Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Bevacizumab

Proprietary Product Name: Avastin

Sponsor: Roche Products Pty Ltd

First round evaluation: 28 February 2014
Second round evaluation: 29 July 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of commonly used abbreviations

Abbreviation	Meaning
AE	adverse event
ALT (SGPT)	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST (SGOT)	aspartate aminotransferase
ATE	arterial thromboembolic event
CA-125	cancer antigen 125
CHF	congestive heart failure
CI	confidence interval
CL	clearance
CR	complete response
CRC	colorectal cancer
CSR	company study report
CT	chemotherapy
CT+BV	chemotherapy plus bevacizumab
CTCAE	common toxicity criteria adverse events
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EOC	epithelial ovarian cancer
EORTC	European Organization for Research and Treatment of Cancer
FACT	Functional Assessment of Cancer Therapy
FOSI NCCN/FACT	Ovarian Symptom Index
FTC	fallopian tube cancer

Abbreviation	Meaning
GCIG	Gynecologic Cancer InterGroup
GCP	good clinical practice
GHS	Global Health Status
GI	gastrointestinal
GIP	gastrointestinal perforation
HADS	Hospital Anxiety and Depression Scale
HR	hazard ratio
HRQoL	Health related quality of life
HTN	hypertension
ICH	International Conference on Harmonization
iDMC	independent Data Monitoring Committee
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	Intent to treat
IV	intravenous
IVRS	Interactive voice response system
LVEF	left ventricular ejection fraction
MCID	minimum clinically important difference
MRI	magnetic resonance imaging
MUGA	Multiple gated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NPT	non–protocol specified anti-cancer therapy

Abbreviation	Meaning
ORR	objective response rate
OS	overall survival
PD	progressive disease
PK	pharmacokinetic
PK - DDI PK drug	drug interaction
PFI	Platinum free interval
PFS	Progression free survival
PLD	pegylated liposomal doxorubicin
PPC	primary peritoneal cancer
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient reported outcome
PS	performance status
q2w	every 2 weeks
q3w	every 3 weeks
q4w	every 4 weeks
QLQ	Quality of Life Questionnaire
RECIST	response evaluation criteria in solid tumors
RPLS	reversible posterior leukoencephalopathy syndrome
SLD	sum of longest diameter
$t_{1/2}$	terminal half life
ULN	upper limit of normal
VTE	venous thromboembolic event

1. Introduction

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

AVASTIN in combination with chemotherapy is currently approved for metastatic Colorectal Cancer, locally recurrent or metastatic Breast Cancer, advanced, metastatic or recurrent non-squamous Non-Small Cell Lung Cancer (NSCLC), advanced and/or metastatic Renal Cell Cancer, Grade IV Glioma, and Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (first-line and for recurrent platinum-sensitive disease).

The additional indication is 'AVASTIN (bevacizumab) in combination with paclitaxel, topotecan or pegylated liposomal doxorubicin is indicated for the treatment of patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimen.'

2. Clinical rationale

2.1. Impact of ovarian cancer

Ovarian cancer is a disease that globally affects nearly a quarter of a million women each year. It is the eighth most common cancer in women and the seventh leading cause of cancer death among women, responsible for approximately 140,000 deaths globally each year. It has the highest mortality rate of all gynecological cancers. In Australia in 2008, 1,272 cases of ovarian cancer were diagnosed, making it the second most common gynaecological cancer in Australia, ranking 10th in terms of the most commonly diagnosed cancers in women. Ovarian cancer was the most common cause of gynaecological cancer death with 848 deaths in 2007, ranking 7th in terms of all causes of cancer deaths among women.

2.2. Treatment

Initial: The definitive diagnosis and staging of ovarian cancer is by surgery and cytological or histological examination of tissue samples. The FIGO surgical staging system is used for ovarian cancer. Because the disease tends to be asymptomatic in early stages or associated with vague, nonspecific symptoms, the majority of patients are diagnosed with advanced-stage disease. Despite the high sensitivity of ovarian cancer to initial treatment with platinum- and taxane-based combination chemotherapy, which is the standard of care in the frontline setting, the majority of women (more than 80%) diagnosed with advanced-stage disease will have a recurrence of their cancer.

Treatment after Recurrence: Following front-line therapy, approximately 20% of women will have a first platinum-resistant recurrence within < 6 months after completing platinum therapy. Once the disease returns, a complete remission is very unlikely and women face repeated therapeutic interventions as long as the disease is responsive or can be stabilized by treatments before going on to end-of-life supportive care. Recurrence is incurable and treatment measures are essentially palliative. Recurrent disease is classified into three groups – platinum-sensitive if the disease recurs more than 6 months after previous platinum therapy; platinum-resistant if the disease recurs less than 6 months after previous platinum therapy; and platinum-refractory if the disease progresses during induction platinum therapy. In the latter two groups, platinums are generally deemed toxic and not sufficiently useful to be part of the treatment plan. This classification is highly prognostic and is important in determining optimal chemotherapeutic treatment options. Treatment is with single-agent, non-platinum chemotherapeutic agents such as pegylated liposomal doxorubicin (PLD), topotecan and paclitaxel. Overall, the prognosis for

platinum-resistant recurrence is poor, with response rates to current therapies at best ranging from 10% to 20%, with few durable responses, median progression-free survival (PFS) ranging from 2 – 5 months, and median overall survival (OS) ≤ 12 months. Hence, there is still an ongoing need to find novel treatments that maximize PFS and improve symptoms in patients with platinum-resistant ovarian cancer.

2.3. Activity of bevacizumab in ovarian cancer

Bevacizumab has been approved in the EU and Australia for initial treatment and for the treatment of recurrent, platinum-sensitive disease, but not in the USA and Canada, on the basis of studies showing a clinically significant increase in Progression-Free Survival (PFS) with significant toxicity but no increase in Overall Survival (OS).

Bevacizumab has also shown activity in recurrent platinum-resistant disease in three phase II studies. In the first, Study GOG-0107D, both platinum-sensitive and platinum-resistant patients were included with a response rate (RR) of 20% (13 of 62), a median PFS of 4.7 months and OS of 17 months. In a second study, Study AVF2949g, of only platinum-resistant patients (n=44), 7 (15%) patients responded, but the trial was stopped because 5 patients experience bowel perforation, one fatal. This adverse event was associated with three or more prior treatments. In the third trial, Garcia et al, using a combination of bevacizumab and daily oral cyclophosphamide, reported 17 partial responses (24%) in 70 patients with recurrent disease after two prior treatments (one platinum). The median Time to Progression (TTP) was 7.2 months and an OS of 16.9 months. However 4 patients experienced a GI perforation or fistula.

Comment:

The trial of Garcia et al was not referred to in the Clinical Overview.

2.4. Rationale for use of bevacizumab in phase III study of recurrent, platinum-resistant ovarian cancer

The basis for this Phase III study was the promising activity of bevacizumab seen in the recurrent disease setting, both with platinum-sensitive and platinum-resistant disease.

Comment and Conclusion:

The Phase II studies above in recurrent platinum-resistant disease show bevacizumabhas activity in a clinical situation in which there are few therapeutic options, and in which the symptoms are often severe and distressing. Although the occurrence of bowel perforation with this agent is of concern, the incidence of this event should be reduced by not enrolling patients in the study who have more than two prior treatments.

For these reasons I find the rationale acceptable.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical dossier documented a development program of a pivotal trial relating to the proposed extension of indications.

The submission contained the following clinical information:

- Report BO17706, PopPK AVITA, 'Population Pharmacokinetic Analysis BO17706', March 28, 2008. This report was a post-hoc analysis (Bayesian feedback) of the pharmacokinetics data

from 100 patients in Study BO17706 that evaluated bevacizumab in the treatment of metastatic pancreatic cancer

- Report 1031796, 'Population Pharmacokinetic Analysis of Bevacizumab. Final Analysis Report', January 9, 2008. This report added data from 224 patients to that in a previous report that included 533 patients. The cancers were those for which bevacizumab was or became an approved indication, namely breast, renal cell, colorectal and non-small cell lung cancers. Bevacizumab pharmacokinetics were characterised by a 2-compartment model with first order elimination, the data having been analysed using non-linear effects modelling (NONMEM)
- Pivotal study report, Study MO22224 (AURELIA), entitled ' A multi-centre, open-label, randomised, two-arm phase III trial of bevacizumab plus chemotherapy versus chemotherapy alone in patients with platinum-resistant, epithelial ovarian, fallopian tube or primary peritoneal cancer. Report No. 1054737, August 2013.'

Comment:

No PK data in patients with ovarian cancer was provided. Instead it was argued in the application that since the PK results for bevacizumab were comparable in the cancers previously studied and approved (metastatic CRC, breast cancer, renal cell cancer and Grade IV gliomas), no PK data were needed in ovarian cancer. This could be argued for the first line treatment of ovarian cancer patients with bevacizumab combined with carboplatinin and paclitaxel since most patients have initial surgery with tumor removal to a maximum extent (minimum residual disease). However in recurrent disease, both platinum-sensitive and platinum- resistant, malignant ascites is often present. In the pivotal study in this application, 31.3% of all patients at baseline had ascites. The concern is that these patients may be at higher risk of toxicity from bevacizumab because of possible accumulation of the drug in the ascitic fluid (a third space) with leakage back into the systemic circulation. This concern that no PK data were available for patients with malignant ascites was raised by the evaluator in the evaluation of bevacizumab for first line therapy, and a statement to this effect was placed in the Product Information (PI). This issue is considered again in the Safety section of this Evaluation Report, and in Questions to the Sponsor.

3.2. Paediatric data

The submission did not include paediatric data. The TGA Form 'Paediatric Development Plan' indicated the sponsor has a waiver from presenting a Paediatric Investigation Plan in the EU (EU Class Waiver # P/63/2010) on the grounds that the requested indication is not applicable to the paediatric population.

3.3. Good clinical practice

Local regulations/Declaration of Helsinki: The investigators were to ensure that this study was conducted in full conformity with the principles of the 'Declaration of Helsinki' or with the laws and regulations of the country in which the research was to be conducted, whichever afforded the greater protection to the individual. The study was to adhere to the principles outlined in 'Guideline for Good Clinical Practice' ICH Tripartite Guideline (January 1997) or with local law if it afforded greater protection to the patient. For studies conducted in the EU/EEA countries, the investigator was to ensure compliance with the EU Clinical Trial Directive (2001/20/EC). In other countries where 'Guideline for Good Clinical Practice' exists Roche and the investigators were to ensure adherence to the stated provisions.

Informed Consent: It was the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulations), to obtain written informed consent from each

patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The investigator or designee was also required to explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

Independent Ethics Committee: The protocol and any accompanying material provided to the patient (such as patient information sheets or descriptions of the study used to obtain informed consent) as well as any advertising or compensation given to the patient, were to be submitted by the investigator to an Independent Ethics Committee. Approval from the committee had to be obtained before starting the study, and was to be documented in a letter to the investigator specifying the date on which the committee met and granted the approval. Any modifications made to the protocol after receipt of the Independent Ethics Committee approval had also to be submitted by the investigator to the Committee in accordance with local procedures and regulatory requirements.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 shows the studies relating to each population pharmacokinetic topic and the location of each study summary.

No PK studies were performed on patients with ovarian cancer and no changes are proposed to the PK section of the Product Information.

The justification for not conducting PK studies in the population of patients with recurrent platinum-resistant ovarian cancer was the same as that used in the previous applications to register the indications for first-line treatment of EOC, and the treatment of recurrent platinum-sensitive disease. In summary the justification was the similarity of the PK parameters of bevacizumab when used to treat a variety of solid cancers such as metastatic colon cancer, metastatic renal cancer, and breast cancer. As well, the PK properties of bevacizumab in the treatment of patients with renal cell cancer were consistent with a model based on an extensive data base of PK data in a Population PK Analysis. The latter had been submitted to the TGA with the application for first line treatment of EOC.

Table 1: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
Population PK analyses	Healthy subjects/Target population	
	Other To develop a population PK model describing the PKs of bevacizumab by pooling 10 clinical trials (phase I, II and III). To test whether the PK of bevacizumab in subjects with metastatic pancreatic cancer is comparable to the previously analyzed populations.	Population PK Analysis of Bevacizumab Final Analysis Report 1031796 Population PK Analysis BO17706

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from the Summary of Clinical Pharmacological Studies. No pharmacological studies were submitted with this application, because the PK parameters of bevacizumab as established in a variety of other cancers were confirmed in the Population PK Analysis of Bevacizumab, Report 1031769 and confirmed for pancreatic cancer in Population PK Analysis BO17706.

4.2.1. Pharmacokinetics in healthy subjects

Not applicable.

4.2.2. Pharmacokinetics in the target population

4.2.2.1. Absorption

Not applicable for this intravenous formulation

4.2.2.2. Bioavailability

Not applicable

4.2.2.3. Distribution

4.2.2.3.1. Volume of distribution

The Australian PI gives the typical value for central volume (Vc) as 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 Vc (+20%) than female patients.

4.2.2.3.2. Plasma protein binding

No information was available from the SCP or the Australian PI.

