in the CPB15+ arm compared to 39.4 months in the CPP arm.

Median survival times may change with further survival follow-up. The Kaplan-Meier curves separated at about 12 months post randomisation in favour of the CPB15+ arm and remained separated during the entire follow-up period. The HR for both the stratified and unstratified analysis for the CPB15 arm versus the CPP arm increased slightly in the updated analysis compared to the original analysis (Table 28).

Table 28. Original and updated analyses of overall survival

GOG-0218						
Overall Survival	**Original (CSR) Analysis**			**Updated Analysis**		
	CPP (n = 625)	**CPB15 (n = 625)**	**CPB15+ (n = 623)**	**CPP (n = 625)**	**CPB15 (n = 625)**	**CPB15+ (n = 623)**
No. pts 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						
HR 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]
p-value[1]		0.2256	0.1909		0.0809	0.1253
Unstratified analysis						
HR 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]
p-value[1]		0.2966	0.1934		0.0992	0.1590

BO17707				
Overall Survival	**Original (CSR) Analysis**		**Updated Analysis**	
	CP (n = 764)	**CPB7.5+ (n = 764)**	**CP (n = 764)**	**CPB7.5+ (n = 764)**
No. pts who died (%)	130 (17.0%)	111 (14.5%)	200 (26.2%)	178 (23.3%)
Median survival time (months)	NR	35.1	NR	NR
[95% CI]	[NE; NE]	[32.6; NE]	[38.9; NE]	[41.1; NE]
Unstratified analysis				
HR relative to CP		0.81		0.85
[95% CI]		[0.63; 1.04]		[0.70; 1.04]
p-value[1]		0.0987		0.1167

NE = not estimated; NR = not reached.
[1] one-sided log-rank p value

Study BO17707 – Updated overall survival analysis

Consistent with the original CSR analysis, no detrimental effect on OS was seen in the updated analysis when comparing the CPB7.5+ arm with the CP arm (see Table 29 below). Due to the low number of events, an estimate of the median survival times in both arms could not be determined. The Kaplan-Meier curves separated at about 9 months in favour of the CPB7.5+ and remained separated until about month 36, when only few patients were still at risk and the curves have to be considered unstable.

The draft Avastin Aus PI has been updated with the updated OS data for Study GOG-0218 as per above. Final OS results for Study GOG-0218 and BO17707 are expected to be available by the end of March 2012 and December 2013 respectively.

As stated by the Delegate, the median PFS increase of 6.2 months demonstrated in Study GOG- 0218 represents a clinically meaningful benefit and it is not necessary to demonstrate an overall survival benefit. Roche wishes to further highlight that;

1. In ovarian cancer, PFS is accepted as representative of clinical benefit and its use as a valid and clinically relevant endpoint is supported by the Gynaecologic Cancer Inter-Group Consensus Conference[26].
2. GOG-0218 is the first study in the past 15 years to demonstrate a statistically significant and clinically relevant benefit for a novel agent in the front-line treatment of advanced ovarian cancer. The clinical significance of a 36% reduction in the risk of progression or death and a gain in median PFS of 6.2 months should be evaluated in this context.
3. The positive benefit-risk of adding bevacizumab to standard of care demonstrated by Study GOG-0218 is supported by the following:

An increase in the time to disease recurrence without the addition of more cytotoxic therapy in this setting, an incurable disease, represents a true clinical benefit, even in the absence of statistically significant OS or QoL improvement.

The clinical significance of the improvement in PFS also lies in the fact that this increase results in a longer time interval between last carboplatin dose and progression of disease, which potentially translates into more platinum sensitive disease at the time of recurrence. Platinum agents are the most active agents in both the front-line and recurrent settings and the rate of response to re-treatment with cisplatin or carboplatin is closely related to the duration of the platinum free-interval (PFI).

In Study GOG-0218, the time interval between the last platinum dose and disease progression was evaluated. In the SAP specified analysis (censored for CA-125 and NPT) the median time between the last dose of carboplatin and progression or death was 7.6 months (CPP) and 14.3 months (CPB15+), respectively (HR = 0.61) (Table 29). This increase in the time between the last platinum dose and disease progression, and consequently the delay in the start of the next line of chemotherapy, strengthens the clinical relevance of bevacizumab for the treatment of first-line ovarian cancer patients.

Table 29. Time from last sose of carboplatin to INV-Assessed progression or death (Study GOG-0218:randomised patients).

Time from Last Dose of Carboplatin to INV-Assessed Progression or Death	CPP N = 625	CPB15 N = 625	CPB15+ N = 623
Median time - months	7.6	8.8	14.3
Hazard ratio [95% CI], relative to CPP		0.81 [0.69; 0.97]	0.61 [0.51; 0.74]

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; NPT = Non-protocol specified cancer therapy.
Notes: Censored for CA-125 and NPT. Median times were estimated from the Kaplan–Meier curves; Stratified hazard ratios were estimated using Cox regression. The strata were GOG performance status (0 vs. 1 or 2) and disease stage (Stage III optimal, Stage III sub-optimally debulked, and Stage IV).

Overall survival is likely to be confounded by subsequent lines of treatment

As identified by the TGA Delegate and acknowledged by international experts, further lines of treatment interfere with the ability to establish an improvement in overall

[26] Stuart G, Kitchener H, Bacon M, duBois A, Friedlander M, et al. 2010 Gynecologic Cancer InterGroup (GCIG) Consensus Statement on Clinical Trials in Ovarian Cancer. Report from the Fourth Ovarian Cancer Consensus Conference. Int J Gynecol Cancer 2011 ;21:750-755.

survival, particularly in diseases with a relatively long median overall survival (such as advanced ovarian cancer).

Statistical models have shown that the ability to detect an improvement in OS in a study showing an improved PFS decreases as the length of the post-progression survival (PPS) increases[27]. In fact, for a median PPS of 12 months, the probability of detecting a statistically significant difference in OS is only 24% in a study powered at 80% for PFS. As the PPS increases, the probability continues to decrease. In front-line ovarian cancer trials the current median OS is 36 months and with an average PFS of 18-24 months, the PPS in this disease setting clearly falls into the group with a low probability of detecting improved OS in the face of improved PFS.

At the time of the data cut-off for the updated analysis of overall survival in Study GOG-0218, the number of patients receiving any non-protocol anti-cancer therapy (NPT) was 454 (72.6%) in the CPP arm, 458 (73.3%) in the CPB15 arm and 397 (63.7%) in the CPB15+ arm The vast majority of these therapies were initiated post disease progression as per protocol criteria. Chemotherapy represented the majority of any NPT use across all arms, where it was used in 67.7%, 68.8% and 60.5% of patients in the CPP, CPB15 and CPB15+ arms, respectively. The number of patients receiving commercial Avastin® was 126 (20.2%) in the CPP arm, 132 (21.1%) in the CPB15 arm and 76 (12.2%) in the CPB15+ arm. That is, patients in the CPP and CPB15 arms received more commercial Avastin® post disease progression than did those in the CPB15+ arm.

The vast majority of patients in Study GOG-0218 received Non-Protocol Therapy (NPT) and a higher number of patients in the CPP arm have received commercially available bevacizumab compared with the CPB15+ arm. Thus, subsequent NPT can potentially confound the effect on OS.

Health related quality of life (HRQoL) is maintained despite prolonged treatment with bevacizumab

The safety profile of bevacizumab is well documented and the adverse events observed in Study GOG-0218, as presented in the CSR, are consistent with this profile. An increase in adverse events was seen in the bevacizumab treatment arms with the majority of these events occurring during the concurrent (chemotherapy and bevacizumab) phase of treatment. This increase in adverse events did, however, not translate into a detriment to the patient's HRQoL.

Advanced ovarian cancer is a very symptomatic disease and the majority of patients report improvement in HRQoL upon institution of front-line chemotherapy. Consistent with this, in Study GOG-0218, increases in HRQoL were observed in all three treatment arms. The increase in HRQoL FACT-O TOI scores over time was more pronounced for patients in the CPB15+ arm compared to CPP arm. The magnitude of this increase met statistical significance, however, it did not meet the threshold for clinical significance (defined as a 5 point difference). Given the fact that in the CPB15+ arm patients stay on active treatment after the end of chemotherapy it would be unrealistic to expect an improvement in quality of life. Despite this, it is reassuring that the HRQoL data demonstrate that QoL is maintained during extended bevacizumab therapy.

Conclusion

PFS is an internationally recognized, clinically relevant endpoint in advanced ovarian cancer. The results from Study GOG-0218 demonstrate a benefit that is clinically meaningful, resulting in a delay of the next cytotoxic chemotherapy treatment and a potential improvement in platinum sensitivity. The magnitude of benefit observed in

[27]Broglio K, Berry D. Detecting an overall survival benefit that is derived from progression-free survival. J Natl Cancer Inst. 2009;101:1642-1649.

Study GOG-0218 is comparable to the benefit afforded by other regimens that have become standard of care, and with a toxicity profile that is comparable to those seen in other approved indications. Furthermore, it is reassuring that the HRQoL is maintained during extended bevacizumab treatment period. Although the sponsor would have liked to be able to detect an improvement in overall survival, the use of subsequent NPT (particularly the imbalance in the percentage of patients receiving commercially available bevacizumab across study arms) can confound the effect on OS. Overall, these data support a positive benefit/risk when bevacizumab, the first novel agent to demonstrate a benefit in the first line treatment of this disease in over a decade, is added to standard of care chemotherapy.

Further comment on clinical evaluation report

Additionally, the sponsor wished to clarify conclusions and interpretations made by the clinical evaluator. The clinical evaluator put emphasis on the treatment period in connection with PFS benefit and highlighted a shorter treatment free interval in the bevacizumab arm compared to the control arm. However, the linear interpolation used (between median PFS, maximum treatment and median OS) to derive a "treatment or disease free interval" is not representative. The observed median treatment duration for the CPB15+ arm was 9 months, (well below the maximum planned treatment duration per protocol specification estimated by the evaluator to be 16.5 months). As a result, the assessment of *1.7 months free of treatment and disease* for the bevacizumab arm (compared to 7.5 months for the control arm) using median PFS of 18.2 months has to be considered inaccurate.