4.2.2.3.3. Tissue distribution

No information was available from the SCP or the Australian PI.

4.2.2.4. Metabolism

4.2.2.4.1. Sites of metabolism and mechanisms / enzyme systems involved

The only information provided was the following from the Australian PI: 'Assessment of bevacizumab metabolism in rabbits following a single IV dose of 125I-bevacizumab suggested that its metabolic profile was similar to that expected for a native IgG molecule which does not bind VEGF.' The EU SPC further adds – 'The metabolism and elimination of bevacizumab is similar to endogenous IgG i.e. primarily via proteolytic catabolism throughout the body, including endothelial cells, and does not rely primarily on elimination through the kidneys and liver. Binding of the IgG to the FcRn receptor results in both protection from cellular metabolism and the long terminal half-life.'

4.2.2.4.2. Non-renal clearance

Australian PI: 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.

4.2.2.5. Excretion

4.2.2.5.1. Routes and mechanisms of excretion

Based on the statement in the EU SPC, the metabolism and excretion of bevacizumab is through metabolism by the endothelial-cell system of the body, as for IgG, with no major contribution

from kidney or liver. From the model derived from population PKs, the terminal half-life (t1/2) of bevacizumab was approximately 20 days (range: 11–50 days).

4.2.2.5.2. Renal clearance

Clearance by the kidneys is not a major means of excretion.

4.2.2.6. Intra- and inter-individual variability of pharmacokinetics

The population PK analysis (Report 1031796) revealed moderate between-subject variability in clearance (CV=23.8%) and the central volume of distribution (CV=14.7%). A higher between-patient variability was estimated for the peripheral volume of distribution (43 %). The covariate most influential on the between-subject variability for clearance and central volume was body weight (not including body weight on CL increased the variability by 26%, and not including body weight on central volume increased the variability by 46%). The covariate most influential on the between-subject variability for peripheral volume was the concomitant administration of cytotoxic chemotherapies (not including cytotoxic chemotherapies on peripheral volume increased the variability by 36%).

4.2.3. Pharmacokinetics in other special populations

4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

The continuous variables of SGOT, SGPT, total bilirubin and serum albumen values were tested in the PK model derived from the population PK analysis. Albumen and body weight had the highest clinical effect on clearance. The bevacizumab clearance increased as albumin levels decreased (decreased albumin levels are a sign of cachexia); if a patient has albumin levels that were 21% lower than the median (5th percentile in the studied population) then the final model predicted a clearance 31% higher than that of the population mean for that patient.

4.2.3.2. Pharmacokinetics in subjects with impaired renal function

No trials have been conducted to investigate the pharmacokinetics of bevacizumab in patients with impaired renal function.

4.2.3.3. Pharmacokinetics according to body weight

For a patient with extreme body weight (47% higher than the median, corresponding to the 95th percentile in the studied population) the final model predicted a clearance 22% higher than that of the population mean for that patient, and had the highest clinical impact on the central volume, giving a 21% change.

4.2.3.4. Pharmacokinetics related to gender

After correction for body weight, male patients had a 26% faster bevacizumab clearance than female patients and a greater central volume.

Comment:

For ovarian cancer patients, this finding indicates that the patient population (females) for the requested indication have a lower rate of clearance that the combined population in the Population PK Analysis.

4.2.3.5. Pharmacokinetics related to tumour burden

The population PK report stated 'In addition tumor burden and sex were found to impact bevacizumab clearance (high tumor burden gives a higher clearance and males have a higher clearance)'; and the Australian PI added that clearance was '…… 7% faster in subjects with higher tumour burden when compared with the typical patient with median …. tumor burden.'

4.2.3.6. Pharmacokinetics in patients with malignant ascites

About one-third of subjects in the pivotal study in this application had ascites at base-line. Ascites would be still present when bevacizumab was administered, raising the question whether this would alter the PKs of bevacizumab by creating a third-space from which bevacizumab could slowly reenter the systemic circulation or to penetrate more directly the gastrointestinal tract, increasing the risk of toxicity.

Comment:

The TGA has advised that to its knowledge no PK studies have been sighted or evaluated of a study of the PKs of bevacizumab in patients with malignant ascites. The sponsor has confirmed this.

4.2.4. Pharmacokinetic interactions

4.2.4.1. Pharmacokinetic interactions demonstrated in human studies

No new PK data on drug-drug interactions were submitted in this application. The Australian PI (page 23, Interactions with Other Medicines) stated that, based on previously evaluated studies, administration of bevacizumab does not affect the PK of co-administered irinotecan and its active metabolite SN38, capecitabine and its metabolite, oxiplatinum, and IFN-alpha 2a.

Comment:

The PI makes no mention of the effects of co-administered chemotherapy drugs on the PKs of bevacizumab.

4.2.4.2. Pharmacokinetic interactions from the clinical overview, summary of clinical pharmacological studies and the population PK analysis (Report 1031796)

Clinical Overview: The Overview notes that in the pivotal study, MO22224, no assessment was made of interaction between bevacizumab and the three chemotherapy agents used with it in combination – paclitaxel, topotecan and PL doxorubicin. It further states that no data are available from previous studies of possible interaction between bevacizumab and topotecan or PL doxorubicin. In one trial, (AVF0757g), in a limited number of patients with non-small cell lung cancer, bevacizumab does not appear to alter the disposition of paclitaxel.

Comment:

Regarding this trial, the Overview does not mention whether a possible effect of paclitaxel on the PK of bevacizumab was assessed.

The next paragraph (Clinical Overview, page 18) states 'A population PK assessment for the influence of combination therapy on bevacizumab disposition has been reported for various chemotherapies and other anti-cancer agents (e.g., erlotinib, trastuzumab, and rituximab). Results show that there were no differences in CL observed between patients treated with single-agent bevacizumab and patients treated with bevacizumab co-administered with chemotherapies (including paclitaxel) or other anti-cancer agents, suggesting that chemotherapies and anti-cancer agents do not alter bevacizumab PK when coadministered with bevacizumab.'

Section 3.1: Summary of Key Results across Studies and Population Pharmacokinetic Models, page 18 of the Clinical Overview was the same as that Section in the Summary of Clinical Pharmacological Studies (SCPS), page 7, in which dot point 7 states 'The cumulative PK-DDI data to date for bevacizumab given in combination with various chemotherapy and other anti-cancer agents across tumor types do not suggest a potential for a PK-DDI between bevacizumab and chemotherapy or other anti-cancer agents.'

Comment:

> The above statements on bevacizumab – chemotherapy interaction are not correct (see Population PK Analysis, following). A charitable interpretation is that it may have been based on the previous Population PK Analysis, not Report 1031796 that was submitted with the present application.

Summary of Clinical Pharmacological Studies (SCPS): Section 3.1, Summary of Key Results across Studies and Population Pharmacokinetic Models, stated (dot point 7) that 'The pharmacokinetics of bevacizumab was not affected by co-administration of chemotherapies or other anti-cancer agents evaluated to date.' Section 3.3.1.3, Influence of Co-administered Chemotherapy on Bevacizumab Clearance claimed that 'In all other bevacizumab combinations [except interferon], the CL of bevacizumab was 17% slower.'

Population PK Analysis. Report 1031796: In contrast to the Clinical Overview and the SCPS, the Population PK Analysis gave the following conclusions on the effects of such agents on the half-life of bevacizumab, predicted from the analysis of the updated model that incorporated additional data to that considered in the previous model. It stated 'The terminal half-life of bevacizumab is 28 days when bevacizumab is co-administered with cytotoxic chemotherapies versus 20 days when bevacizumab is administered alone or in combination with interferon alpha. In the previous model, the terminal half-life of bevacizumab was equal to 24 days when bevacizumab was co-administered with the following cytotoxic chemotherapies (5FU+LV or carboplatin/ paclitaxel or capecitabine or doxorubicin) versus 20 days when bevacizumab was administered alone or in combination with IFL. Those results are quite consistent, considering the differences between the two models already mentioned and considering that fact the concomitant medication effect is affecting the peripheral volume in the actual model versus the clearance in the previous model.'

Comment:

> It is noted that the previous population PK model referred to in the more recent report (Report 1031796) above, was based on a smaller data base, and found an increase in the half-life of bevacizumab from 20 to 24 days when co-administered with the drugs shown. This represented a 20% increase so the SCPS may have used these outdated results to arrive at a value of 17%. The updated model that included additional clinical data found the half-life was increased from 20 days to 28 days, an increase of 40%, a clinically significant increase.

4.2.4.3. Clinical implications of findings of population PK analysis report 1031796

The clinical implications of the findings of the Population PK Analysis are important, especially the covariate found to slow significantly the rate of clearance of bevacizumab, namely co-administered chemotherapy, since this has the potential to increase toxicity of bevacizumab. On the other hand, the faster rate of clearance seen with a reduced concentration of serum albumen and excessive body weight is less significant clinically as the faster rate of clearance would be unlikely to affect the efficacy of bevacizumab.

4.2.5. Evaluator's overall conclusions on pharmacokinetics

No pharmacokinetic data were provided with this application. Justification included:

1. The PK parameters of bevacizumab found in a variety of solid tumors were similar and would be expected to apply to the present clinical population.
2. The predictions from Population PK modelling and the actual PK parameters found in patients with pancreatic cancer treated with bevacizumab (Population PK Analysis BO17706) were comparable.

PK Deficiencies - Sponsor should comment (see Section 11):

1. The PK parameters for bevacizumab in patients with malignant ascites may differ from patients with solid tumours who have no ascites (see Section 4.2.4.6).
2. A possible clinical effect of the reduced rate of clearance of bevacizumab by 40% from co-administered anti-cancer drugs as shown in the Population PK Analysis Report 1031796 has not been considered.
3. The Australian PI presents the results of the population PK analysis showing effects of low albumen and high tumour burden on the PK parameters of bevacizumab including clearance, but does not mention co-administered anti-cancer drugs that slow the rate of clearance of bevacizumab.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

No pharmacodynamic (PD) data were included in the present application. The Australian PI gives the following information about those PD effects that are related to the anti-cancer action of bevacizumab. No information is provided on those PD effects responsible for the drug's toxicity. '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.'

5.2. Summary of pharmacodynamics

No pharmacodynamics data were submitted

5.3. Evaluator's overall conclusions on pharmacodynamics

Not applicable.

6. Dosage selection for the pivotal studies

The Summary of Clinical Efficacy (SCE), Module 2.7.3, gives the following justification for the selection in the pivotal study MO22224 of a dose of bevacizumab of 10 mg/kg q2w or 15 mg/kg q3w.

'*This dosage was selected to be within the linear pharmacokinetic range resulting in serum bevacizumab concentrations in excess relative to circulating VEGF concentrations (3–20 mg/kg every 2 or 3 weeks, or 1.5-10 mg/kg/week).*

The dose of bevacizumab 10 mg/kg IV q2w or bevacizumab 15 mg/kg IV q3w, which is equivalent to a dose of 5 mg/kg/week, is the most commonly used dose of bevacizumab that has been shown to be effective in clinical trials across multiple tumor types (e.g. non-small cell lung cancer, metastatic breast cancer, advanced renal cell carcinoma, metastatic carcinoma of the colon or rectum, and front-line and recurrent treatment of EOC, FTC, and PPC) [references were given in the SCE)

Phase II trials GOG-170D and AVF2949g, in ovarian cancer patients demonstrated that a dose of bevacizumab equivalent to 15 mg/kg q3w had activity in the recurrent setting. Furthermore, it is the currently approved dose in the front-line and recurrent platinum-sensitive ovarian cancer

settings the EU and Australia'. (Note: These indications for ovarian cancer are not approved in the USA).

Comment:

After the above text in the SCE are the following sentences ' Bevacizumab should be administered in combination with chemotherapy until PD or unacceptable toxicity. Bevacizumab may be continued as a single agent if chemotherapy is discontinued earlier.' The first usage is acceptable, but the second is ambiguous since the wording allows bevacizumab to be continued if the patient were receiving chemotherapy plus bevacizumab, and then the chemotherapy was stopped early, say for toxicity. The CSR on the other hand specifically stated that only patients in the chemotherapy alone arm were to cross over on disease progression to receive monotherapy with bevacizumab. The sponsor needs to confirm that only patients in the chemotherapy alone arm cross-over to receive bevacizumab monotherapy (see Section 11 Clinical Questions).

7. Clinical efficacy

7.1. 'AVASTIN (bevacizumab) with chemotherapy to treat recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer in patients who received no more than two prior chemotherapy regimens.'

7.1.1. Pivotal efficacy Study BO22224 (also identified as Avastin use in platinum-resistant EpitheLIal ovarian cancer [AURELIA])

7.1.1.1. Study design, objectives, locations and dates

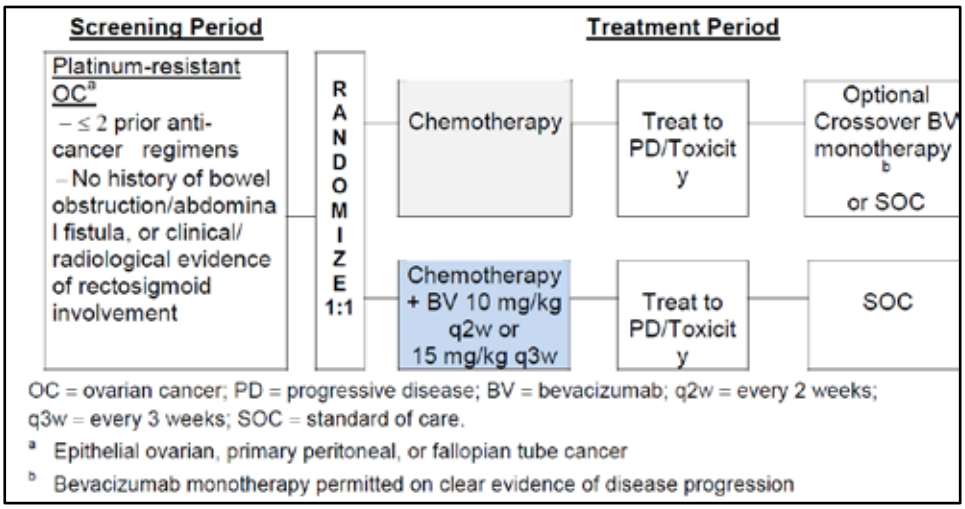
Study design: Study MO22224 evaluated the efficacy and safety of bevacizumab in combination with chemotherapy for platinum-resistant ovarian cancer. This study was designed as an open-label, randomized, two-arm Phase III evaluation of bevacizumab plus chemotherapy (CT+BV) versus chemotherapy (CT) alone. Eligible patients had ovarian cancer that recurred within < 6 months of previous platinum therapy. Patients with refractory disease (i.e., progression while on therapy) were excluded. At the decision of the investigator, patients were assigned to receive one of three chemotherapy agents (paclitaxel, topotecan, or PLD) then patients were randomized in a 1:1 ratio to receive either CT alone or CT+BV. The study design is shown in Figure 1.

Objectives: The primary objective was a comparison of the time of Progression Free Survival (PFS) of patients in the two treatment arms. The secondary and exploratory objectives are shown in Section 7.1.1.5 Efficacy variables and outcomes.

Locations: The study was carried out in 96 centers in 14 European countries: France (31), Germany(18), Spain (14), Denmark (4), Italy (6), Belgium (4),Norway (2), Bosnia and Herzegovina (2), Sweden (3), the Netherlands (4), Portugal (2), Turkey (4), Greece (1), and Finland (1).

Dates: The first patient was randomized on 29 October 2009, and the trial continued until 14 November 2011 (clinical database cut-off for primary efficacy analysis) and 25 January 2013 (clinical database cut-off for final overall survival and safety analyses).

Figure 1: Design of Study MO22224



7.1.1.2. Study amendments

The protocol was finalized on 4 May 2009 and was subsequently amended three times.

Amendment 1: The first amendment was finalized on 24 November 2009, by which date 6 patients were randomized.

Comment:

The amendments were extensive but since this was early in the study and the changes have been incorporated in the study design described in this evaluation report, they will not be provided separately.

Amendment 2: The study was amended a second time on 28 October 2010, by which date 236 patients were randomized.

Comment:

The amendments were mainly for clarification, and the changes made were not such to affect the data analysis.

Amendment 3: The protocol was amended a third time on 23 January 2013 in order to:

- Allow for a potential retrospective scan collection and a review of scans by an independent review committee (IRC).
- Clarify that the duration of survival follow-up should continue for a minimum of 12 months after end of treatment for all patients.

Comment:

The retrospective review did not occur.

Statistical Analysis Plan Amendments: The Statistical Analysis Plan (SAP) was amended (SAP Amendment 1) on 13 Jan 2012, 12 days before the final clinical database cut-off and final analysis, 'to clarify the planned analyses'. The SAP was again amended (SAP Amendment 2) on 19 Dec 2012, 11 months after the final analysis (CORRECTION from S31 response – to read 13 months after the data cut-off for the primary efficacy analysis).

The analyses were performed and are reported in the CSR according to the plan outlined in the SAP Amendment 2 which superseded those specified in the Protocol for Study MO22224 and the previous versions of the SAP. The date of the report of the pivotal trial MO-22224 is August 2013.

Comment:

> The reason given for SAP Amendment 2 by the applicant (page 1534, CSR) is that 'The plan emphasizes analyses that would meet the expectations of Regulatory Agencies in their review processes for approval of the new indication.'

The amendment was made 11 months (CORRECTION fromS31 response: this should read 1 month) after the close of the clinical data-base of the trial. Until this time, the SAP had been the same in all the amended protocols, and assessments of the various endpoints would have been made by the investigators following these trial protocols up to closure of the clinical data-base. It is therefore possible that results or early impressions of these assessments may have led to the SAP Amendment 2, which was not part of the original study design. Therefore selection bias in the changes to the SAP cannot be excluded. This now requires a more detailed review of these changes to exclude possible bias or the appearance of bias, especially as the reason given could be interpreted as making the changes to emphasize/select positive results would make it more likely to meet 'expectations of Regulatory Agencies'.

Review by Clinical Evaluator of Changes to the Statistical Analysis Plan made in Amendment 2 of that Plan (19 Dec 2012)

Changes that are acceptable as being for clarification or as being more conservative:

1. Primary Analysis:

1.1 The assessment of the progressive disease for the primary progression-free survival (PFS) has been changed to assessment by investigator according to Response Evaluation Criteria In Solid Tumors (RECIST) or by symptom deterioration, whichever occurs first, and could not be declared on the basis of rising cancer antigen 125 (CA125) levels alone.

Comment:

> This change would be for clarification as assessment of the Primary Efficacy Variable in Section 8.1.1 (p1340) of the latest Trial Protocol (23 Jan 2013) and of the earlier versions of the protocol did not mention deterioration in symptoms as a criterion of disease progression. However it did refer to Appendix 1 of the protocol for assessment with non-measureable disease in which one criterion for disease progression was 'Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression. Patients should be classified as having 'symptomatic deterioration'.

In the same section (8.1.1), no mention was made of use of the CA-125 levels in assessment of disease progression, but Appendix 1, in Progression or Recurrence Based on Serum CA- 125 Levels (p1354) does define Biological Progression Free Interval (PFI_{BIO}), using this measurement.

Conclusion: This amendment is acceptable, being for clarification.

1.2. Primary analysis of PFS will be a log-rank test stratified by chemotherapy selected (paclitaxel; pegylated liposomal doxorubicin [PLD]; Topotecan daily and weekly), prior anti-angiogenic therapy (yes or no), and platinum-free interval (<3; 3-6 months). It will be further supported by a more comprehensive plan of sensitivity analyses.

Conclusion: This change is acceptable, and would not introduce bias.

2. Secondary Analyses:

2.1. No analysis will be performed on the objective response rate (ORR) assessed by RECIST or CA125 criterion, nor on the biological progression-free interval, which is considered an exploratory objective.

2.2. The ORR on the basis of rising CA125 alone has been considered exploratory.

2.3. Duration of ORR per RECIST has been added as one of the secondary efficacy outcome measures.

3. Other Analyses:

3.1. Safety analyses, including summaries of deaths and all adverse events, will be conducted by two study periods, which are the primary study period and the crossover bevacizumab monotherapy period.

3.2. The final analysis of overall survival (OS) was planned when 253 deaths from the two treatment arms are observed. The projected timing for the final OS analysis will be approximately 22 months after the last patient is enrolled.

3.3. The type I error rate for the interim and final OS analyses is controlled at the $\alpha = 0.05$ level. At the interim OS analysis, OS will be tested at the $\alpha = 0.001$ level. The remaining α of 0.049 will be allocated for the final OS analysis.

Changes that are not acceptable because of possible bias:

1. Among all patient-reported outcomes (PROs), only the Quality of Life Questionnaire-OV28 abdominal/gastrointestinal (GI) symptom scale has remained as one of the secondary endpoint measures. For the PRO analysis, any postdosing assessment after disease progression, non−protocol-specified anticancer therapy (NPT), 30 days from the last study treatment dosing date, or the crossover bevacizumab monotherapy in the chemotherapy (CT) arm will be excluded from the PRO analysis. The validated scoring scheme for European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ) OV28 is used. For each instrument, the responders are defined by the minimal important difference established in the literature.

The others have been considered exploratory.

Comment:

In all the trial protocols, Quality of Life (QOL) was to be assessed by investigators during the course of the trial using multiple HRQoL instruments, including the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ) ovarian cancer module with 28 items (OV28). Such assessments would have been completed at the time of clinical data-base cut-off (25 Jan 2013), after which no more assessments for QOL were done. The above changes to the SAP (Amendment 2) were made 11 months (CORRECTION: to read 1 month) later on 19th Dec 2013(CORRECTION: to read 19th Dec 2012). In that period, the results of the investigators' assessments of trial patients' QOL using all instruments would have been in whole or in part or potentially available for scrutiny. For the sponsor then to decide that the results from all instruments were no longer to be part of the secondary objectives as pre-defined in the protocols and used throughout, and to regard these outcomes as exploratory only rather than secondary objectives, then to select only the Quality of Life Questionnaire-OV28 abdominal/ (GI) symptom scale to be a secondary objective for QOL introduces the strong possibility of data selection and bias.

Therefore it would be unsafe to accept this change, and I will evaluate QOL as determined by all instruments as a secondary objective of the trial as planned, and as stated in the trial protocols.

7.1.1.3. Inclusion and exclusion criteria

Inclusion criteria: The main criteria were:

· Patients must have platinum-resistant disease defined as progression within < 6 months from completion of a minimum of 4 platinum therapy cycles. The date of completion was from the date of the last administered dose of platinum therapy

- Patients must have disease that was measurable according to RECIST or assessable according to the Gynaecologic Cancer InterGroup (GCIG) CA-125 criteria and required chemotherapy treatment.

Exclusion criteria: The main criteria were:

- Patients whose disease was refractory to their previous platinum treatment (Refractory disease was defined as those patients who progressed during the preceding platinum treatment)
- Previous treatment with more than two anti-cancer regimens
- Any prior radiotherapy to the pelvis or abdomen
- Surgery (including open biopsy) within 4 weeks prior to the start of study, or anticipation of the need for major surgery during study treatment.

Comment:

The number (n=29) of exclusion criteria is large, and may suggest the selected patient population is not representative of the general population with this stage of disease. However most conditions listed for exclusion are relatively rare in this population, and for this type of cancer. One concern may be exclusion criterion 25 – 'History of bowel obstruction, including sub-occlusive disease, related to the underlying disease and history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess. Evidence of recto-sigmoid involvement by pelvic examination or bowel involvement on CT scan or clinical symptoms of bowel obstruction.' as patients with recurrent ovarian cancer may well have these complications. However given the possible serious adverse event of gastro-intestinal perforation with AVASTIN, this exclusion is appropriate.

7.1.1.4. Study treatments

In this study, bevacizumab was considered to be the 'investigational study drug'. The chosen chemotherapy (paclitaxel, topotecan, or PLD) was considered to be the standard-of-care 'non-investigational drug'. Collectively, both the investigational and non-investigational study drugs were known as the 'study treatments'. This trial consisted of two treatment arms: chemotherapy alone (CT arm) and chemotherapy plus bevacizumab (CT+BV arm). Patients were randomly assigned (1:1) to either arm. Study treatments were administered as follows.

CT Arm (chemotherapy alone): Eligible patients received one of the following chemotherapies at the discretion of the investigator:

- Paclitaxel 80 mg/m2 as a 1-hour IV infusion on Days 1, 8, 15, and 22 q4w
- Topotecan 4 mg/m2 as a 30 minute IV infusion on Days 1, 8, and 15 q4w. Alternatively, a 1.25 mg/m2 dose could be administered over 30 minutes on Days 1–5 q3w
- PLD 40 mg/m2 as a 1 mg/min IV infusion on Day 1 only q4w. After Cycle 1, the drug could be delivered as a 1 hour infusion.

Depending on the chosen chemotherapy, pre-medication was implemented according to local practices.

7.1.1.4.1. Eligibility of patients in CT arm to receive bevacizumab monotherapy

The investigator was to make a careful benefit-risk assessment for each patient in the CT arm at the time of progression in order to assess whether they could go on to receive crossover bevacizumab monotherapy. Patients had to have ECOG PS 0–2 and adequate hematological (ANC> 1.5 x109/L, platelets ≥ 100 x 109/L, hemoglobin ≥ 9g/dL), hepatic (total bilirubin ≤ 1.5 x ULN, AST, ALT≤ 2.5 x ULN [or ≤ 5× ULN in the presence of liver metastases]), and renal function (serum creatinine ≤ 2.0 mg/dL or 177 µmol/L), and these assessments were performed and

documented before each administration of bevacizumab. The patients from the CT arm who received bevacizumab monotherapy for the first time also had to meet all bevacizumab-specific eligibility criteria as defined in the protocol at study entry.

CT+BV Arm (chemotherapy plus bevacizumab):

- The chemotherapy was selected from one of those described in the CT arm
- The chosen chemotherapy was combined with bevacizumab 10 mg/kg IV q2w (or bevacizumab 15 mg/kg q3w if used in combination with topotecan 1.25 mg/m2 on Days 1–5 on a q3w schedule).