The sponsor acknowledged that treatment free interval is an important concept, however, Roche also wished to add that in this patient population, where the majority of patients will experience disease progression, there is great benefit in prolonging PFS with a tolerable regimen, compared to extending the treatment free interval. Both GOG-0218 and BO17707 demonstrate that bevacizumab given in combination with chemotherapy and continued as a single agent results in a clinically and statistically significant prolongation of PFS. While there are toxicities associated with bevacizumab, they do not impact QoL and therefore the treatment is considered tolerable.

As stated above, Roche believes that prolonging PFS in advanced ovarian cancer patients is important and clinically significant.

Overall Response Rate (ORR) Study GOG-0218

ORR in Study GOG-0218 was assessed in patients with measurable disease at baseline. The clinical evaluator stated that the ORR group is a different patient population (from all randomised) and suggested that the response rates to chemotherapy may be different between the two patient populations. The sponsor acknowledged that the ORR was determined in a subset of patients with measurable disease at baseline, however, it is important to note that clinically, patients are treated the same regardless of whether they have measurable disease or not, and there is no data to suggest that this ORR data would not be relevant to the general patient population. The evaluation of response rate only, in patients with measurable disease, allows for the use of standardised imaging criteria and avoids the potential variations in CA-125 that may occur with bevacizumab treatment. It is also important to note that in the first line setting ORR is considered to be problematic as a primary end-point and the GCIG consensus statement defines other end-points to more representative of clinical benefit[28].

Study A VF2949g

The 11% GI perforation rate observed in the small Phase II trial, AVF2949g, raised a concern that GI perforation rates in patients with ovarian cancer might be much higher than in patients with other solid tumours. The low rates of GI perforation seen in both the Phase III trials, GOG- 0218 and BO17707, demonstrate that while GI perforations are observed with the use of Avastin, the rate is entirely consistent with rates seen in other solid tumors. The difference in the patient populations between these two large Phase III randomised studies in chemo-naive patients, and that in Study AVF2949g (a small Phase II study (n = 44) in heavily pre-treated patients), could account for the difference in the rates of GI perforation seen. However, a much larger study in patients with recurrent disease, AVF4095g/OCEANS (484 pts randomised) had a 0% rate of GI perforation, providing further reassurance regarding the overall safety of this agent in ovarian cancer.

Study BO17707 (ICONV)

The clinical evaluator pointed out that the sensitivity analysis performed in Study BO17707, in which PFS time was censored on, or before the initiation of NPT, showed a reduction in the PFS increase to 7.6% (from 17.1 to 18.4 months) for the period before NPT was used. The sponsor would like to clarify that this analysis was exploratory and does not provide any definitive conclusions on the magnitude of PFS benefit. Nevertheless, this exploratory analysis supports the primary PFS analysis showing improved PFS in patients receiving bevacizumab.

Advisory committee considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM agreed with the Delegate and considered this product to have a positive benefit-risk profile for the further indication;

> *In combination with carboplatin and paclitaxel for the first line treatment of patients with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer.*

The ACPM noted the evidence supporting greater clinical outcomes for the higher risk patient population.

[28]Thigpen et al. First-line therapy in ovarian cancer trials. Int J Gynecol Cancer 2011;21:756-762

The ACPM noted the trial population was a difficult population to treat, with few options. The clinical endpoint for such a trial should ideally be overall survival, however, it was recognised that there are many confounding factors in the measurement of such an endpoint and that progression free survival in such situations is a valuable surrogate. It was considered that the optimal group and duration of treatment has not yet been established.

The ACPM supported the amendments proposed by the Delegate to the Product Information (PI) and Consumer Medicines Information (CMI).

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided, would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Avastin injection vial containing bevacizumab *rch*100 mg/4 mL and 400 mg/16 mL for the new indication:

> "*In combination with carboplatin and paclitaxel for the first line treatment of patients with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube or primary peritoneal cancer".*

Specific Conditions Applying to these Therapeutic Goods include:

1. It is a condition of registration that the sponsor implement in Australia the bevacizumab rch Risk Management Plan (RMP), (EU-RMP version 9.0 dated 18 November 2010, and the Australian-RMP addendum version 1.0 dated 25 February 2011) and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au
Reference/Publication #

NAME OF THE MEDICINE

AVASTIN®

bevacizumab (rch)

CAS 216974-75-3

Bevacizumab is an immunoglobulin G (IgG) composed of two identical light chains, consisting of 214 amino acid residues and two 453 residue heavy chains containing an N-linked oligosaccharide and has a molecular weight of approximately 149,000 daltons.

DESCRIPTION

AVASTIN is a clear to slightly opalescent, colourless to pale brown, sterile solution for intravenous (IV) infusion. AVASTIN is not formulated for intravitreal use (see *PRECAUTIONS; Severe Eye Infections Following Compounding for Unapproved Intravitreal Use*).

AVASTIN is available in 100 mg and 400 mg single dose vials containing 4 mL and 16 mL, respectively, of bevacizumab (25 mg/mL). AVASTIN also contains a,a-trehalose dihydrate, monobasic monohydrate sodium phosphate, dibasic sodium phosphate, polysorbate 20 and water for injections.

PHARMACOLOGY

Mechanism of Action

AVASTIN is an antineoplastic agent containing the active ingredient, bevacizumab. Bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to and neutralises the biologic activity of human vascular endothelial growth factor (VEGF). Bevacizumab contains human framework regions with antigen binding regions of a humanised murine antibody that binds to VEGF. Bevacizumab is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system in a nutrient medium containing the antibiotic gentamicin and is purified by a process that includes specific viral inactivation and removal steps. Gentamicin is detectable in the final product at £ 0.35 ppm.

AVASTIN inhibits the binding of VEGF to its receptors, Flt-1 and KDR, on the surface of endothelial cells. Neutralising the biologic activity of VEGF reduces the vascularisation of tumours, thereby inhibiting tumour growth. Administration of bevacizumab or its parental murine antibody to xenotransplant models of cancer in nude mice resulted in extensive anti-tumour activity in human cancers, including colon, breast, pancreas and prostate. Metastatic disease progression was inhibited and microvascular permeability was reduced.

PHARMACOKINETICS

The pharmacokinetics of bevacizumab were characterised in patients with various types of solid tumours. The doses tested were 0.1-10 mg/kg weekly in phase I; 3-20 mg/kg every two weeks (q2w) or every three weeks (q3w) in phase II; 5 mg/kg (q2w) or 15 mg/kg q3w in phase III. In all clinical trials, bevacizumab was administered as an IV infusion.

As observed with other antibodies, the pharmacokinetics of bevacizumab are well described by a two-compartment model. Overall, in all clinical trials, bevacizumab disposition was characterised by a low clearance, a limited volume of the central compartment (V_c), and a long elimination half-life. This enables target therapeutic bevacizumab plasma levels to be maintained with a range of administration schedules (such as one administration every 2 or 3 weeks).

In the population pharmacokinetics analysis there was no significant difference in the pharmacokinetics of bevacizumab in relation to age (no correlation between bevacizumab clearance and patient age [the median age was 59 years with 5th and 95th percentiles of 37 and 76 years]).

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

Absorption and Bioavailability

Not applicable.

Distribution

The typical value for central volume (V_c) was 2.73 L and 3.28 L for female and male patients, respectively, which is in the range that has been described for IgGs and other monoclonal antibodies. After correcting for body weight, male patients had a larger V_c (+20%) than female patients.

Metabolism

Assessment of bevacizumab metabolism in rabbits following a single IV dose of ^{125}I-bevacizumab suggested that its metabolic profile was similar to that expected for a native IgG molecule which does not bind VEGF.

Elimination

The pharmacokinetics of bevacizumab are linear at doses ranging from 1.5 to 10 mg/kg/wk.

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

Pharmacokinetics in Special Populations

The population pharmacokinetics of bevacizumab were analysed to evaluate the effects of demographic characteristics. The results showed no significant difference in the pharmacokinetics of bevacizumab in relation to age.

Children and adolescents: The pharmacokinetics of bevacizumab have been studied in a limited number of paediatric patients. The resulting pharmacokinetic data suggest that the volume of distribution and clearance of bevacizumab were comparable to that in adults with solid tumours.

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

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

Patients with ascites: No studies have examined the effect of ascites on the pharmacokinetic parameters of bevacizumab.

CLINICAL TRIALS

Metastatic Colorectal Cancer
The safety and efficacy of AVASTIN in metastatic colorectal cancer were studied in two randomised, active-controlled clinical trials. AVASTIN was combined with two chemotherapy regimens:

AVF2107g: A weekly schedule of irinotecan/bolus fluorouracil/leucovorin† (IFL) for a total of 4 weeks of each 6 week cycle

AVF0780g: In combination with bolus fluorouracil/leucovorin† (FU/LV) for a total of 6 weeks of each 8 week cycle (Roswell Park regimen)

Two additional studies were conducted in first (NO16966) and second line (E3200) treatment of metastatic carcinoma of the colon or rectum, with AVASTIN administered in the following dosing regimens, in combination with FOLFOX-4 (FU/LV/Oxaliplatin) and XELOX (Capecitabine/Oxaliplatin):

NO16966: AVASTIN 7.5 mg/kg of body weight every 3 weeks in combination with oral capecitabine and IV oxaliplatin (XELOX) or AVASTIN 5 mg/kg every 2 weeks in combination with leucovorin† plus fluorouracil bolus, followed by fluorouracil infusion, with IV oxaliplatin (FOLFOX-4).

E3200: AVASTIN 10 mg/kg of body weight every 2 weeks in combination with leucovorin† and fluorouracil bolus, followed by fluorouracil infusion, with IV oxaliplatin (FOLFOX-4).

† The Australian Approved Name for leucovorin is folinic acid

Study AVF2107g
This was a phase III randomised, double-blind, active-controlled clinical trial evaluating AVASTIN in combination with IFL as first-line treatment for metastatic colorectal cancer. Eight hundred and thirteen patients were randomised to receive IFL plus placebo (Arm 1) or IFL plus AVASTIN (Arm 2), see Table 1. A third group of 110 patients received FU/LV plus AVASTIN (Arm 3). Enrolment in Arm 3 was discontinued, as pre-specified, once safety of AVASTIN with the IFL regimen was established and considered acceptable. The median age of patients was 60 years (range 21-88), 60% were male.