The initial bevacizumab infusion was over 90 minutes, with subsequent infusions over 60 minutes and then 30 minutes, as tolerated.

Duration of treatment: Bevacizumab was administered in combination with chemotherapy until PD or unacceptable toxicity. Bevacizumab could be continued as a single agent if chemotherapy is discontinued earlier.

Comment:

> However see Section 6. Dosage selection for the pivotal study regarding concerns about the continuing single agent use of bevacizumab in the presence of PD in patients already treated with bevacizumab.

Criteria for Dose Modification or Withdrawal from Treatment: In general, any Grade 4 non-hematologic adverse event led to the withdrawal of the patient from the treatment. A dosing delay of up to 3 weeks was allowed in case of Grade 3 non-hematologic adverse events to reduce toxicity to baseline or Grade 0–1. Dose levels were adjusted individually for each chemotherapy drug. No dose reescalation's were planned following dose reduction for toxicity for any of the study treatments.

Patients had the right to withdraw from the study at any time for any reason. The investigators also had the right to withdraw patients from the study in the event of intercurrent illness, adverse events, treatment failure after a prescribed procedure, protocol violation, cure, administrative, or other reasons. If a patient decided to withdraw, all efforts were made to complete and report the observations as thoroughly as possible.

Concomitant Medications: Investigators were permitted to use their clinical judgement when prescribing concomitant medications and treatments for trial patients. Local prescribing information and institutional guidelines were followed as applicable. Prophylactic pre-medication for prevention of treatment-related side effects like nausea or hypersensitivity reactions was distinguished from new supportive medication used to maintain existing medical conditions (e.g. prophylactic heparin for prior DVT), to control cancer-related symptoms (e.g., pain killers) or for treatment-related complications (e.g., platelet transfusion in case of severe thrombocytopenia or granulocyte colony-stimulating factor support in case of severe neutropenia). Prophylactic pre-medication did not need to be documented whereas supportive medication was documented within the eCRF.

7.1.1.5. Efficacy variables and outcomes

The primary efficacy variable was Progression Free Survival (PFS) defined as the time from randomization to investigator-assessed disease progression or death from any cause, whichever occurred first. The disease progression was determined by the investigator according to RECIST

Version 1.0 or by symptomatic deterioration, whichever occurred first, and was not declared on the basis of rising CA-125 levels alone. Disease progression was determined as described in Table 2 Evaluation of Residual Disease, Evaluation of and Definitions of Response and Progression.

Table 2: Evaluation of Residual Disease, Evaluation of and Definitions of Response and Progression

Assessment of residual disease:

- An assessment of residual disease which remains after surgery is required for randomisation. This should be based on details in the surgical report. Residual disease will be classified as
  - Optimally debulked: no macroscopic residual disease.
  - Suboptimally debulked: presence of macroscopic residual disease.

Measurable disease:

- Patients will be classified as having measurable or non-measurable disease according to RECIST)61 at baseline and at each imaging assessment. A baseline radiological assessment is required between 4 weeks before the start of treatment to 2 weeks after day 1 of the first cycle of treatment (chemotherapy +/- bevacizumab). If the chemotherapy has been commenced within 2 weeks of surgery then the baseline scan should be performed at week 4 (± 5 days).

Method of assessment:

- A CT scan is the preferred method of evaluation of the pelvis and abdomen, but also of the chest. An MRI scan of the pelvis and abdomen is acceptable for patients allergic to radiographic contrast media. A chest X-ray is also acceptable. The same method of assessment should be used at baseline and for all scans during follow-up.

Definition of measurable disease lesions:

- Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter [LD] to be recorded). Each lesion must be ≥20 mm when measured by conventional techniques, including palpation, plain X-ray, CT, and MRI, or ≥10 mm when measured by spiral CT.

Definition of non-measurable lesions:

- These are all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e. bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

Baseline documentation of “target” and “non-target” lesions:

- All measurable lesions, up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically)
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Definition of response:

- These definitions are based on the RECIST criteria but have been modified to include criteria for response based on CA-125 and a definition of biological progression free interval based on elevation of CA-125.

Response Criteria based on RECIST criteria.

Evaluation of target lesions:

- *Complete Response (CR): Disappearance of all target lesions
- *Partial Response (PR): At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
- *Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started
- *Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions:

- *Complete Response (CR): Disappearance of all non-target lesions and normalisation of tumour marker level. No evidence of new lesions.
- *Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) or/and
- Maintenance of tumour marker level above the normal limits
- *Progressive Disease (PD): Unequivocal progression of existing non-target lesions

Evaluation of best objective response:

- The best objective response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	New Lesions	Objective response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

Confirmation:

- The main goal of confirmation of overall response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed

- To be assigned a status of PR or CR, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met.

CA-125 defined response and biological progression free interval:

- In MO22224 AURELIA changes in CA-125 will be used as part of the routine monitoring and to define response and biological progression-free interval. This is particularly helpful for patients who have no residual disease at baseline, who could not previously be included in an assessment of response based on tumour measurements alone.

CA-125 responses:

- Guidelines for using CA-125 response have been developed. These are provided at <http://www.gcig.igcs.org/CA-125.html>. Patients should have a pre-treatment CA-125 of at least twice the ULN in order to be considered for CA-125 response. Patients are not evaluable by CA 125 if they have received mouse antibodies or if there has been
- Medical and/or surgical interference with their peritoneum or pleura during the previous 28 days. In those patients, a CA-125 response would be obtained the moment the CA-125 is reduced by 50% and this should be confirmed with a consecutive CA-125 assessment not earlier than 28 days after the previous one, with however the date of the first 50% reduction to be the reference date for the CA-125 response.

Definition of progression.

For patients with measurable disease at randomisation.

Progression is defined as ANY of the following:

- At least a 20% increase in the sum of LD target lesions taking as reference the smallest sum LD recorded since study entry.
- In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam which is not radiographically measurable, a 50% increase in the LD is required taking as reference the smallest LD recorded since study entry.
- The appearance of one or more new lesions.
- Death due to disease without prior objective documentation of progression.
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression. Patients should be classified as having ''symptomatic deterioration''. Every effort should be made to document the objective progression even after discontinuation of treatment.
- Unequivocal progression of existing non-target lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician (in this circumstance an explanation must be provided).

7.1.1.6. For patients with non-measurable disease at randomisation

Progression, for patients with non-measurable disease at randomisation, is defined as ANY of the following:

- The appearance of one or more new measurable lesions.
- Unequivocal progression of existing non-target lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician (in this circumstance an explanation must be provided).
- Death due to disease without prior objective documentation of progression.

- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression. Patients should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

7.1.2. Progression or recurrence based on serum ca-125 levels

Biological Progression Free Interval (PFIBIO) will be defined on the basis of a progressive serial elevation of serum CA-125 according to the following criteria:

- In patients with radiologically measurable disease, progression during protocol treatment cannot be declared on the basis of CA-125 alone
- Patients with elevated CA-125 pre-treatment and normalisation of CA-125 must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart or
- Patients with elevated CA-125 pre-treatment, which never normalises must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart or
- Patients with CA-125 in the normal range pre-treatment must show evidence of CA 125 greater than or equal to two times the upper normal limit on two occasions at least one week apart
- Elevated values must be confirmed by two separate measurements obtained at least one week apart. PFIBIO will be assigned the date of the first measurement that meets the criteria as noted.

The PFS data for patients who had not experienced disease progression and who had not died at the clinical cut-off date were censored at the date of the last tumor assessment on or before the clinical cut-off date, regardless of the initiation of non−protocol-specified anti-cancer therapy (NPT) or crossover of patients in the CT arm to bevacizumab monotherapy. Of note, crossover to bevacizumab monotherapy prior to disease progression was not allowed per protocol. PFS data for patients with no postbaseline tumor assessments and no death captured in the clinical database were censored at the date of randomization plus 1 day.

Secondary efficacy outcomes included:

Objective Response Rate per RECIST - An objective response was a complete or partial overall confirmed response as determined by investigators according to RECIST. Best objective response was determined and confirmed.

Duration of Objective Response per RECIST - For randomized patients who achieved an objective response per RECIST, duration of objective response was defined as the time from the date of the first occurrence of a CR or PR (whichever occurred first) until the date that PD or death was documented (whichever occurred first). Patients who had an objective response and did not experience disease progression or death by the time of analysis were censored at the time of the last tumor assessment. The duration of objective response was not censored at the start of NPT or crossover to bevacizumab monotherapy before disease progression.

Overall Survival (OS) - OS was defined as the time from randomization to death from any cause. The OS data for patients for whom no death was captured in the clinical database were censored at the last time they were known to be alive.

Health-Related Quality of Life (HRQoL) Measurements - The HRQoL instruments used to assess HRQoL were

- The symptom and functional scales, and Global Health Status (GHS)/QoL scale of EORTC QLQ-C30

- European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ) ovarian cancer module with 28 items (OV28)
- Total score from the National Comprehensive Cancer Network (NCCN)/FACT Ovarian Symptom Index (FOSI)
- The depression and anxiety scale from the Hospital Anxiety Depression Scale (HADS).

In general, responder analysis was applied to all HRQoL measures. For all QLQ-C30 and QLQ-OV28 scales including symptoms, functions, and GHS/QoL, a difference of 10 points was considered as the minimum clinically important difference (MCID) including the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ) ovarian cancer module with 28 items (OV28). For HADS, a difference of 1.5 points was used to define a significant difference. For FOSI, a difference of 2 points was used.

In SAP Amendment 1, the abdominal/GI symptom scale in the EORTC QLQ-OV28 was specified as the primary HRQoL measure. In SAP Amendment, it was further clarified that the proportion of patients who had experienced a clinically meaningful improvement at Week 8 or 9 in the abdominal/ GI symptom scale was considered as one of the secondary efficacy endpoints.

Comment:

> This measure of HROoL as stated in Amendment 2 to the SAP is a change from the pre-planned assessment in all the trial protocols and used by investigators throughout the trial. It was retrospective, and has the risk of introducing real or perceived bias.

CA-125 defined response and biological progression free interval:

Changes in CA-125 were to be used as part of the routine monitoring and to define response and biological progression-free interval. This is particularly helpful for patients who have no residual disease at baseline, who could not previously be included in an assessment of response based on tumour measurements alone. The method of assessment given in Table 2 Evaluation of Residual Disease, Evaluation of and Definitions of Response and Progression, but this was later amended as described in the following.

Comment:

> The use of CA 125 in the pivotal trial was as described above and followed the guidelines of the Gynaecological Cancer Inter-Group (ref and Appendix), with two exceptions. The first, as stated above for PFS, was that Ca 125 was not used in the present study to determine progressive disease for the primary efficacy analysis. The second was that confirmation of the CA-125 level was not required at least a week after the first, as in the GCIG guidelines. Per protocol, patients with disease progression based on RECIST were discontinued from study treatment. The study required collection of the last CA-125 measurement at the safety follow-up visit, which was usually scheduled within one month after the RECIST progression; however, this was not consistently performed. Specifically, CA-125 measurement was not mandatory once patients were discontinued from the study treatment following the RECIST disease progression. As a result, the analysis of time to confirmed biological progression by CA-125 would be confounded by the RECIST disease progression. Analysis of time to biological progression by CA-125 without requiring the subsequent CA-125 measurement for confirmation was considered more likely to provide an unbiased result.
>
> The following statement is noted in the abstract of that paper 'The criteria for defining progression are now acceptable in clinical trials of recurrent disease as they have since been validated ([information redacted], personal communication, 2010). The GCIG requests that data from all clinical trials using these definitions are made available to GCIG trial centers so that continual validation and improvement can be accomplished. **These definitions were developed from analyzing patients receiving cytotoxic**

chemotherapy and have not yet been validated in patients receiving molecular targeting agents' (my emphasis). The sponsor needs to address the question whether the definitions have since been validated in patients receiving molecular targeting agents and whether the personal communication of [information redacted] referred to above has been published in a peer-reviewed journal. If neither or either is the case, justification for the use of the guidelines is needed (see Section The Use of CA 125 to Assess Response).

7.1.2.1. Randomisation and blinding methods

Randomisation: Participating institutions registered eligible patients in this study via an interactive voice response system (IVRS). Eligible patients were allocated in a randomized 1:1 ratio to receive chemotherapy alone (CT arm) or chemotherapy plus bevacizumab (CT+BV arm).

To ensure the equal distribution of prognostic factors and chemotherapy partners in the two study arms, patients were stratified according to the following parameters:

- Selected chemotherapy cohort (paclitaxel vs. PLD vs. topotecan; patients who were selected to receive topotecan underwent further stratification by daily for 5 days vs. weekly administration)
- Previous anti-angiogenic therapy (yes vs. no). If a patient had been previously included in a blinded trial with an anti-angiogenic agent, the patient was enrolled in the same stratum as those patients who were known to have previously received an anti-angiogenic agent
- PFI (<3 months vs. 3–6 months from the last administered dose of previous platinum therapy to subsequent disease progression).