Table 1: Treatment regimens in study AVF2107g

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

Fluorouracil: IV bolus injection immediately after folinic acid

Folinic acid: IV bolus injection (over 1- 2 minutes) immediately after each irinotecan dose

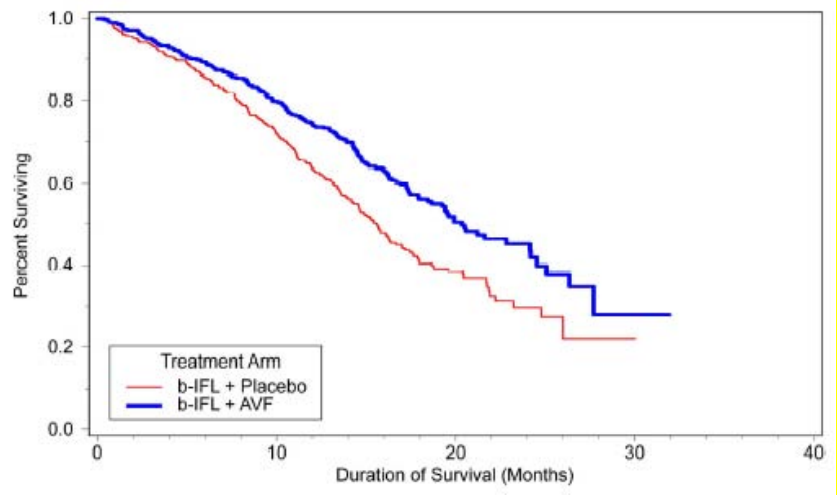
The primary efficacy endpoint of the trial was overall survival. At the time of data cut-off, 399 deaths had occurred in patients randomised to Arm 1 (n = 225) and Arm 2 (n = 174). The addition of AVASTIN to IFL resulted in a statistically significant increase in overall survival. Results are presented in Table 2 and Figure 1. The clinical benefit of AVASTIN, as measured by survival, progression-free survival and objective response, was seen in all pre-specified patient subgroups, see Figure 2.

Table 2: Efficacy results for study AVF2107g

	Arm 1 IFL plus placebo (*n* = 411)	Arm 2 IFL plus AVASTIN[a] (*n* = 402)	Arm 3 FU/LV plus AVASTIN[a] (*n* = 110[b])
Overall Survival			
Median (months)	15.6	20.3	18.3
Hazard ratio[c] (95% CI)	0.660 (0.54, 0.81)		
p-value (log rank)	0.00004		☐
Progression-Free Survival			
Median (months)	6.2	10.6	8.8
Hazard ratio (95% CI)	0.54 (0.45, 0.66)		
p-value (log rank)	<0.0001		☐
Overall Response Rate			
Rate (percent)	34.8	44.8	40.0
Between-arm difference (%) (95% CI)	10 (3.3, 16.7)		–
p-value (log rank)	0.0036		☐
Duration of Response			
Median (months)	7.1	10.4	8.5
25–75 percentile (months)	4.7-11.8	6.7-15.0	5.5-11.9

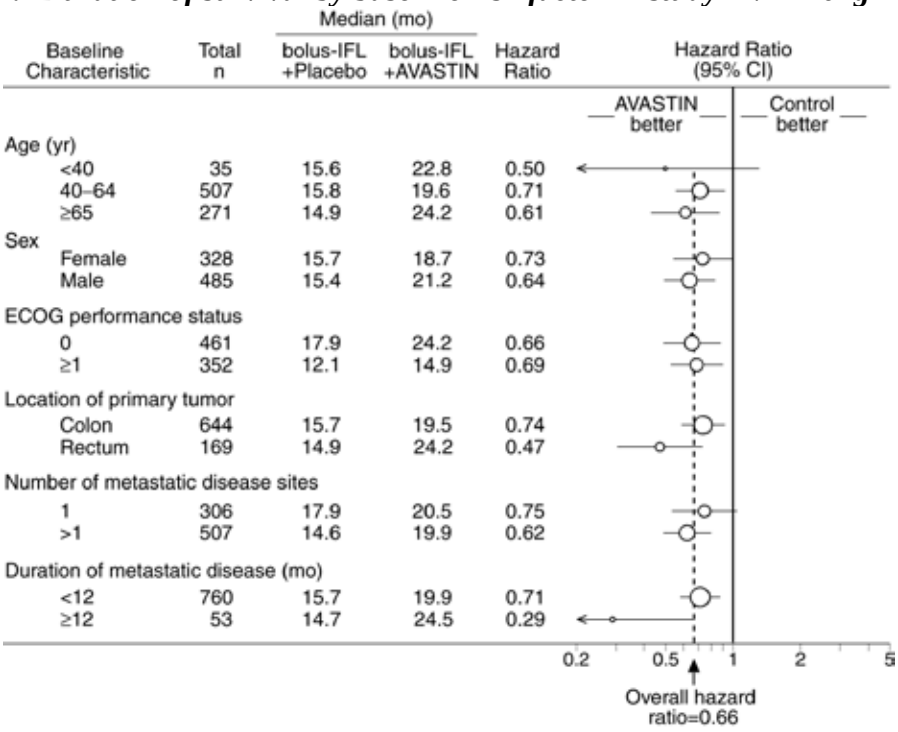
[a] 5 mg/kg every 2 weeks; [b] Recruitment stopped as per protocol; [c] Relative to control arm

Figure 1: Plot of Kaplan Meier estimates for survival in study AVF2107g



IFL =irinotecan/ fluorouracil/ leucovorin (folinic acid); AVF = AVASTIN

Figure 2: Duration of survival by baseline risk factor in study AVF2107g

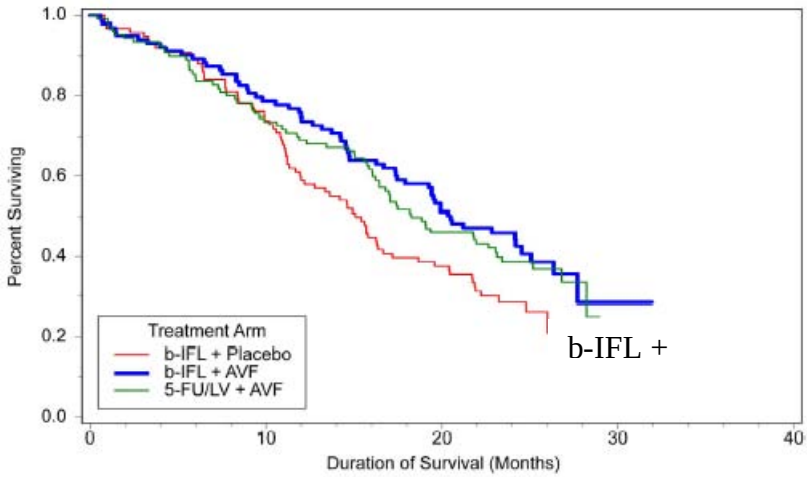


CI= interval; IFL= irinotecan/fluorouracil/ leucovorin (folinic acid);.

Hazard ratio <1 indicates a lower hazard of death in the IFL plus AVASTIN arm compared with the IFL plus placebo arm. Size of circle is proportional to the number of patients in the subgroup. Confidence interval is indicated by the horizontal line.

Results for the 110 patients in Arm 3 were compared to the first 100 patients enrolled in Arm 1 and Arm 2. There was a trend towards prolonged survival in the AVASTIN plus FU/LV arm as compared to the IFL plus placebo arm in this subset of patients, see Figure 3. Although the results did not show a statistical difference, the results were consistently better for the AVASTIN plus FU/LV arm than for IFL plus placebo arm for all efficacy parameters measured.

Figure 3: Plot of Kaplan Meier Estimates for survival in study AVF2107g: Patients enrolled in Arm 3 and concurrently enrolled patients in Arms 1 and 2



IFL = irinotecan/ fluorouracil/ leucovorin (folinic acid); AVF = AVASTIN

Study AVF0780g

This was a phase II randomised, active-controlled, open-labelled clinical trial investigating AVASTIN in combination with FU/LV as first-line treatment of metastatic colorectal cancer. Seventy one patients were randomised to receive bolus FU/LV or FU/LV plus AVASTIN (5 mg/kg every 2 weeks). A third group of 33 patients received bolus FU/LV plus AVASTIN (10 mg/kg every 2 weeks). Patients were treated until disease progression. The median age was 64 years (range 23-85), 57% were male. The primary efficacy endpoints of the trial were objective response rate and progression-free survival. The addition of AVASTIN (5 mg/kg every two weeks) to FU/LV resulted in higher objective response rates, longer progression-free survival and a trend in longer survival, compared with FU/LV chemotherapy alone, see Table 3. This efficacy data is consistent with the results from study AVF2107g.

Table 3: Efficacy results for study AVF0780g

	FU/LV (*n* = 36)	FU/LV plus AVASTIN[a] (*n* = 35)	FU/LV plus AVASTIN[b] (*n* = 33)
Overall Survival			
Median (months)	13.6	17.7	15.2
Hazard ratio[c]	-	0.52	1.01
p-value (log-rank)	-	0.073	0.978
Progression-Free Survival			
Median (months)	5.2	9.0	7.2
Hazard ratio[c]	-	0.44	0.69
p-value (log-rank)	-	0.005	0.217
Overall Response Rate			
Rate[d] (percent) (95% CI)	16.7 (7.0-33.5)	40.0 (24.4-57.8)	24.2 (11.7-42.6)
p-value (log-rank)	-	0.03	0.43
Duration of Response			
Median (months)	NR	9.3	5.0
25–75 percentile (months)	5.5 - NR	6.1 - NR	3.8–7.8

[a] 5 mg/kg every 2 weeks; [b] 10 mg/kg every 2 weeks; [c] Relative to control arm; [d] independent review; *NR = Not reached*

Study NO16966

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

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

Table 4: Treatment Regimens in Study N016966

	Treatment	Starting Dose	Schedule
FOLFOX-4 or FOLFOX-4 + AVASTIN	Oxaliplatin Leucovorin† Fluorouracil	85 mg/m^2 IV 2 h 200 mg/m^2 IV 2 h 400 mg/m^2 IV bolus, 600 mg/ m^2 IV 22 h	Oxaliplatin on Day 1 Leucovorin† on Day 1 and 2 Fluorouracil IV bolus/infusion, each on Days 1 and 2
	Placebo or AVASTIN	5 mg/kg IV 30-90 min	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX+ AVASTIN	Oxaliplatin Capecitabine	130 mg/m^2 IV 2 h 1000 mg/m^2 oral bid	Oxaliplatin on Day 1 Capecitabine oral bid for 2 weeks (followed by 1 week off treatment)
	Placebo or AVASTIN	7.5 mg/kg IV 30-90 min	Day 1, prior to XELOX, q 3 weeks
Fluorouracil: IV bolus injection immediately after leucovorin			

† The Australian Approved Name for leucovorin is folinic acid

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

Superiority of the AVASTIN containing arms versus the chemotherapy alone arms in the overall comparison was demonstrated in terms of progression-free survival in the ITT population (see Table 5).

Secondary PFS analyses, based on Independent Review Committee and 'on-treatment'-based response assessments, confirmed the significantly superior clinical benefit for patients treated with AVASTIN.

Table 5: Key efficacy results for the superiority analysis (ITT population, Study NO16966)

Endpoint (months)	FOLFOX-4 or XELOX + Placebo (*n* = 701)	FOLFOX-4 or XELOX + AVASTIN (*n* = 699)	*p* value
Primary endpoint			
Median PFS^^	8.0	9.4	0.0023
Hazard ratio (97.5% CI)[a]	0.83 (0.72 - 0.95)		
Secondary endpoints			
Median PFS (on treatment)^^[b]	7.9	10.4	<0.0001

Hazard ratio (97.5% CI)	0.63 (0.52 - 0.75)		
Overall response rate (Investigator Assessment)^^	49.2%	46.5%	
Median overall survival^	19.9	21.2	0.0769
Hazard ratio (97.5% CI)	0.89 (0.76 - 1.03)		

^ Overall survival analysis at clinical cut-off 31 January 2007

^^ Primary analysis at clinical cut-off 31 January 2006

[a] relative to control arm: [b] PFS on-treatment: based on investigator tumour assessments and death events that occurred no later than 28 days after the last confirmed intake of any study medication in the primary study treatment phase (5-FU, oxaliplatin, capecitabine, or AVASTIN/placebo, which ever was taken last)

Overall response rate was similar in the chemotherapy plus AVASTIN arm (46.5%) and in chemotherapy alone arm (49.2%).

Study ECOG E3200

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

The primary efficacy parameter of the trial was overall survival, defined as the time from randomisation to death from any cause. Eight hundred and twenty-nine patients were randomised (292 FOLFOX-4, 293 AVASTIN +_FOLFOX-4 and 244 AVASTIN monotherapy). The addition of AVASTIN to FOLFOX-4 resulted in a statistically significant prolongation of survival. Statistically significant improvements in progression-free survival and objective response rate were also observed (see Table 6).

Table 6: Efficacy Results for Study E3200

	FOLFOX-4	FOLFOX-4 + Avastin[a]
Number of Patients	292	293
Overall Survival		
Median (months)	10.8	13.0
95% confidence interval	10.12 – 11.86	12.09 – 14.03
Hazard ratio[b]	0.751	
95% confidence interval	(0.632, 0.893)	
	(*p*-value = 0.0012)	
Progression-Free Survival		
Median (months)	4.5	7.5
Hazard ratio	0.518	
95% confidence interval	(0.416, 0.646)	
	(*p*-value < 0.0001)	
Objective Response Rate		
Rate	8.6 %	22.2 %
	(*p*-value < 0.0001)	

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

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

Locally recurrent or metastatic Breast Cancer

(Note that the efficacy and safety of the combination of AVASTIN and paclitaxel have not been compared with anthracycline-based therapies for first-line therapy in metastatic breast cancer. The efficacy of the combination of AVASTIN and paclitaxel in second and third line treatment of metastatic breast cancer has not been demonstrated.)

E2100 was an open-label, randomised, active controlled, multicentre clinical trial evaluating AVASTIN in combination with paclitaxel for locally recurrent or metastatic breast cancer in patients who had not previously received chemotherapy for locally recurrent and metastatic disease. Prior hormonal therapy for the treatment of metastatic disease was allowed. Adjuvant taxane therapy was allowed only if it was completed at least 12 months prior to study entry.

Patients were randomised to paclitaxel alone (90 mg/m^2 IV over 1 hour once weekly for three out of four weeks) or in combination with AVASTIN (10 mg/kg IV infusion every two weeks). Patients were to continue assigned study treatment until disease progression. In cases where patients discontinued chemotherapy prematurely, treatment with AVASTIN as a single agent was continued until disease progression. The primary endpoint was progression free survival (PFS), as assessed by investigators. In addition, an independent review of the primary endpoint was also conducted.

Of the 722 patients in the study, the majority of patients (90%) had HER2-negative disease. A small number of patients had HER-2 receptor status that was either unknown (8%) or positive

(2%). Patients who were HER2-positive had either received previous treatment with trastuzumab or were considered unsuitable for trastuzumab. The majority (65%) of patients had received adjuvant chemotherapy including 19% who had prior taxanes and 49% who had prior anthracyclines. The patient characteristics were similar between the study arms.

The results of this study are presented in Table 7 and Figure 4. The addition of AVASTIN to paclitaxel chemotherapy resulted in a significant reduction of risk of disease progression or death, as measured by PFS (HR = 0.42; $p < 0.0001$). The resulting median PFS in AVASTIN-containing arm was 11.4 months compared with 5.8 months in the control arm. The small improvement in overall survival was not statistically significant.

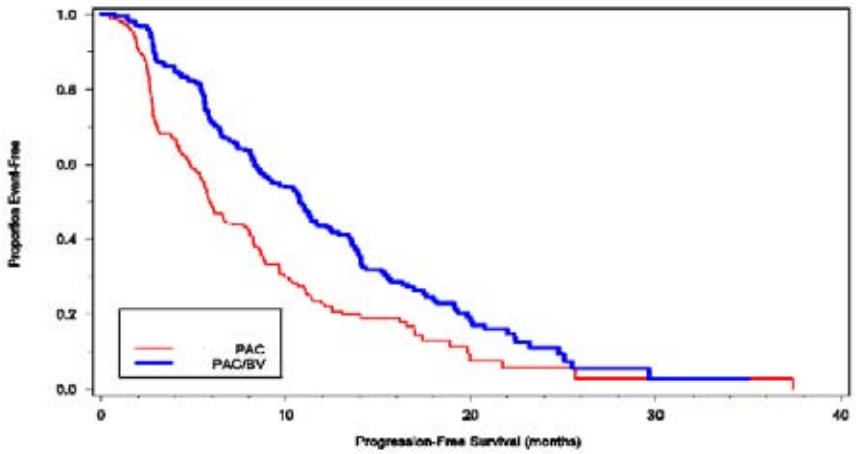
Table 7: Study E2100 Efficacy Results: Eligible Patients

Progression-Free Survival				
	Investigator Assessment^		IRF Assessment	
	Paclitaxel (n = 354)	Paclitaxel/AVASTIN (n = 368)	Paclitaxel (n = 354)	Paclitaxel/AVASTIN (n = 368)
Median PFS (months)	5.8	11.4	5.8	11.3
Hazard Ratio (95% CI)	0.421 (0.343 ; 0.516)		0.483 (0.385 ; 0.607)	
p-value	< 0.0001		< 0.0001	
Progression-Free Survival				
Response Rates (for patients with measurable disease)				
	Investigator Assessment		IRF Assessment	
	Paclitaxel (n = 273)	Paclitaxel/AVASTIN (n = 252)	Paclitaxel (n = 243)	Paclitaxel/AVASTIN (n = 229)
% pts with objective response	23.4	48.0	22.2	49.8
p-value	< 0.0001		< 0.0001	

Overall Survival (Investigator assessment)		
	Paclitaxel (*n* = 354)	Paclitaxel/AVASTIN (*n* = 368)
Median OS (months)	24.8	26.5
Hazard Ratio (95% CI)	0.869 (0.722 ; 1.046)	
p-value	0.1374	

^ primary analysis; IRF = independent review facility

Figure 4: Kaplan-Meier curves for progression free survival in study E2100



The efficacy and safety of AVASTIN in combination with anthracycline-based therapies have not been studied for first-line therapy in metastatic breast cancer.

Advanced, metastatic or recurrent Non-Small Cell Lung Cancer

The safety and efficacy of AVASTIN in the first-line treatment of patients with non-small cell lung cancer (NSCLC) other than predominantly squamous cell histology, was studied in addition to carboplatin/paclitaxel-based chemotherapy in study E4599 (*n* = 878). E4599 was an open-label, randomised, active-controlled, multicentre clinical trial evaluating AVASTIN as first-line treatment of patients with locally advanced (Stage IIIB with malignant pleural effusion), metastatic or recurrent NSCLC other than predominantly squamous cell histology.

Patients were randomised to platinum-based chemotherapy (paclitaxel 200 mg/m^2 and carboplatin AUC = 6.0, both by IV infusion) (PC) on day 1 of every 3 week cycle for up to 6 cycles or PC in combination with AVASTIN at a dose of 15 mg/kg IV infusion day 1 of every 3 week cycle. Patients with predominant squamous histology (mixed cell type tumours only), central nervous system (CNS) metastasis, gross haemoptysis (≥ ½ tsp of red blood), clinically significant cardiovascular disease and medically uncontrolled hypertension were excluded. Other exclusion criteria were: therapeutic anticoagulation, regular use of aspirin (> 325 mg/day, NSAIDs or other agents known to inhibit platelet function, radiation therapy within 21 days of enrolment and major surgery within 28 days before enrolment.

Among 878 patients randomised to the two arms, the median age was 63, 46% were female, 43% were ≥ age 65, and 28% had ≥ 5% weight loss at study entry. 11% had recurrent disease and of the remaining 89% with newly diagnosed NSCLC, 12% had Stage IIIB with malignant pleural effusion and 76% had Stage IV disease.