Blinding: The study was a multicenter, open-label, randomized, two-arm Phase III trial.

7.1.2.2. Analysis populations

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

For HRQoL, the analysis population was the ITT population who completed the baseline assessment before starting any study treatment and who completed at least one postbaseline assessment.

The **primary safety** population consisted of all randomized patients who received any full or partial dose of bevacizumab or chemotherapy (paclitaxel, topotecan, and PLD). For safety analyses, patients were grouped according to whether or not any dose of bevacizumab (full or partial) was received.

7.1.2.3. Sample size

Analysis of PFS: The null hypothesis for the primary efficacy analysis was that there was no difference in the PFS survivor functions between the two treatment arms. In the original protocol, on the basis of a one-sided log-rank test at an α level of 0.05 for the comparison of the primary.

Endpoint, at least 228 PFS events in the two treatment arms combined were required to achieve 80% power to detect an HR of 0.72, corresponding to an improvement of median PFS from 4.0 months in the CT arm to 5.56 months in the CT+BV arm under the exponential assumption. By taking into consideration a potential 15% patient drop-out rate, the sample size was planned to be 300 patients.

The assumptions were modified in the first amendment finalized on 24 November 2009, by which date 6 patients were randomized. On the basis of a two-sided log-rank test at an α level of

0.05 for the comparison of the primary endpoint at least 247 PFS events in the two treatment arms combined were required to achieve 80% power to detect an HR of 0.70, corresponding to an improvement of median PFS from 4.0 months in the CT arm to 5.7 months in the CT+BV arm under the exponential assumption. By taking into consideration a potential 15% patient drop-out rate, the sample size was planned to be 332 patients.

In January 2011, when approximately 300 patients were enrolled, the sample size was increased to 360 patients per the recommendation of the iDMC.

Analysis of OS: The final analysis of OS was planned when 253 deaths from the two treatment arms had been observed. Under the assumption that the median OS was 14 months in the CT arm and the observed HR for death with the addition of bevacizumab was 0.78, approximately 253 deaths would be required to limit the upper bound of the 95% confidence interval (CI) for the HR to be 1.

Comment:

> As the efficacy results will show, the estimates for PFS used to calculate sample size were conservative. The estimates of the median times for PFS in the CT and CT+BV arms were 4 months and 3.4 months respectively, whereas the actual times in the study analysis were 5.7 and 6.8 months respectively. The better than predicted outcome contributed to the HR of 0.38 rather than the predicted 0.7.
>
> For OS, the estimates were closer, with 14 months estimated, and 13.3 months found in the CT arm and 16.6 months in the CT+BV arm. The estimated HR for death was similar, 0.8 estimated, and 0.9 found (rounded to one decimal place).

7.1.2.4. Statistical methods

Methods of Analysis: The analyses of the time-to-event endpoints, including PFS, OS, and the duration of objective response, were adjusted for three stratification factors at randomization. Specifically, the Cox proportional hazard regression model included the following three covariates: chemotherapy selected (paclitaxel, PLD, or Topotecan daily and weekly); prior anti-angiogenic therapy (yes or no); and platinum-free interval (< 3 or 3 – 6 months). The stratified analysis provided an estimation of the HR taking into account the possible confounding effects from the stratification factors. There were some discrepancies between the stratification data captured on the electronic Case Report Forms (eCRFs) and the Interactive Voice Response System (IVRS). Stratification data collected on the eCRFs, which were verified against source documentation, were used in the analyses.

The analysis of the ORR using the Cochran–Mantel–Haenszel test to compare two proportions is adjusted for the same three stratification factors as the time-to-event analyses.

The analyses of the HRQoL endpoints were not adjusted for any covariates as the HRQoL data can be sparse due to patients not contributing any post-dosing measurements and an increase in missing data over time as HRQoL was not assessed following disease progression.

All **subgroup analyses** were not adjusted for any covariates due to small sample sizes of the subgroups.

Handling of Dropouts and Missing Data: Prior to PD or death, patients may have dropped out of the study for reasons such as consent withdrawal or being lost to follow-up, which led to missing data in the primary analysis of PFS. In the primary analyses of PFS, data from patients who had not died nor experienced PD by the clinical cut-off date (14 November 2011) were censored at the date of last available post-dosing tumor assessment or at Day 1 otherwise.

Two sensitivity analyses of PFS were performed to assess the impact of this censoring rule. First, an event of disease progression was imputed at the date of the first missing tumor assessment for all patients who had at least two missing tumor assessments immediately prior

to the data cut-off date. Second, as a worst case scenario, this imputation rule was applied only to patients in the CT+BV arm.

For the analyses of OS, dropouts and missing data were handled by censoring the survival data at the date on which the patient was last known to be alive.

All patients with measurable disease at baseline were to have post-baseline tumor assessments, and were included in the analysis of ORR.

For the analyses of HRQoL data, patients with no post-baseline assessment were excluded from the analysis. Missing values were not imputed.

Multiple comparisons: There was no pre-specified plan to control experiment-wise type I error rate for any hypothesis testing that included the primary endpoint.

In SAP Amendment 2 (19 December 2012), a plan was included to control the type I error rate for multiple hypothesis testing based on the OS data. The 'experiment wise' type I error rate for the OS analyses was controlled at the $\alpha = 0.05$ level (interim OS analysis $\alpha = 0.001$ and the remaining α of 0.049 was allocated for the final OS analysis).

Use of an 'Efficacy Subset' of Patients: All randomized patients were included in the PFS analyses and the OS analyses as per the ITT principle.

For the secondary endpoints, only patients with measurable disease at baseline were used for analysis of ORR; only patients with RECIST objective response were used for analysis of duration of objective response; the analysis of the HRQoL endpoints excluded patients with no post-baseline assessment.

SubGroups: Examination of subgroups was performed in an exploratory fashion. The consistency of both the PFS and OS results across demographic and baseline characteristics were examined, in order to demonstrate the robustness of the overall results.

The frequency of paracentesis was summarized for patients with and without ascites at baseline.

Sensitivity Analyses: A number of sensitivity analyses were performed using the statistical methods applied in the primary analysis of PFS. These will be described together with the results in a later Section of this Evaluation Report.

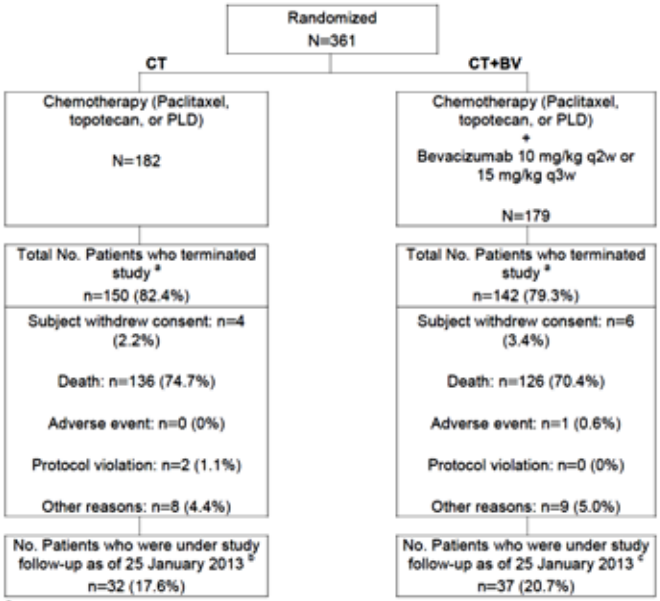
7.1.2.5. Participant flow

Dates: The first patient was randomized on 29 October 2009, and the last patient was enrolled on 15 April 2011. In the paclitaxel cohort, the first patient was randomized on 18 November 2009, and the last patient was randomized on 8 April 2011. In the topotecan cohort, the first patient was randomized on 26 January 2010, and the last patient was randomized on 15 April 2011. In the PLD cohort, the first patient was randomized on 29 October 2009, and the last patient was randomized on 7 October 2010.

The study results reported in this CSR represent two different clinical data cut-off dates: the first cut-off date was 14 November 2011 for the primary efficacy analysis of PFS, ORR, and HRQoL, and the second cut-off date was 25 January 2013 for the final overall survival analysis, as well as safety analyses.

Overall Patient Disposition: In this pivotal study, 383 patients were screened and 361 patients were randomized into the CT and CT+BV arms. Of the 361 patients randomized, 182 patients were randomized to the CT arm and 179 patients were randomized to the CT+BV arm. In the CT arm, all patients were treated with chemotherapy, and one patient received one dose of bevacizumab in error. In the CT+BV arm, all patients except for one patient were treated with CT+BV. Participant flow is shown in Figure 2 Patient Disposition and Reason for End of Study Randomized Patients

Figure 2: Patient Disposition and Reason for End of Study: Randomized Patients



[a] Reasons for termination of study on or before the cutoff dates for the final analysis of OS (25 January 2013) are included.

[b] At the cutoff date for the primary analysis of PFS (14 November 2011), 78 patients (42.9%) were continuing study follow-up.

[c] At the cutoff date for the primary analysis of PFS (14 November 2011), 93 patients (52.0%) were continuing study follow-up.

Patient disposition as of data cut-off date for primary analysis of progression-free survival.

As of 14 November 2011, the cut-off date for the primary analysis of PFS, nearly all randomized patients in the CT and CT+BV arms (CT: 97.8% versus CT+BV: 92.7%) had discontinued chemotherapy treatment. The primary reason for discontinuation of chemotherapy treatment was disease progression per RECIST, which occurred in a higher proportion of patients in the CT arm (72.0%) than the CT+BV arm (39.7%). Compared with the CT arm, a higher proportion of patients in the CT+BV arm discontinued chemotherapy treatment due to unacceptable toxicity (CT: 2.7% versus CT+BV: 15.6%) and adverse events (CT: 3.3% versus CT+BV: 11.2%). Reasons for study discontinuation such as withdrawal of consent, protocol violation, or death were infrequent. In addition, 9.3% and 16.8% of randomized patients in the CT and CT+BV arms, respectively, discontinued chemotherapy treatment for 'other' reasons, of which the majority were due to physician's decision. A smaller proportion of patients (CT: 2.7% versus CT+BV: 3.9%) discontinued due to 'other reason considered progressive', which included PD that did not meet RECIST (e.g., PD solely determined on the basis of elevated serum CA-125 levels or symptomatic deterioration).

One hundred and fifty four (154) patients (86.0%) discontinued bevacizumab treatment. In the CT+BV arm, the primary reasons were similar to those for discontinuation of chemotherapy treatment, with 42.5% ending bevacizumab treatment due to disease progression and 25.7% due to adverse events or unacceptable toxicity.

Patient disposition as of data cut-off date for final overall survival analysis

As of 25 January 2013, 100.0% and 99.4% of randomized patients in the CT and CT+BV arms, respectively, had discontinued chemotherapy treatment. The primary reason for discontinuation of chemotherapy alone in either treatment arm was disease progression per RECIST (CT: 73.6% versus CT+BV: 43.6%). Compared with the CT arm, a higher proportion of patients in the CT+BV arm discontinued chemotherapy treatment due to unacceptable toxicity (CT: 2.7% versus CT+BV: 16.2%) and adverse events (CT: 3.8% versus CT+BV: 11.7%). Reasons for study discontinuation such as withdrawal of consent, protocol violation, or death were infrequent. In addition, 8.2% and 16.8% of randomized patients in the CT and CT+BV arms,

respectively, discontinued chemotherapy treatment for 'other' reasons, of which the majority were due to physician's decision. A smaller proportion of patients (CT: 3.3% versus CT+BV: 4.5%) discontinued due to 'other reason considered progressive', which included PD that did not meet RECIST (e.g. PD based solely on elevated serum CA-125 levels or symptomatic deterioration).

Among the 179 patients in the CT+BV arm, 174 patients (97.2%) discontinued bevacizumab treatment. The primary reasons were similar to those for discontinuation of chemotherapy, with 51.4% due to disease progression per RECIST and 27.4% due to adverse event or unacceptable toxicity.

Comment:

Details were given in the CSR in tabular form and in the supplementary data of patient disposition and the reasons for termination of treatment at the time of the primary analysis of PFS, 14 Nov, 2011, and on 25 Jan 2013(data cut-off), including the patient disposition data for each of the three CT regimens, with (CT+B) and without (CT) bevacizumab. As well details were provided of patient disposition and the reasons for termination of bevacizumab (all patients) and of bevacizumab monotherapy as of 25 Jan 2013. The table showing the data at the time of the PFS analysis, 14 Nov, 2011 (all treatment) presented in Table 9 Patient Disposition and Reason for End of Treatment Chemotherapy Alone by November 14 2011 All Randomized Patients (see below), because these are the data used in the primary analysis.

Note: The caption of Table 9 (Table 114, page 330, CSR) was in error as confirmed by the sponsor in Response 7 (Section 11.1.2.4 Obscure meaning of captions on two tables). Table 9 has been corrected.

Table 3. Patient Disposition and Reason for End of Treatment - Chemotherapy Alone: by November 14, 2011 All Randomized Patients

	CT (N=182)	CT+BV (N=179)
Patients treated	182 (100.0%)	178 (99.4%)
Patients who ended treatment	178 (97.8%)	166 (92.7%)
Primary reason for end of treatment		
Unacceptable toxicity	5 (2.7%)	28 (15.6%)
Disease progression as per RECIST [1]	131 (72.0%)	71 (39.7%)
Adverse Event	6 (3.3%)	20 (11.2%)
Symptomatic deterioration	4 (2.2%)	3 (1.7%)
Protocol Violation	2 (1.1%)	(0.0%)
Death	7 (3.8%)	2 (1.1%)
Withdrew Consent	1 (0.5%)	5 (2.8%)
Other reason	17 (9.3%)	30 (16.8%)
Other reason considered progressive	5 (2.7%)	7 (3.9%)

7.1.2.6. Major protocol violations/deviations

A total of 11 patients were recorded with major protocol violations. Ten patients (2 in the CT arm and 8 in the CT+BV arm) received NPT prior to PD, and one patient in the CT arm incorrectly received bevacizumab.

Comment:

The rates of major deviations, 1.6% (n=3) and 4.5% (n=8) in the CT and CT+B arms respectively were low.

7.1.2.7. Baseline data

Demographics: Nearly all patients were white. The median age was 61.0 (range: 25–84) years, and 36.8% of all patients were 65 years or older. The majority of patients in both arms had an ECOG PS of 0 (CT: 56.4% vs. CT+BV: 61.2%). In the CT arm, the percentage of patients with an

ECOG PS of 1 or ≥2 was 38.7% and 5.0%, and in the CT+BV arm, the percentage of patients with an ECOG PS of 1 or ≥2 was 29.8% and 9.0%.

Bevacizumab

Comment:

> The patient demographic characteristics were balanced between the two arms. The greater percentage of ECOG PS 2 and 3 (9%) in the CT+BV compared with 5.0% in the CT arm is not regarded as significant, given the small numbers involved.

Baseline Disease Characteristics: The primary site of cancer in the majority of patients (90%) was ovary. The most common staging was Féderation Internationale de Gynécologie et d'Obstétrique (FIGO) Stage IIIC (55.2%), with the second most common FIGO Stage IV (26.2%). The majority (62.4%) of tumors were histologic Grade 3 (poorly differentiated). The most frequently reported histologic subtype was serous carcinoma (71.2% of patients), with an additional 2.3% with serous carcinoma mixed with other subtypes. In both treatment arms, the majority of patients had measurable disease at baseline (79.2%) and baseline CA-125 levels ≥2 × ULN (87.0%). Approximately one-third of randomized patients had ascites at baseline (31.3%). Most patients had a PFI of 3–6 months (72.6%) compared with a PFI of <3 months (27.4%).

Comment:

> The disease characteristics were reasonably balanced between the two arms. As noted previously, 31.3% (n=113) of patients in total had ascites at baseline with 29.7% (n=54) in the CT arm and 33% (n=59) in the CT+BV arm.

Previous Treatment and Procedures: Given that patients must have had platinum-resistant disease, all randomized patients had received first-line platinum-based chemotherapy treatment for ovarian cancer. Approximately 87% of all randomized patients had received initial surgical management for their ovarian cancer. Less than half of all randomized patients (CT: 42.9% vs. CT+BV: 40.2%) had received second-line chemotherapy treatment. Of these patients, the majority (88.0%) had received a platinum-based regimen.

Previous anti-angiogenic therapy was not an exclusion criterion. A total of 27 randomized patients (7.5%) had received bevacizumab or other anti-angiogenic therapy at baseline. These included patients who had been enrolled in ongoing placebo controlled blinded clinical trials, and due to the blinded nature of these studies, some of these patients may have received treatment with placebo.

Comment:

> The previous treatment and procedures showed no significant imbalances between the two arms.

Note: The sponsor in its response to Question 10 (Section 12.1.2.7, The Number of Patients who Received Prior Anti Angiogeneic Therapy) confirmed that the figure of 27 patients is more accurate being bades on verified data in the eCRF rather than on the interactive voice response system (IVRS) from investigators; and that previous anti-angiogenic treatment was unknown, due to previous trial blinding, in 33.3% of the cases (in 9 out of 27 patients).

Concomitant Medications and Therapy: During the protocol treatment period (i.e., from baseline to time of PD), the use of any post-baseline medication and therapy (e.g., new supportive medication used to maintain existing medical conditions or medication to control cancer-related symptoms or treatment-related complications) was 52.5% in the CT+BV arm compared with 48.9% in the CT arm.

The post-baseline use of medications for HTN was higher in the CT+BV arm compared with the CT arm and included: calcium channel–blocking agents, (CT: 3.8% vs. CT+BV: 6.1%),

angiotensin-II receptor antagonists (CT: 2.2% vs. CT+BV: 4.5%), diuretics (CT: 0.5% vs. CT+BV: 4.5%), and loop diuretics (CT: 0.5% vs. CT+BV: 4.5%). Conversely, the post-baseline use of paracentesis procedures to reduce ascites was higher in the CT arm compared with the CT+BV arm.

Non-Protocol Specified Anti-Cancer Therapy (NPT) prior to Disease Progression: NPT was defined as any anti-cancer therapy, including surgery, not consistent with protocol specifications. Patients who received NPT prior to documented PD were not censored in the primary analysis of PFS. The overall percentage of patients who initiated NPT prior to PD was low; however, more patients in the CT+BV arm received NPT compared with the CT arm (CT: 1.1% vs. CT+BV: 4.5%). Across both arms, most common NPTs received were chemotherapy, followed by surgery.

7.1.2.8. Results for the primary efficacy outcome

The data cut-off dates for this report were 14 November 2011 for the primary efficacy analyses of PFS, ORR, and HRQoL and 25 January 2013 for the final overall survival analysis.

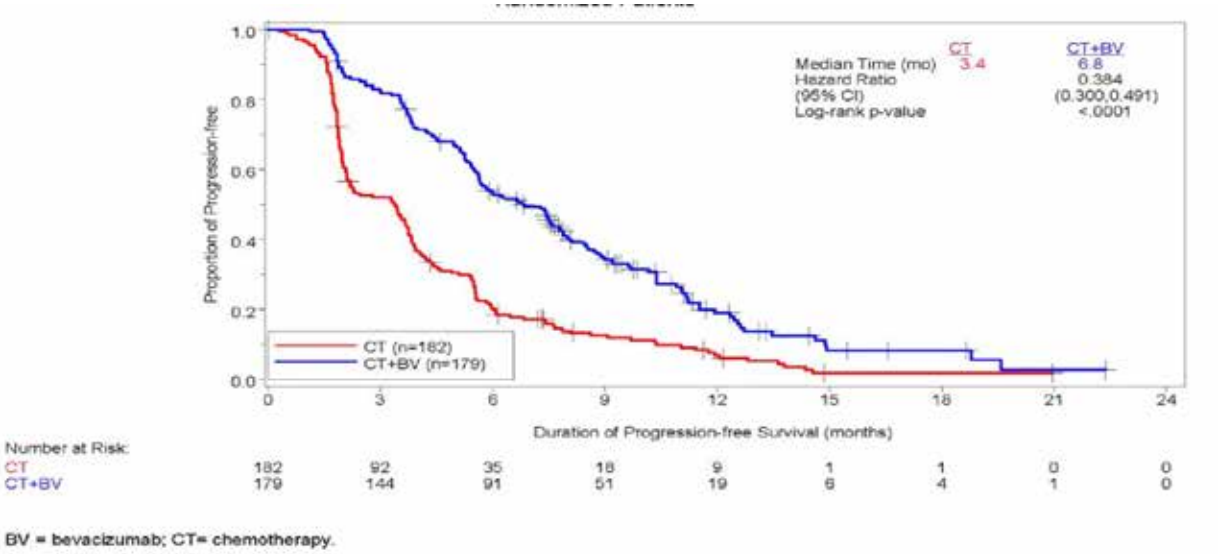
7.1.2.8.1. Primary efficacy parameter

At the time of data cut-off of the primary efficacy analysis (14 November 2011), 168 PFS events (92.3%) in the CT arm and 140 PFS events (78.2%) in the CT+BV arm had occurred. The efficacy results for PFS were as follows, for the CT and CT+BV arms respectively:

No. (%) patients with progression:	168 (92.3%) cf 140 (78.2%)
No. (%) patients without progression:	14 (7.7%) cf 39 (21.8%)
Median time to event, months:	3.4 (95% CI 2.10-3.75) cf 6.8 (5.62-7.79)
Hazard Ratio, relative to CT	0.384 (95% CI 0.300- 0.491)
Log-rank p-value	< 0.0001

The Kaplan-Meier plot showed separation of the curves from the very beginning in favour of the CT+BV arm (Figure 3). The separation increased in extent two months after randomization, and was maintained over time.

Figure 3: Kaplan-Meier Plot of Progression-Free Survival: Randomized Patients



BV = bevacizumab; CT= chemotherapy.

7.1.3. Sensitivity analyses for PFS:

7.1.3.1. Imputing PFS events at missing tumor assessments

If a patient missed two or more assessments scheduled prior to the date of the data cut-off, regardless of the reason, a PFS event would be imputed on the date of the first of these missing assessments. For example, if a patient withdrew consent from the study prior to the data cut-off and did not have further tumor assessments, the patient was considered as having progressed at the first scheduled date of the missing assessments.

The sensitivity analyses were performed under two scenarios. First, the imputation rule was applied to both arms. In this analysis, there were 174 PFS events (95.6%) in the CT arm and 147 PFS events (82.1%) in the CT+BV arm. The stratified HR was estimated to be 0.391 (95% CI: 0.307, 0.498; log-rank p < 0.0001). The median PFS in the CT arm remained the same as the result from the primary analysis (3.4 months) and was estimated at 6.6 months in the CT+BV arm. Second, the imputation rule was applied only to patients in the CT+BV arm. The stratified HR was estimated to be 0.398 (95% CI: 0.312, 0.509), and the median PFS remained the same as the first analysis above. These results indicate that missing scheduled assessments are unlikely to have an impact on the results of the primary endpoint.

Effect of discontinuation because of toxicity: After discontinuation of study treatment (either chemotherapy or bevacizumab), tumor assessments should have continued on the same schedule in the absence of confirmation of disease progression per protocol. However, in some cases, a patient may have undergone tumor assessments at a schedule different from what was mandated by the protocol or may have had no further tumor assessments, with either scenario potentially having an impact on the assessment of disease progression for patients who discontinued study treatment due to adverse event or unacceptable toxicity.

In this analysis, the PFS data for these patients were censored at the time of the last tumor assessment prior to the discontinuation. A total of 161 PFS events (88.5%) in the CT arm and 96 PFS events (53.6%) were reported in the CT+BV arm. The stratified HR was estimated to be 0.304 (95% CI: 0.231, 0.401; log-rank p< 0.0001), and the median PFS was 3.4 months in the CT arm and 7.8 months in the CT+BV arm.

These results indicate that discontinuation due to toxicity is unlikely to have an impact on the results of the primary endpoint.

Effect of NPT and bevacizumab monotherapy: In the primary analysis of PFS, PFS was not censored for patients who started NPT or who crossed over from the CT arm to bevacizumab monotherapy prior to PD or death. In this sensitivity analysis, the PFS data were censored at the last tumor assessment prior to initiation of the NPT or to the crossover to bevacizumab prior to PD or death. The stratified HR was estimated to be 0.378 (95% CI: 0.294, 0.487), and the median PFS remained the same as in the primary analysis.

Further, the impact of NPT use and crossover to bevacizumab monotherapy was assessed by imputing a PFS event at the time of the last tumor assessment prior to the initiation of NPT or bevacizumab monotherapy. The stratified HR was estimated to be 0.384 (95% CI: 0.300, 0.490; log-rank p < 0.0001), and the median PFS was 2.5 months in the CT arm and 6.3 months in the CT+BV arm. These results indicate that the use of NPT and the crossover from the CT arm to bevacizumab monotherapy is unlikely to have an impact on the results of the primary endpoint.

Backdating progressive disease date only in the CT+BV arm (worst case scenario): Under the worst case scenario, where the dates of disease progression were backdated to the last tumor assessment dates prior to disease progression only in the CT+BV arm, the stratified HR was estimated to be 0.541 (95% CI: 0.427, 0.685; log-rank p < 0.0001), and the median PFS was 4.8 months in the CT+BV arm.

Similarly, when the dates of the PFS event in the primary analysis were backdated to the last tumor assessment dates **prior to disease progression or death** only in the CT+BV arm, the

stratified HR was estimated to be 0.603 (95% CI: 0.476, 0.764; log-rank p < 0.0001), and the median PFS was 4.6 months in the CT+BV arm.

Based on these analyses, the same conclusion as for the primary PFS analysis was reached. The addition of bevacizumab to the selected chemotherapy led to a clinically meaningful and statistically significant increase in PFS compared with chemotherapy alone and investigator bias is unlikely to have an impact on the primary endpoint.