After completion of six cycles of carboplatin-paclitaxel chemotherapy or upon premature discontinuation of chemotherapy, patients on the AVASTIN + carboplatin–paclitaxel arm continued to receive AVASTIN as a single agent every 3 weeks until disease progression.

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

The primary endpoint was overall survival (OS). The secondary endpoints, PFS (progression free survival) and ORR (overall response rate), were based on investigator assessment and were not independently verified.

Overall survival was statistically significantly higher for patients receiving AVASTIN + PC chemotherapy compared with those receiving PC alone. Results are presented in Table 8.

Table 8: Efficacy results for study E4599

	Arm 1 Carboplatin/Paclitaxel	Arm 2 Carboplatin/ Paclitaxel + AVASTIN 15 mg/kg q 3 weeks
Number of Patients	444	434
Overall Survival		
Median (months)	10.3	12.3
Hazard ratio		0.80
		95% CI (0.69, 0.93)
p-value[a]		$p = 0.003$
Progression-Free Survival		
Median (months)	4.8	6.4
Hazard ratio		0.65
		95% CI (0.56, 0.76)
p-value[a]		$p < 0.0001$
Overall Response Rate		
Rate (percent)	12.9	29.0
p-value[b]		$p < 0.0001$

[a] stratified logrank test; [b] stratified c^2 test includes patients with measurable disease at baseline.

Advanced and/or metastatic Renal Cell Cancer

Study BO17705

BO17705 was a multicentre, randomised, double-blind phase III trial conducted to evaluate the efficacy and safety of AVASTIN in combination with interferon (IFN) alfa-2a (ROFERON-A®) versus IFN alfa-2a alone as first-line treatment in metastatic renal cell cancer (mRCC). The 649 randomised patients (641 treated) had clear cell mRCC, Karnofsky Performance Status (KPS) of ≥ 70%, no CNS metastases and adequate organ function. IFN alfa-2a (9 MIU three times a week) plus AVASTIN (10mg/kg q2w) or placebo was given until disease progression. For patients who were unable to tolerate IFN alfa-2a treatment, treatment with AVASTIN was permitted to continue in the absence of progressive disease. A lower starting IFN alfa-2a dose (3 or 6 MIU) was permitted as long as the recommended 9MIU dose was reached within the first 2 weeks of treatment. If 9 MIU was not tolerated, IFN alfa-2a dosage reduction to a minimum of 3 MIU three times a week was also permitted. Patients were stratified according to country and Motzer score and the treatment arms were shown to be well balanced for the prognostic factors.

The primary endpoint was overall survival, with secondary endpoints for the study including progression free survival (PFS). The addition of AVASTIN to IFN alfa-2a significantly increased PFS and objective tumour response rate. These results have been confirmed through an independent radiological review. However, the increase in the primary endpoint of overall survival by 2 months was not significant (HR = 0.91). A high proportion of patients (approximately 63% IFN/placebo; 55% AVASTIN/IFN) received a variety of non-specified post-protocol anti-cancer therapies, including anti-neoplastic agents, which may have impacted the analysis of overall survival. The efficacy results are presented in Table 9.

Table 9: Efficacy Results for Study BO17705

	IFN + Placebo	IFN + AVASTIN
Number of Patients	322	327
Progression-Free Survival		
Median (months)	5.4	10.2
Hazard ratio [95% CI]	0.63 [0.52; 0.75]	
	(*p*-value < 0.0001)	
Objective Response Rate (%) in Patients with Measurable Disease		
n	289	306
Response rate	12.8 %	31.4 %
	(*p*-value < 0.0001)	
Overall Survival		
Median (months)	**21.3**	23.3
Hazard ratio [95% CI]	0.91 [0.76; 1.10]	
	(*p*-value = 0.3360)	

Ninety seven patients in the IFN arm and 131 patients in the AVASTIN/IFN arm reduced the dose of IFN alfa-2a from 9 MIU to either 6 or 3 MIU, three times a week as pre-specified in the protocol.

Grade IV Glioma

Study AVF3708g

The efficacy and safety of AVASTIN as treatment for patients with GBM was studied in an open-label, multicentre, randomised, non-comparative study (AVF3708g).

Patients in first or second relapse after prior radiotherapy (completed at least 8 weeks prior to receiving AVASTIN) and temozolomide, were randomised (1:1) to receive AVASTIN (10mg/kg IV infusion every 2 weeks) or AVASTIN plus irinotecan (125 mg/m2 IV or 340 mg/m2 IV for patients on enzyme-inducing anti-epileptic drugs every 2 weeks) until disease progression or until unacceptable toxicity. The primary endpoints of the study were 6-month progression-free survival (PFS) and objective response rate (ORR) as assessed by an independent review facility. Other outcome measures were duration of PFS, duration of response and overall survival. Results are summarised in Table 10.

Table 10: Efficacy Results from Study AVF3708g

	AVASTIN		Historical controls[#]
Number of patients	85		225
	IRF	Inv	-
Primary endpoints			
6-month progression-free survival (97.5% CI)	42.6% (29.6, 55.5)	43.6% (33.0, 54.3)	15% (p < 0.0001)
Objective Response Rate (ORR) (97.5% CI)	28.2% (18.5, 40.3)	41.2% (30.6, 52.3)	5% (p < 0.0001)
Secondary endpoints			
Progression-free survival (months) Median (95% CI)	4.2 (2.9, 5.8)	4.2 (3.0, 6.9)	2.1
Duration of objective response (months) Median (95% CI)	5.6 (3.0, 5.8)	8.1 (5.5, ^)	-
Overall survival (months) Median (95% CI)	9.3 (8.2, ^)	9.3 (8.2, ^)	5.7

ORR and progression were determined using modified Macdonald criteria; CI = confidence interval; Inv = Investigator's assessment; IRF = Independent Review Facility [#] protocol-defined statistical comparison with the integrated analysis of Wong et al(1999).^ Upper limit of the CI could not be obtained.

The majority of patients who were receiving steroids at baseline, including responders and non-responders, were able to reduce their steroid utilisation over time while receiving AVASTIN. The majority of patients experiencing an objective response or prolonged PFS (at week 24) were able to maintain or improve their neurocognitive function at the time of response and at week 24, respectively, compared to baseline. The majority of patients that remained in the study and were progression free at 24 weeks, had a Karnofsky performance status (KPS) that remained stable.

Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer

Study GOG-0218

The GOG-0218 trial was a phase III multicentre, randomised, double-blind, placebo controlled, three arm study evaluating the effect of adding AVASTIN to an approved chemotherapy regimen (carboplatin and paclitaxel) in patients with optimally or sub-optimally debulked Stage III or Stage IV epithelial ovarian, fallopian tube or primary peritoneal cancer.

A total of 1873 patients were randomised in equal proportions to the following three arms:

Carboplatin/Paclitaxel/Placebo (CPP) arm: Placebo in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles followed by placebo alone, for a total of 15 months of therapy.

Carboplatin/Paclitaxel/Bevacizumab (CPB15) arm: Five cycles of AVASTIN (15 mg/kg q3w) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles (AVASTIN commenced at cycle 2 of chemotherapy) followed by placebo alone, for a total of 15 months of therapy.

Carboplatin/Paclitaxel/Bevacizumab (CPB15+) arm: Five cycles of AVASTIN (15 mg/kg q3w) in combination with carboplatin (AUC 6) and paclitaxel (175 mg/m^2) for 6 cycles (AVASTIN commenced at cycle 2 of chemotherapy) followed by continued use of AVASTIN (15 mg/kg q3w) as single agent for a total of 15 months of therapy.

The primary endpoint was progression-free survival (PFS) based on investigator's assessment of radiological scans. In addition, an independent review of the primary endpoint was also conducted.

The results of this study are summarised in Table 11 (the p-value boundary for primary treatment comparisons was 0.0116).

Table 11: Efficacy Results from Study GOG-0218

Progression-Free Survival						
	Investigator Assessment[1]			IRC Assessment		
	CPP (n = 625)	CPB15 (n = 1248)[2]	CPB15+ (n =1248)[2]	CPP (n = 625)	CPB15 (n = 1248)[2]	CPB15+ (n = 1248)[2]
Median PFS (months)	12.0	12.7	18.2	13.1	13.2	19.1
Hazard ratio (95% CI)[3]		0.842 [0.714, 0.993]	0.644 [0.541, 0.766]		0.941 [0.779, 1.138]	0.630 (0.513, 0.773)
p–value[4]		0.0204[5]	< 0.0001[5]		0.2663	< 0.0001

Objective Response Rate[6] 0						
	Investigator Assessment			IRC Assessment		
	CPP (n = 396)	CPB15 (n = 393)	CPB15+ (n = 403)	CPP (n = 474)	CPB15 (n = 460)	CPB15+ (n = 499)
% pts with objective response	63.4	66.2	66.0	68.8	75.4	77.4
p–value[4]		0.2341	0.2041		0.0106	0.0012

Overall Survival[7]			
	CPP (n = 625)	CPB15 (n = 625)	CPB15+ (n = 623)
Median OS (months)	39.4	37.9	43.4
Hazard Ratio (95% CI)[3]		1.14 (0.95, 1.37)	0.90 (0.74, 1.08)
p-value[4]		0.0809	0.1253

IRC: Independent Review Committee;

[1] primary PFS analysis;

[2] events prior to cycle 7 from the CPB15 and CPB15+ arms were pooled for the analysis;

[3] stratified hazard ratio relative to the control arm;

[4] one-sided p-value;

[5] subject to a p-value boundary of 0.0116;

[6] patients with measurable disease at baseline;

[7] overall survival analysis performed when approximately 36% of the patients had died

- The trial met its primary objective of PFS improvement. Compared with patients treated with chemotherapy (carboplatin and paclitaxel) alone, patients who received first-line AVASTIN at a dose of 15 mg/kg q3w in combination with chemotherapy and continued to receive AVASTIN alone, had a clinically meaningful and statistically significant improvement in PFS.
- Although there was an improvement in PFS for patients who received first-line AVASTIN in combination with chemotherapy and did not continue to receive AVASTIN alone, the improvement was not statistically significant compared with patients who received chemotherapy alone.