Including biological progression in the assessment of progressive disease: In this sensitivity analysis, the definition of disease progression took into account the biological progression according to the GCIG criteria on the basis of the tumor marker CA-125. Biological progression by CA-125 was considered as an event in the absence of radiographic or clinical evidence of progression. The stratified HR was estimated to be 0.392 (95% CI: 0.306, 0.501; log-rank p < 0.0001), and the median PFS was 3.3 months in the CT arm and 5.6 months in the CT+BV arm. Including biological progression on the basis of the serum CA-125 levels as an event in the PFS analysis did not impact the results of the primary PFS analysis.

Missing data: In the CT+BV arm (PLD cohort), one patient had 3 tumor assessments performed during the efficacy follow-up period after discontinuation from study treatment. Based on the tumor assessment data collected at the third follow-up visit, this patient had disease progression; however, the tumor assessment data from these 3 visits were considered invalid in error and were not included in the PFS analyses presented in this CSR.

A sensitivity analysis was performed including this additional event of disease progression. Based on the addition of this patient, the HR was estimated to be 0.382 (95% CI: 0.298, 0.489), and the median PFS estimates were not changed. Therefore, these missing data did not impact the study outcome.

Conclusions from the sensitivity analyses of PFS: In summary, all sensitivity analyses performed on the PFS endpoint consistently supported the primary analysis of PFS. The stratified HRs ranging from 0.304 to 0.603 demonstrate the robustness of the benefit in PFS observed in the primary analysis.

Other analyses of PFS: Subgroup analyses: Exploratory analyses were performed to evaluate the consistency of the PFS benefit in subgroups defined by demographic factors or prognostic factors at baseline, including:

- age, ECOG PS, randomization stratification variables (chemotherapy selected, prior antiangiogenic
- therapy, and platinum-free interval), measurable disease, SLD category, and ascites.

The unstratified HRs in most subgroups were consistent with that reported in the primary analysis of PFS; however, in some subgroups, the sample sizes were too small to draw any conclusions. The difference in the median PFS between the CT and CT+BV arms in the various subgroups was also close to the 3.4-month benefit reported in the primary analysis of PFS.

Two subgroups showed no statistical benefit in PFS. The first was patients with an ECOG PS of 2 or more. In the CT arm, 9 of 182 patients in the CT arm had progression, with a median PFS of 3.3 months, and in the CT+BV arm, 15 of 179 patients progressed with a median PFS of 5.2 month. In this subgroup the HR was 0.64 (CI 0.27-1.51). The second group was patients who had previous anti-angiogenic therapy. In this subgroup, in the CT arm, 12 of 182 patients has progression, with a median PFS of 4.3 months, and in the CT+BV arm, 10 of 179 patients progressed, with a median PFS of 5.4 months. In this subgroup, the HR was 1.1 (CI 0.46-2.69).

Also of interest were the results of the subgroup of patients with and without ascites. In patients without ascites in the two arms, the HR was 0.47 (CI 0.36-0.63) and for those with ascites, 0.36 (CI 0.24-0.56), showing a statistically significant benefit of CT+BV.

Comment:

In the ECOG PS 2 or more subgroup, the failure to show an improvement of statistical significance in PFS with additional BV therapy was likely due to the small numbers of patients with progression in each treatment arm, since the mean values indicated a trend towards clinical benefit (3.3 cf 5.2months; HR 0.64). This was not the case in the second subgroup, patients previously treated with anti-angiogenic agents. Here lack of benefit is not unexpected on biological grounds, and the mean values for each treatment arm were similar (4.3 cf 5.4months; HR 1.1), although the numbers were small as stated.

The benefit to patients with ascites is noted, and drug-related toxicity in this subgroup will be assessed later.

7.1.4. Investigators' assessments and PFS:

This study was an open-label trial and an independent review of scans was not conducted. Analysis of simulated IRC data was performed in order to further support the robustness of the results of the primary PFS analysis. This simulation evaluated the likelihood that the PFS primary analysis conclusion would be changed by an IRC due to discordance in tumor assessments between the investigators and IRC or due to potential bias in the investigator assessment of disease progression. The IRC tumor assessment data were simulated under different scenarios.

In the first set of simulations, the same assumptions were made for both arms regarding the rates at which the investigator-determined PD events were either lost or assessed at an earlier tumor assessment date. The first assumption was that in both arms, 20% of PD events were not considered as PD events by IRC. The second assumption was that in both arms, 20% and 20% of PD events were backdated to the last and the second last tumor assessment dates before the PD dates, respectively.

In the second set of simulations, more conservative assumptions were made in favor of the CT arm. The first was that in the CT arm, 20% of PD events were not considered as PD events by IRC, and in the CT+BV arm, 1% of PD events. The second assumption was that in the CT arm, 10% and 10% of PD events were backdated to the last and the second last tumor assessment dates before the PD dates, respectively; and in the CT+BV arm, 20% and 20% of PD events were backdated to the last and the second last tumor assessment dates before the PD dates, respectively.

Under all scenarios, the log-rank p-values were below 0.05, even for the worst case scenario simulated, when almost all PD events (99%) in the CT+BV arm would be confirmed by IRC while only 80% of those in the CT arm would be confirmed, and only 20% of the confirmed PD events in the CT arm versus 40% of confirmed PD events in the CT+BV arm were assessed at an earlier date.

Based on these assumptions, of 10,000 simulated datasets, the median of the stratified HRs was 0.56 (range: 0.50–0.62).

The analysis of these simulated data indicate that the results of an IRC-determined PFS analysis would likely have been consistent with that of the primary analysis based on investigator assessments, and therefore an independent review of tumor scans would not have impacted the study conclusion.

7.1.4.1. Results for other efficacy outcomes

The same data cut-off date (14 November 2011) used for the primary endpoint of PFS was used for the analysis of secondary efficacy endpoints (ORR and duration of response), interim OS analysis and the HRQoL endpoints. The final OS analysis was based on a data cut-off date of 25 January 2013.

Objective response rate (ORR): The analysis included only randomized patients with measurable disease at baseline. The number of patients with measurable disease at baseline was well balanced between the two arms, with 144 patients in the CT arm and 142 patients in the CT+BV arm.

The ORR was 12.5% (n=18) and 28.2% (n=40) for the CT arm and the CT+BV arm, respectively, with a difference in ORRs of 15.7% (95% CI: 6.5%-24.8%; p = 0.0007). In both arms, 3.5% (n=5) of patients experienced a CR. More patients (24.6%; n=35) in the CT+BV arm experienced a PR as their best confirmed response than in the CT arm (9.0%; n=13).

Objective response rate to bevacizumab in patients progressing on CT.

Comment:

> The ORR for this group of patients was not provided. Table 5, CSR, showed that 72 patients treated with CT alone then received BV monotherapy. Of these, 54 (73.6%) had disease progression by the date of clinical cut-off, 25 Jan 2013. The ORR of the 72 patients remains uncertain. This result is important in assessing the therapeutic impact of treatment with BV at this time, given the lack of significant benefit on OS of CT+BV compared to CT that contrasted to the effect on PFS. The sponsor has been asked to provide this information (see Section Continuing treatment with bevacizumab after disease progression).

Duration of objective response: The analysis of the duration of objective response included only randomized patients with an objective response. For the 18 patients in the CT arm and 40 patients in the CT+BV arm with an objective response, the median duration of objective response was 5.4 months (CI (3.81-9.23months) in the CT arm and 9.4 months (6.60-11.63months) in the CT+BV arm.

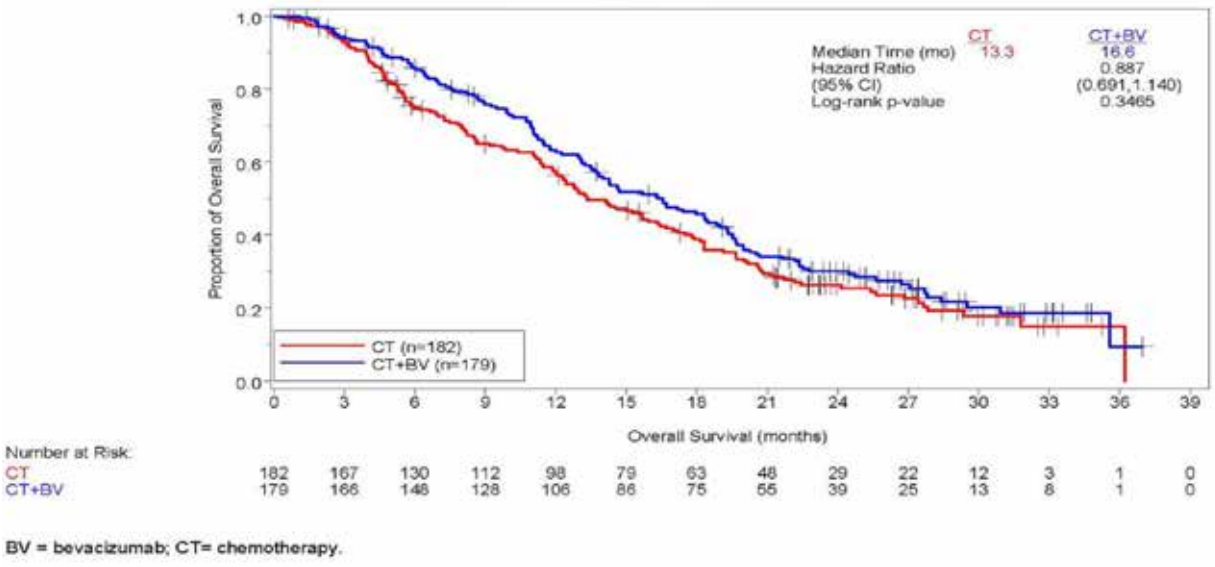
Comment:

> As shown, the CI intervals overlap. The HR was 0.45 (CI 0.23-0.90), and the p values 0.02 (log-rank).

Overall survival (OS): An interim analysis of OS was performed at the time (14 Nov 2011) of analysis of the primary endpoint and will not be reviewed here. A final analysis of OS was performed when a total of 264 patients (73.1%) had died (clinical cut-off date 25 January 2013). At this time in the CT arm, 136 patients had died and in the BV arm 128. The median duration of follow-up was 27.4 months in each treatment arm.

The median duration of survival was 13.3 months (CI 11.89-16.43months) in the CT arm and 16.6 (CI 13.70-18.99months) in the CT+BV arm, with a HR (stratified) of 0.88 (CI 0.69-1.14), and a p value of 0.35 (log-rank).The Kaplan-Meier plot is shown in Figure 4 Kaplan Meier Plot of Overall Survival Final Analysis: Randomized Patients.

Figure 4: Kaplan-Meier Plot of Overall Survival: Final Analysis: Randomized Patients



BV = bevacizumab; CT= chemotherapy.

7.1.4.2. Additional OS analyses

Missing Data: The data from two patient deaths had not been captured in the above analysis. A sensitivity analysis including these data gave the same median durations of survival.

Subgroup Analyses: Exploratory analyses were performed to assess the consistency of OS results across subgroups defined by important demographic and baseline characteristics. The results obtained from the analyses of the various subgroups were generally consistent with the final OS results.

7.1.4.2.1. Quality of Life (QOL) assessments

As described in Sections 7.1.1.2 Study Amendments and 7.1.1.5 Efficacy variables and outcomes, the QOL assessment using the Quality of Life Questionnaire-OV28 abdominal/gastrointestinal (GI) symptom scale is not acceptable as the only secondary outcome of the QOL assessments. For the reasons given in those sections, the results of all the QOL assessments will be considered equally as secondary objectives of the study as set out in the original study design.

Note: The following results are not those in the text of the CSR, but are taken from the actual data in the tables in the CSR, Table 23, onwards. The results below include both favourable and unfavourable results of QOL assessments and do not use only selected favourable data, as in the CSR. The data showed the percentage of patients (responders) whose ratings improved by 10 points on the questionnaire scales for the QLQ-C30 and QLQ-OV28 scales. The difference between the response rates (Arm 2 [CT+BV] – Arm 1 [CT]) was shown and a 95%CI interval estimated. A negative result in the symptom scale showed a beneficial effect with symptom improvement, a positive result showed that symptoms worsened.

Since the Global Health Status was an overall measure of QOL, this will be specifically presented. For HADS, a difference of 1.5 points was used, and for FOSI a difference of 2 points.

1. Global Health Status/Quality of Life in EORTC QLQ-C30

Compliance: The compliance rate for the CT and CT+BV groups were 94.5% and 93.9% respectively at baseline falling to 42.4% and 62.2% at Week 30.

Outcome: The results were presented at weeks 8/9, 16/18, 24 and 30, and each assessment included 5 functional scales, 10 symptom scales and one Global Health Status (GHS). Since it is not possible to present so much data in this evaluation, the results from weeks 8/9 and week 30 are presented in summary from Table 114, page 513 CSR.

For all outcomes of the functional and symptom scales, the CI of the difference between the arms included 0, so that no significant difference was shown between the two arms.

The CI values for difference in the GHS at weeks 8/9 were -2.4 to 10.7, and at week 30, -9.5 to 20.6.

Conclusion: No benefit of added bevacizumab to the HRQoL was demonstrated in this assessment.