INDICATIONS

Metastatic Colorectal Cancer

AVASTIN (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for the treatment of patients with metastatic colorectal cancer.

Locally recurrent or metastatic Breast Cancer
AVASTIN (bevacizumab) in combination with paclitaxel is indicated for the first-line treatment of metastatic breast cancer in patients in whom an anthracycline-based therapy is contraindicated. (see Clinical Trials).

Advanced, metastatic or recurrent non-squamous Non-Small Cell Lung Cancer (NSCLC)
AVASTIN (bevacizumab), in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent, non-squamous, non-small cell lung cancer.

Advanced and/or metastatic Renal Cell Cancer
AVASTIN (bevacizumab) in combination with interferon alfa-2a is indicated for treatment of patients with advanced and/or metastatic renal cell cancer.

Grade IV Glioma
AVASTIN (bevacizumab) as a single agent, is indicated for the treatment of patients with Grade IV glioma after relapse or disease progression after standard therapy, including chemotherapy.

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer
AVASTIN (bevacizumab) in combination with carboplatin and paclitaxel, is indicated for first-line treatment of patients with advanced (FIGO stages IIIB, IIIC and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer.

CONTRAINDICATIONS

AVASTIN is contraindicated in patients with:

- known hypersensitivity to any components of the product; Chinese hamster ovary cell products or other recombinant human or humanised antibodies

PRECAUTIONS

Gastrointestinal Perforations
Patients may be at increased risk for the development of gastrointestinal (GI) perforation and gallbladder perforation when treated with AVASTIN. AVASTIN should be permanently discontinued in patients who develop GI perforation.

AVASTIN has been associated with serious cases of GI perforation. GI perforations have been reported in clinical trials with an incidence of < 1% in patients with metastatic breast cancer or NSCLC, and up to 2% in patients with metastatic colorectal cancer or ovarian cancer (first-line treatment). Cases of GI perforations have also been observed in patients with relapsed glioblastoma. Fatal outcome was reported in approximately a third of serious cases of GI perforations, which represents between 0.2% - 1% of all AVASTIN-treated patients.

The presentation of these events varied in type and severity, ranging from free air seen on the plain abdominal X-ray, which resolved without treatment, to intestinal perforation with abdominal abscess and fatal outcome. In some cases underlying intra-abdominal inflammation was present, either from gastric ulcer disease, tumour necrosis, diverticulitis or chemotherapy-

associated colitis. A causal association of intra-abdominal inflammatory process and GI perforation to AVASTIN has not been established.

Hypertension

An increased incidence of hypertension was observed in patients treated with AVASTIN. 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 AVASTIN therapy. Monitoring of blood pressure is recommended during AVASTIN therapy.

In most cases hypertension was controlled adequately using standard anti-hypertensive treatment appropriate for the individual situation of the affected patient. 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 (see *ADVERSE EFFECTS; Post-Marketing Experience*).

An increased incidence of hypertension (all grades) of up to 34% has been observed in patients treated with AVASTIN compared with up to 14% in the comparator arm. In clinical trials across all indications the overall incidence of Grade 3-4 hypertension in patients receiving AVASTIN ranged from 0.4% to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 1.0% of patients treated with AVASTIN compared to up to 0.2% patients treated with the same chemotherapy alone.

Hypertension was generally treated with oral anti-hypertensives such as angiotensin-converting enzyme inhibitors, diuretics and calcium-channel blockers. It rarely resulted in discontinuation of AVASTIN treatment or hospitalisation.

Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal (see *ADVERSE EFFECTS; Post-Marketing Experience*). The risk of AVASTIN-associated hypertension did not correlate with the patients' baseline characteristics, underlying disease or concomitant therapy.

Wound Healing

AVASTIN may adversely affect the wound healing process, AVASTIN therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experience wound healing complications during AVASTIN therapy, AVASTIN should be withheld until the wound is fully healed. AVASTIN therapy should be withheld for elective surgery.

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

In locally recurrent and metastatic breast cancer, National Cancer Institute-Common Toxicity Criteria (NCI-CTC) Grade 3-5 wound healing complications were observed in up to 1.1% of patients receiving AVASTIN compared with up to 0.9% of patients in the control arms.

In Study AVF3708g, patients with relapsed GBM, the incidence of post-operative wound healing complications (craniotomy site wound dehiscence and cerebrospinal fluid leak) was 3.6% in patients treated with single-agent AVASTIN and 1.3% in patients treated with AVASTIN and irinotecan.

Thromboembolism

Arterial thromboembolic events

An increased incidence of arterial thromboembolic events has been observed in patients treated with AVASTIN across indications including cerebrovascular accidents, myocardial infarction, transient ischaemic attacks, and other arterial thromboembolic events.

In clinical trials, the overall incidence ranged up to 3.8% in the AVASTIN-containing arms compared with up to 1.7% in the chemotherapy control arms. Fatal outcome was reported in 0.8% of patients receiving AVASTIN in combination with chemotherapy compared to 0.5% of patients receiving chemotherapy alone. Cerebrovascular accidents (including transient ischaemic attacks) were reported in up to 2.3% of AVASTIN-treated patients versus 0.5% of patients in the control group. Myocardial infarction was reported in 1.4% of AVASTIN treated versus 0.7% of patients in the observed control group.

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

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 AVASTIN therapy. Caution should be taken when treating such patients with AVASTIN.

Venous thromboembolic events

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

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) venous thromboembolic events, including pulmonary embolism. Patients with thromboembolic events ≤ Grade 3 need to be closely monitored.

Grade 3-5 venous thromboembolic events have been reported in up to 7.8% of patients treated with chemotherapy plus AVASTIN compared with up to 4.9% in patients with chemotherapy alone. Patients who have experienced a venous thromboembolic event may be at higher risk for a recurrence if they receive AVASTIN in combination with chemotherapy versus chemotherapy alone.

Haemorrhage

Patients treated with AVASTIN have an increased risk of haemorrhage, especially tumour-associated haemorrhage. AVASTIN should be permanently discontinued in patients who experience Grade 3 or 4 bleeding during AVASTIN therapy.

In clinical trials across all indications the overall incidence of NCI-CTC Grade 3-5 bleeding events ranged from 0.4% to 5% in AVASTIN-treated patients, compared to 0 to 2.9% of patients in the chemotherapy control group. Haemorrhagic events observed in AVASTIN clinical trials

were predominantly tumour-associated haemorrhage and minor mucocutaneous haemorrhage (e.g. epistaxis).

Patients with untreated central nervous system (CNS) metastases have been routinely excluded from clinical studies with AVASTIN, based on imaging procedures or signs and symptoms. However, 2 studies of AVASTIN in ovarian cancer provide a comparison with standard carboplatin/paclitaxel therapy of the incidence of CNS and non-CNS haemorrhage in patients without cerebral metastases. In Study GOG-0218, three patients who received extended treatment with AVASTIN developed CNS haemorrhage, with 1 death, and the same number in the AVASTIN arm of Study BO17707, also with 1 death. No CNS haemorrhage occurred in the control arms. Non-CNS haemorrhages were observed in Study GOG-0218 in 16% of control patients vs. 35.6% and 36.7% in the short and extended duration AVASTIN arms; in B017707 they were observed in 11% of control patients and 39.4% of the AVASTIN-treated patients. Most of the non-CNS haemorrhages were Grade 3 or less (GOG-0218: three events in the AVASTIN arm were Grade 4; B017707: one patient in the AVASTIN arm had a Grade 4 event and 2 patients in the control arm had a Grade 4 or higher event, one Grade 4 event and one Grade 5 event). 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 therapy, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating AVASTIN therapy in these patients. However, patients who developed venous thrombosis while receiving AVASTIN therapy did not appear to have an increased rate of Grade 3 or above bleeding when treated with full dose of warfarin and AVASTIN concomitantly.

Tumour-associated haemorrhage

Major or massive pulmonary haemorrhage/haemoptysis has been observed primarily in studies in patients with NSCLC. Possible risk factors include squamous cell histology, treatment with antirheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, AVASTIN therapy, previous medical history of atherosclerosis, central tumour location and cavitation of tumours prior to or during therapy. The only variables that showed statistically significant correlations with bleeding were AVASTIN therapy and squamous cell histology. Patients with NSCLC of known squamous cell histology or mixed cell type with predominant squamous cell histology were excluded from subsequent studies, while patients with unknown tumour histology were included.

In patients with NSCLC excluding predominant squamous histology, all grade events were seen with a frequency of up to 9% when treated with AVASTIN plus chemotherapy compared with 5% in the patients treated with chemotherapy alone. Grade 3-5 events have been observed in up to 2.3% of patients treated with AVASTIN plus chemotherapy as compared with < 1% with chemotherapy alone. Major or massive pulmonary haemorrhage/haemoptysis can occur suddenly and up to two thirds of the serious pulmonary haemorrhages resulted in a fatal outcome.

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

Tumour-associated haemorrhages have also been seen rarely in other tumour types and locations and include cases of CNS bleeding in patients with CNS metastases and glioblastoma (GBM). In an exploratory retrospective analysis of data from 13 completed randomised trials in patients with

various tumour types, 3 patients out of 91 (3.3%) with brain metastases experienced CNS bleeding (all Grade 4) when treated with AVASTIN, compared to 1 case (Grade 5) out of 96 patients (1%) that were not exposed to AVASTIN. In 2 ongoing studies in patients with treated brain metastases, 1 case of Grade 2 CNS haemorrhage was reported in 83 subjects treated with AVASTIN (1.2%) at the time of interim safety analysis.

Intracranial haemorrhage can occur in patients with relapsed GBM. In study AVF3708g, CNS haemorrhage was reported in 2.4% (2/84) of patients in the single-agent AVASTIN arm (Grade 1) and in 3.8% (3/79) of patients treated with AVASTIN and irinotecan (Grades 1, 2 and 4).

Mucocutaneous haemorrhage
Mucocutaneous haemorrhages were seen in up to 50% of patients treated with AVASTIN, across all AVASTIN clinical trials. These were most commonly NCI-CTC Grade 1 epistaxis that lasted < 5 minutes, resolved without medical intervention and did not require any changes in AVASTIN treatment regimen. Clinical safety data suggest that the incidence of minor mucocutaneous haemorrhage (e.g. epistaxis) may be dose-dependent. There have been less common events of minor mucocutaneous haemorrhage in other locations such as gingival bleeding or vaginal bleeding.

Pulmonary haemorrhage/haemoptysis
Patients with NSCLC treated with AVASTIN may be at risk for serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis. Patients with recent pulmonary haemorrhage/haemoptysis (> $^1/_2$ teaspoon red blood) should not be treated with AVASTIN.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
There have been rare reports of AVASTIN-treated patients developing signs and symptoms that are consistent with Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a rare neurological disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. 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 (see *ADVERSE EFFECTS; Post-Marketing Experience*).

Proteinuria
Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with AVASTIN. There is evidence suggesting that all Grade proteinuria may be dose-dependent. Testing for proteinuria is recommended prior to the start of AVASTIN therapy. In most clinical studies urine protein levels of≥ 2 g/24 h led to the holding of AVASTIN until recovery to < 2 g/24 h.

In clinical trials, the incidence of proteinuria was higher in patients receiving AVASTIN in combination with chemotherapy compared to those who received chemotherapy alone. Grade 4 proteinuria (nephrotic syndrome) was uncommon in patients with AVASTIN. In the event of Grade 4 proteinuria AVASTIN treatment should be permanently discontinued.

In clinical trials, proteinuria has been reported within the range of 0.7% to 38% of patients receiving AVASTIN. Proteinuria ranged in severity from clinically asymptomatic, transient,

trace proteinuria to nephrotic syndrome. Grade 3 proteinuria was reported in < 3% of treated patients, except in advanced and/or metastatic renal cell cancer where it was reported in up to 7% of patients. Grade 4 proteinuria (nephrotic syndrome) was seen in up to 1.4% of treated patients. The proteinuria seen in AVASTIN clinical trials was not associated with renal impairment and rarely required permanent discontinuation of AVASTIN therapy.

Congestive Heart Failure
Caution should be exercised when treating patients with clinically significant cardiovascular disease or pre-existing congestive heart failure (CHF).

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

Events consistent with CHF were reported in clinical trials in all cancer indications studied to date. The findings 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 were present.

In phase III studies in patients with metastatic breast cancer, CHF Grade 3 or higher was reported in up to 3.5% of patients treated with AVASTIN in combination with chemotherapy compared with up to 0.9% in the control arms. Most patients who developed CHF during mBC trials showed improved symptoms and/or left ventricular function following appropriate medical therapy.

In most clinical trials of AVASTIN, patients with pre-existing CHF of NYHA II-IV were excluded, therefore, no information is available on the risk of CHF in this population.

An increased incidence of CHF has been observed in a phase III clinical trial of patients with diffuse large B-cell lymphoma when receiving AVASTIN with a cumulative doxorubicin dose greater than 300 mg/m^2. This clinical trial compared rituximab / cyclophosphamide / doxorubicin / vincristine / prednisone (R-CHOP) plus AVASTIN to R-CHOP without AVASTIN. While the incidence of CHF was, in both arms, above that previously observed for doxorubicin therapy, the rate was higher in the R-CHOP plus AVASTIN arm.

Neutropenia
Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus AVASTIN in comparison to chemotherapy alone.

Fistulae
Patients may be at increased risk for the development of fistulae when treated with AVASTIN. AVASTIN use has been associated with serious cases of fistulae including events resulting in death.

In AVASTIN clinical trials, gastrointestinal fistulae have been reported with an incidence of up to 2% in patients with metastatic colorectal cancer, but were also reported less commonly in patients with other types of cancer. Uncommon (≥ 0.1% to < 1%) reports of other types of fistulae that involve areas of the body other than the GI tract (e.g. bronchopleural, urogenital, biliary fistulae) were observed across various indications. Fistulae have also been reported in post-marketing experience.

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

Permanently discontinue AVASTIN in patients with tracheo-oesophageal 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.

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

Patients may be at risk of developing infusion/hypersensitivity reactions. Close observation of the patient during and following the administration of AVASTIN 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.

Severe Eye Infections Following Compounding for Unapproved Intravitreal Use
Individual cases and clusters of serious ocular adverse events have been reported (including infectious endophthalmitis and other ocular inflammatory conditions) following unapproved intravitreal use of AVASTIN compounded from vials approved for intravenous administration in cancer patients. Some of these events have resulted in various degrees of visual loss, including permanent blindness (see *ADVERSE EFFECTS*; *Post-marketing Experience*).

Effects on Fertility
AVASTIN may impair female fertility, therefore fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with AVASTIN.

No specific studies in animals have been performed to evaluate the effect of bevacizumab on fertility. No adverse effect on the male reproductive organ was observed in repeat dose toxicity studies in cynomolgus monkeys, but inhibition of ovarian function was observed in females. This was characterised by decreases in ovarian and/or uterine weight and the number of corpora lutea, a reduction in endometrial proliferation and an inhibition of follicular maturation in cynomolgus monkeys treated with AVASTIN. The lowest dose tested in the 26 week study (2 mg/kg weekly which corresponds to 0.6-fold the human therapeutic dose based on AUC) caused a reduction in uterine weight, however the reduction was not statistically significant. In rabbits, administration of 50 mg/kg of bevacizumab IV for 3 or 4 doses every 4 days resulted in decreases in ovarian and/or uterine weight and number of corpora lutea. The changes in both monkeys and rabbits were reversible upon cessation of treatment. The inhibition of angiogenesis following administration of bevacizumab is likely to result in an adverse effect on female fertility.

Use in Pregnancy – Category D
There are no adequate and well-controlled studies in pregnant women. IgGs are known to cross the placental barrier, and AVASTIN may inhibit angiogenesis in the foetus. Angiogenesis has been shown to be critically important to foetal development. The inhibition of angiogenesis

following administration of AVASTIN could result in an adverse outcome of pregnancy. Therefore, AVASTIN should not be used during pregnancy.

In women with childbearing potential, appropriate contraceptive measures are recommended during AVASTIN therapy. Based on pharmacokinetic considerations, contraceptive measures are recommended for at least 6 months following the last dose of AVASTIN.

Bevacizumab has been shown to be embryotoxic and teratogenic when administered to rabbits. Observed effects included decreases in foetal body weights, an increased number of foetal resorptions and an increased incidence of specific gross and skeletal foetal alterations. Adverse foetal outcomes were observed at all tested doses. At the lowest dose tested, maternal serum AUC values were about 0.7-fold those observed in humans at the recommended clinical dose.

Use in Lactation
Immunoglobulins are excreted in milk, although there are no data specifically for bevacizumab excretion in milk. Since bevacizumab could harm infant growth and development, women should be advised to discontinue breastfeeding during AVASTIN therapy and not to breast feed for at least 6 months following the last dose of AVASTIN.

Paediatric Use
The safety and effectiveness of AVASTIN in children and adolescent patients have not been established.

Use in the Elderly
In randomised clinical trials, age > 65 years was associated with an increased risk of developing arterial thromboembolic events including cerebrovascular accidents, transient ischaemic attacks and myocardial infarction, as compared to those aged ≤ 65 years when treated with AVASTIN. Other reactions with a higher frequency seen in patients over 65 were Grade 3-4 leucopenia and thrombocytopenia; and all grade neutropenia, diarrhoea, nausea, headache and fatigue.

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

Carcinogenesis and Mutagenesis
Studies to evaluate the carcinogenic and mutagenic potential of AVASTIN have not been performed.

Effects on the Ability to Drive or Operate Machines
No studies on the effects on the ability to drive and use machines have been performed. However, there is no evidence that AVASTIN treatment results in an increase in adverse events that might lead to impairment of the ability to drive or operate machinery or impairment of mental ability.

INTERACTIONS WITH OTHER MEDICINES

Effect of antineoplastic agents on bevacizumab pharmacokinetics
No clinically relevant pharmacokinetic interaction of co-administered chemotherapy on AVASTIN pharmacokinetics has been observed based on the results of a population pharmacokinetic analysis. There was neither statistical significance nor clinically relevant difference in clearance of AVASTIN in patients receiving AVASTIN monotherapy compared to patients receiving AVASTIN in combination with IFN alfa-2a or other chemotherapies (IFL, 5-FU/LV, carboplatin-paclitaxel, capecitabine, doxorubicin or cisplatin/gemcitabine).

Effect of bevacizumab on the pharmacokinetics of other antineoplastic agents
Results from a drug-drug interaction study, AVF3135g, demonstrated no significant effect of bevacizumab on the pharmacokinetics of irinotecan and its active metabolite SN38.

Results from study NP18587 demonstrated no significant effect of bevacizumab on the pharmacokinetic of capecitabine and its metabolites, and on the pharmacokinetics of oxaliplatin, as determined by measurement of free and total platinum.

Results from study B017705 demonstrated no significant effect of bevacizumab on the pharmacokinetics of IFN alfa-2a.

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

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

Radiotherapy
The safety and efficacy of concomitant administration of radiotherapy and AVASTIN have not been established.

ADVERSE EFFECTS

Experience from Clinical Trials
Clinical trials have been conducted in more than 3500 patients with various malignancies treated with AVASTIN, predominantly in combination with chemotherapy. The safety profile from the clinical trial population is presented in this section.

The most serious adverse drug reactions were:

- Gastrointestinal Perforations (see *PRECAUTIONS*)
- Haemorrhage including pulmonary haemorrhage/haemoptysis, which is more common in NSCLC patients (see *PRECAUTIONS*)

· Arterial and venous thromboembolism (see *PRECAUTIONS*)

Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with AVASTIN therapy are likely to be dose-dependent (see *PRECAUTIONS)*.

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

Table 12 lists adverse drug reactions associated with the use of AVASTIN in combination with different chemotherapy regimens in multiple indications. These reactions had occurred either with at least a 2% difference compared to the control arm (NCI-CTC Grade 3-5 reactions) or with at least a 10% difference compared to the control arm (NCI-CTC Grade 1-5 reactions), in at least one of the major clinical trials. The adverse drug reactions listed in Table 12 fall into the following categories: Very Common (≥ 10%) and Common (≥ 1%-< 10%). Adverse drug reactions have been included in the appropriate category in Table 12 according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping adverse drug reactions are presented in order of decreasing seriousness. Some of the adverse reactions are reactions commonly seen with chemotherapy (e.g. palmar-plantar erythrodysaesthesia syndrome with capecitabine and peripheral sensory neuropathy with paclitaxel or oxaliplatin); however, an exacerbation by AVASTIN therapy cannot be excluded.

Table 12: Very Common and Common Adverse Drug Reactions

System Organ Class (SOC)	NCI-CTC Grade 3-5 Reactions (≥ 2% difference between the study arms in at least one clinical trial)		All Grade Reactions (≥ 10% difference between the study arms in at least one clinical trial)
	Very common	Common	Very Common
Infections and infestations		Sepsis Abscess Infection	
Blood and the lymphatic systems disorders	Febrile neutropenia Leucopenia Neutropenia Thrombocytopenia	Anaemia	
Metabolism and nutrition disorders		Dehydration	Anorexia

System Organ Class (SOC)	NCI-CTC Grade 3-5 Reactions (≥ 2% difference between the study arms in at least one clinical trial)		All Grade Reactions (≥ 10% difference between the study arms in at least one clinical trial)
	Very common	Common	Very Common
Nervous system disorders	Peripheral sensory neuropathy	Cerebrovascular accident Syncope Somnolence Headache	Dysgeusia Headache Dysarthria
Eye disorders			Eye disorder Lacrimation increased
Cardiac disorders		Cardiac failure congestive Supraventricular tachycardia	
Vascular disorders	Hypertension	Thromboembolism (arterial) Deep vein thrombosis Haemorrhage	Hypertension
Respiratory, thoracic and mediastinal disorders		Pulmonary embolism Dyspnoea Hypoxia Epistaxis	Dyspnoea Epistaxis Rhinitis
Gastrointestinal disorders	Diarrhoea Nausea Vomiting	Intestinal Perforation Ileus Intestinal obstruction Abdominal pain Gastrointestinal disorder Stomatitis	Constipation Stomatitis Rectal haemorrhage Diarrhoea

System Organ Class (SOC)	NCI-CTC Grade 3-5 Reactions (≥ 2% difference between the study arms in at least one clinical trial)		All Grade Reactions (≥ 10% difference between the study arms in at least one clinical trial)
	Very common	Common	Very Common
Endocrine disorders			Ovarian failure
Skin and subcutaneous tissue disorders		Palmar-plantar erythrodysaesthesia syndrome	Exfoliative dermatitis Dry skin Skin discolouration
Musculoskeletal, connective tissue and bone disorders		Muscular weakness Myalgia Arthralgia	Arthralgia
Renal and urinary disorders		Proteinuria Urinary Tract Infection	Proteinuria
General disorders and administration site conditions	Asthenia Fatigue	Pain Lethargy Mucosal inflammation	Pyrexia Asthenia Pain Mucosal inflammation

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

Across clinical trials, the following Grade 3 and 4 laboratory abnormalities were seen with an increased (≥ 2%) incidence in patients treated with AVASTIN compared to those in the control groups: hyperglycaemia, decreased haemoglobin, hypokalaemia, hyponatraemia, decreased white blood cell count, increased prothrombin time and normalised ratio.

Post-Marketing Experience

Table 13: Adverse reactions reported in post-marketing setting

System Organ Class (SOC)	Reactions (frequency^)
Nervous system disorders	Hypertensive encephalopathy (very rare) (see *PRECAUTIONS*) Reversible Posterior Leukoencephalopathy Syndrome (rare) (see *PRECAUTIONS*)
Vascular disorders	Renal Thrombotic Microangiopathy, clinically manifested as proteinuria (not known). (See *PRECAUTIONS*).
Respiratory, thoracic and mediastinal disorders	Nasal septum perforation (not known) Pulmonary hypertension (not known) Dysphonia (common)
Gastrointestinal disorders	Gastrointestinal ulcer (not known)
Hepatobiliary disorders	Gallbladder perforation (not known)
Immune system disorders	Hypersensitivity, infusion reactions; possibly associated with the following co-manifestations: dyspnoea/difficulty breathing, flushing/redness/rash, hypotension or hypertension, oxygen desaturation, chest pain, rigors and nausea/vomiting
Eye disorders (reported from unapproved intravitreal use)	Infectious endophthalmitis[1,5] (some cases leading to permanent blindness) (not known) Intraocular inflammation[1,2] (some cases leading to permanent blindness) such as sterile endophthalmitis, uveitis, and vitritis (see *PRECAUTIONS*) Retinal detachment (not known) Retinal pigment epithelial tear (not known) Intraocular pressure increased (not known) Intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage (not known) Conjunctival haemorrhage (not known) Increased risk for cataract surgery[1,2]
Systemic events (reported from unapproved intravitreal use)	**Increased risk for haemorrhagic stroke[1,2] (see *PRECAUTIONS*)** Increased risk for overall mortality[1,2,3] Increased risk for serious systemic adverse events, most of which resulted in hospitalization (adjusted risk ratio 1.29; 95% CI: 1.01, 1.66) (Incidence 24.1%; comparator 19.0%)[1,4]

System Organ Class (SOC)	Reactions (frequency^)
Muscular, skeletal disorders	Cases of osteonecrosis of the jaw (ONJ) have been observed in AVASTIN-treated patients mainly in association with prior or concomitant use of bisphosphonates.

^ if specified, the frequency has been derived from clinical trial data

[1] As compared to an approved treatment in patients treated for wet age-related macular degeneration

[2] Gower et al. Adverse Event Rates Following Intravitreal Injection of Avastin or Lucentis for Treating Age-Related Macular Degeneration ARVO 2011, Poster 6644, Data on file

[3] Curtis LH, et al. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration. Arch Ophthalmol. 2010;128(10):1273-1279

[4] CATT Research Group, Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration. 10.1056/NEJMoa1102673

[5] One case reported extraocular extension of infection resulting in meningoencephalitis

DOSAGE AND ADMINISTRATION

Recommended Dose

Metastatic Colorectal Cancer

The recommended dose of AVASTIN, administered as an IV infusion, is as follows;

- First-line treatment: 5 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg of body weight given once every 3 weeks
- Second-line treatment: 10 mg/kg of body weight given every 2 weeks or 15 mg/kg of body weight given once every 3 weeks.

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

Locally recurrent or metastatic Breast Cancer

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

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

Advanced, metastatic or recurrent non-squamous Non-Small Cell Lung Cancer

The recommended dose of AVASTIN in combination with carboplatin and paclitaxel is 15 mg/kg of body weight given once every 3 weeks as an IV infusion.

AVASTIN is administered in addition to carboplatin and paclitaxel for up to 6 cycles of treatment followed by AVASTIN as a single agent until disease progression.

Advanced and/or metastatic Renal Cell Cancer

The recommended dose of AVASTIN is 10 mg/kg given once every 2 weeks as an IV infusion.

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

AVASTIN should be given in combination with IFN alfa-2a (ROFERON-A®). The recommended IFN alfa-2a dose is 9 MIU three times a week, however, if 9 MIU is not tolerated, the dosage may be reduced to 6 MIU and further to 3 MIU three times a week (see *CLINICAL TRIALS*). Please also refer to the ROFERON-A Product Information.

Grade IV Glioma

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

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

Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

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

AVASTIN should be given in combination with carboplatin and paclitaxel for up to 6 cycles of treatment, followed by continued use of AVASTIN as single agent.

It is recommended that AVASTIN treatment be continued for a total of 15 months therapy or until disease progression, whichever occurs earlier.

Dose reduction

Dose reduction of AVASTIN for adverse reactions is not recommended. If indicated, AVASTIN should either be discontinued or temporarily suspended (see *PRECAUTIONS*).

Special Dosage Instructions

Children and adolescents: The safety and efficacy of AVASTIN in children and adolescents have not been established.

Elderly: No dose adjustment is required in the elderly.

Renal impairment*:* The safety and efficacy of AVASTIN have not been studied in patients with renal impairment.

Hepatic impairment*:* The safety and efficacy of AVASTIN have not been studied in patients with hepatic impairment.

Preparing the Infusion

AVASTIN should be prepared by a healthcare professional using aseptic technique. Withdraw the necessary amount of AVASTIN and dilute to the required administration volume with 0.9% sodium chloride solution. The concentration of the final AVASTIN solution should be kept within the range of 1.4-16.5 mg/mL.

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

AVASTIN infusions should not be administered or mixed with dextrose or glucose solutions.

Method of Administration
The initial AVASTIN dose should be delivered over 90 minutes as an IV infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60 minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

Do not administer as an intravenous push or bolus.

AVASTIN is not formulated for intravitreal use (see PRECAUTIONS; Severe Eye Infections Following Compounding for Unapproved Intravitreal Use).

OVERDOSAGE

The highest dose tested in humans (20 mg/kg body weight, IV) was associated with severe migraine in several patients.

Treatment of overdose should consist of general supportive measures.

Contact the Poisons Information Centre for advice on management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

AVASTIN is available as:

- 100 mg pack containing one 4 mL single-dose vial
- 400 mg pack containing one 16 mL single-dose vial
- Store vials at 2-8°C. (Refrigerate. Do not freeze.) Do not shake.
- Protect from light. Keep vial in outer carton due to light sensitivity until use.

AVASTIN does not contain any antimicrobial agent; therefore care must be taken to ensure the sterility of the prepared solution. Product is for single use in one patient only. Discard any residue. Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration.

Chemical and physical in-use stability has been demonstrated for 48 hours at 2-30°C in 0.9% sodium chloride solution. To reduce microbiological hazard, the product should be used as soon as practicable after preparation. If storage is necessary, in-use storage times and conditions are the responsibility of the user and would not be longer than 24 hours at 2-8°C.

Disposal of Medicines
The release of medicines into the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Unused or expired medicine should be returned to a pharmacy for disposal.

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

R

NAME AND ADDRESS OF THE SPONSOR

Roche Products Pty Limited
ABN 70 000 132 865

4- 10 Inman Road
Dee Why NSW 2099
AUSTRALIA

Customer enquiries: 1800 233 950

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

24 February 2005

DATE OF MOST RECENT AMENDMENT

23 February 2012