2. Quality of Life Questionnaire-OV28

Compliance: The compliance rate for the CT and CT+BV groups were 89.0%% and 88.3% respectively at baseline falling to 42.4% and 54.9% at Week 30.

Outcome: The percentages of responders of those patients assessed before randomisation at weeks 8/9 were 19.4% (95%CI 10.4 to 31.4%) in the CT arm and 25% (CI 16.9 to 34.7%), with a difference of 5.6% (CI -8.7% to 19.9%) and a p value of 0.45. At week 30, the rate for the CT arm was 25% (CI 3.2 to 65.1%), and for the CT+BV arm 26.5% (CI 12.9% to 44.4%) with a difference of 1.5% (CI -40.0% to 42.7%) and a p value of 1.0.

The results were also analysed by considering the change in actual point score during the trial, although this was not a measure defined pre-treatment. Two scales, one Functional and the other Symptomatic were used.

Functional Scale: This scale assessed 3 conditions – body image, attitude to disease/treatment, sexuality. The scores at baseline were balanced between the two arms. Table 107, page 500 CSR, showed the differences in the scores with their 95% CI intervals. At week 8/9 and week 30 the CI for all 3 conditions had CIs that included 0, showing no significant difference between arms.

Symptomatic Scale: This scale assessed 9 symptoms – abdominal/GI symptoms (NOT DEFINED IN THE APPLICATION REPORTS), hair loss, peripheral neuropathy, hormonal/menopausal symptoms, taste difference, muscle and joint pain, hearing, frequent urination, and skin problems. For all, the CI for the difference between the symptom scores for each arm overlapped, and the p values showed no significant difference.

For the symptom category abdominal/GI symptoms at week 8/9, the percentage of responders in the CT arm was 19% (CI 11.3% to 29.1%), and in the CT+BV arm, 27.9% (CI 20.1% to 36.7%), with a p value of 0.19 (rounded). Similarly, no significant difference was found for the other times assessed (weeks 16/18), week 24 and week 30.

Conclusion: Of the 3 functional states and 9 symptoms assessed, including abdominal/GI symptoms, none showed a significant benefit from the addition of bevacizumab to CT.

3. The National Comprehensive Cancer Network (NCCN)/FACT Ovarian Symptom Index (FOSI)

The FACT/NCCN Ovarian Symptom Index (FOSI) is an index designed to measure Physical well-being (7 items), Social/Family well-being (7 items), Emotional well-being (6 items), Functional well-being (7 items), and Additional Concerns (12 items)in patients with ovarian cancer.

Comment:

> No directions were given in any of the 4 versions of the trial protocol on the use of this instrument. The symptoms listed in the Physical Well-being section were general, eg pain, nausea, feeling ill, while those in the Additional Concern included symptoms more closely related to ovarian cancer eg abdominal swelling, control of bowels.

In the assessment of differences in scores, a difference of 2 points was regarded as clinically significant. The percentage at baseline was calculated on the basis of the number of patients who did not die, were not withdrawn from the study, did not enter the safety follow-up period, did not start the non-protocol specified anti-cancer therapy, or did not switch from the CT arm

to the CT + BV arm at the start of the assessment window. After baseline, the denominator excluded patients who had experienced PD at the start of the assessment window.

Compliance: A similar percentage (87%) of patients in each arm completed this questionnaire at baseline. At week 30, 42.4% in the CT arm and 52.4% in the CT+BV arm had completed the questionnaire.

Outcome: At week 8/9 the median scores in each arm were 23.0, and at week 30, 25.0 in the CT arm and 25.2 in the CT+BV arm.

Conclusion: No difference was demonstrated using this HRQoL instrument.

4. Hospital Anxiety Depression Scale (HADS)

Hospital Anxiety Depression Scale (HADS) is a self-rating scale of 14 items designed to measure anxiety and depression (7 items for each subscale). The HADS comprises statements which the patient rates based on their experience over the past week. In the assessment of differences in scores, a difference of 1.5 points was regarded as clinically significant. Estimation were as for the FOSI questionnaire.

Compliance: A similar percentage (92.3% in the CT arm and 91.1% in the CT+BV arm) of patients completed this questionnaire at baseline. At week 30, 42.4% in the CT arm and 61.0% in the CT+BV arm had completed the questionnaire.

Outcome: At week 8/9 the median scores for anxiety were 8.0 in the CT arm and 7.0 in the CT+BV arm; and for depression, 5.0 and 5.8 respectively. At week 30, the scores for anxiety were 7.0 and 6.0 in the respective arms and for depression, 6.0 and 4.0.

Conclusion: With the exceptions of the results for depression at 30 weeks and for anxiety at 24 weeks (not shown above), no significant difference was found.

Exploratory Endpoints

Time to Biological Progression by CA-125:

Analysis of time to biological progression by CA-125 without requiring the subsequent CA-125 measurement for confirmation was performed. In this analysis, time to biological progression, if occurring after a RECIST PD date + 35 days, were censored at the last CA-125 assessment date prior to RECIST PD date + 35 days.

In the CT and CT+BV arms 51 of 182 patients and 70 of 179 respectively showed biological progression as defined, with a median time to progression of 7.1 months (95%CI 6.01 to 9.49 months) in the CT arm, and 8.5 months (CI 7.49 to 11.27 months). The unstratified HR was 0.716 (95% CI 0.498 to 1.030; log-rank p=0.071); and the stratified HR 0.640 (95% CI: 0.434, 0.944; log-rank p = 0.023).

Comment:

> No significant difference was shown in the median times to progression. The CIs of both the median times and the HR ratios overlapped, and the p value (unstratified) was 0.071.

CA-125 Response rate

CA-125 response was evaluable if patients had a pre-treatment CA-125 measurement within 14 days prior to the start of protocol treatment with a level of at least 2 ×ULN. A CA-125 response was defined according to the GCIG criteria as a ≥ 50% decrease, which had to be confirmed by another measurement at least 28 days later. A total of 150 patients in the CT arm and 152 patients in the CT+BV arm had CA-125 levels at least 2 × ULN at baseline. The CA-125 response rate was 52.0% in the CT+BV arm compared with the 27.3% in the CT arm. The absolute difference in CA-125 response rate between the CT+BV arm and the CT arm was 24.6% (95% CI: 14.0%, 35.3%; p < 0.0001).

7.1.4.2.2. Frequency of paracentesis

Frequency of paracenteses performed on patients while on-study was summarized by treatment period for patients with ascites at baseline, as well as patients without ascites at baseline.

Patients with ascites at baseline were well balanced between the two arms, with 54 patients in the CT arm and 59 patients in the CT+BV arm. Among patients in the CT arm, 8 patients required a total of 15 post-dosing paracenteses during the protocol treatment periods (cycles) 1 through 8 on the basis of the data captured on the CRF. In contrast, in the CT+BV arm, only one patient required one post-dosing paracentesis, which occurred during treatment cycle 1.

Comment:

No formal statistical analysis was performed, but the number of patients in total requiring paracentesis during the 8 treatment periods was substantially less among patients treated with CT+BV. However a foot-note to Table 26, p135 CSR, states that one patient in the CT group had multiple paracenteses, but the number of paracenteses on that patient was not given. It appears that this one patient who required multiple paracentesis procedures may have been counted in each treatment period when paracenteses were done. It is not clear if the figure of 8 in the CT includes this patients on multiple occasions. In assessing these data, it is important to know how many paracentesis procedures each patient had throughout. The sponsor should provide this information (see Section 11.1.2.5 Assessment of Response of Malignant Ascites to Treatment).

7.1.5. Evaluator's conclusions on clinical efficacy of AVASTIN to treat patients with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens.

The Clinical Overview did not provide a section of Conclusions, only one of Benefits. The Summary of Clinical Efficacy (SCE) gives a Conclusions section. Any differences from the latter are identified in the following.

7.1.5.1. Primary end-point:

The regimen of bevacizumab in combination with chemotherapy (paclitaxel, topotecan, or PLD) resulted in a statistically significant and clinically important improvement in investigator-assessed PFS from a mean value of 3.4 months (95% CI 2.10-3.75) in the CT arm to 6.8 months (95%CI 5.62-7.79), with a stratified HR = 0.384; 95% CI: 0.300, 0.491; log-rank p-value < 0.0001. Subgroup and sensitivity analyses, including simulated IRC results, supported these results.

Note: Addendum - As a result of requests to the sponsor (under Section 31, first round evaluation), corrections of incorrect dates of trial events found and submitted by the sponsor, and an independent blinded radiological review of assessments of PD by investigator's (submitted as a response to Section 31 request), the figures above have changed a little but the benefit and significance of the improvement seen with CT+BV has been maintained. The changes were as follows:

PFS After correction of dates of event for 1 patient: PFS 3.4 months (95%PI 2.10-3.75) and 6.7mths (5.62-7.79) in the CT+BV arm; HR 0.379 (0.296-0.485), log-rank p value<0.0001;

Time to Treatment Failure (time from randomization to discontinuation of treatment for any reason, including progressive disease or death or withdrawal of treatment due to adverse events/unacceptable toxicity, withdraw consent, symptomatic deterioration, or other reason considered progressive) : **TTF** 3.4 months (interquartile range 1.8-5.5) in the CT arm and , and 5.4 months (interquartile range 3.4-9.3) in the CT+BV arm; HR 0.422 (95% CI: 0.333, 0.536; log-rank p-value < 0.0001).

PFS using data from the Independent Review Committee after reviewing PD as assessed by investigators: PFS 3.9 months (95% CI: 3.4, 5.2) in the CT arm and 8.1 months (95% CI: 6.9, 9.6) in the CT+BV arm; HR of 0.484 (95% CI: 0.370, 0.632; p < 0.0001).

Secondary end-points:

- A statistically significant and clinically meaningful improvement in ORR was observed in the small number of responders. The ORR was increased from 12.5%, n=18,[CI 7.1% to 17.9%] in the chemotherapy alone arm to 28.2%, n=40,[CI 20.8 to 35.6%] in the bevacizumab combination arm, with a p value of 0.001 (unstratified).
- The **ORR of the 72 patients who received monotherapy** with bevacizumab after disease progression to bevacizumab monotherapy cannot be assessed without further data from the sponsor (requested).

Comment:

This outcome was not presented in the CSR

Note: Addendum – The sponsor responded (Section 11.1.2.1 Continuing treatment with bevacizumab after disease progression) that these data were not available due to the study design.

- The **median duration of objective response** was 5.4 months (CI (3.81-9.23months) in the CT arm and 9.4 months (6.60-11.63months) in the CT+BV arm. Although the p value was 0.02, the overlapping CI intervals weaken any conclusion of the benefit of BV as measured by this outcome.

Comment:

This outcome was not included in the conclusions in the SCE.

- Analysis of overall survival at one interim and at the final analysis found these analyses did not meet statistical significance. At the time of the final OS analysis when 73% of patients had died, the median duration of survival was 13.3 months (CI 11.89-16.43months) in the CT arm and 16.6 (CI 13.70-18.99 months) in the CT+BV arm, with a HR (stratified) of 0.88 (CI 0.69-1.14), and a p value of 0.35 (log-rank).

  Note: Addendum - After the inclusion of the dates of death of 2 additional patients by the sponsor, the following results were obtained: 276 (73.7%) rather than 274 (73.1%) patients had died. The median duration of survival was unchanged in each arm and the HR was 0.87 (95%CI 0.678-1.116), and a p value of 0.27 (log-rank).

- The following four instruments used in the assessment of the Health Related Quality of Life (HRQoL) failed to show any significant clinical benefit of combining bevacizumab with chemotherapy – the functional, the symptom and the Global Health Scales of EORTC QLQ-30; the functional scale, and 8 of 9 symptoms in the OV28 instrument; the 19 symptoms in the FOSI instrument and the HADS scale.

Comment:

This conclusion differs from that in the Clinical Overview, SCE and CSR. The applicant selected one outcome (abdominal/GI symptom OV28), ignored the approximately 28 other negative symptom outcomes in the FOSI and OV28 instruments, made the one outcome the only secondary objective for HQoL and placed all the other negative outcomes in an 'Exploratory Outcomes' category, contrary to the trial protocol.

8. Clinical safety

8.1. Studies providing evaluable safety data

The pivotal study, MO22224, provided evaluable safety data.

For the safety analyses, the data cut-off date for this report was 25 January 2013. The safety analyses were based on the safety population. The denominator used in the analyses was the number of patients who actually received each treatment rather than the treatment to which patients were randomized. The primary safety analyses were conducted to evaluate the safety of bevacizumab plus the chemotherapy in comparison to chemotherapy alone. In the CT arm, if the patient had received crossover bevacizumab monotherapy, only data on or prior to the crossover were included in the primary analyses. The data after the crossover for these patients were summarized separately for evaluation of safety parameters for the crossover bevacizumab monotherapy period (see Section 8.6.2 After Cross Over Treatment).

The definition and reporting requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 was followed.

8.1.1. Pivotal efficacy study MO22224

In the pivotal efficacy study,

- General adverse events (AEs) were assessed by medical examination of the patient at each visit during the treatment period. How patients' reports of symptoms were obtained and collected was not stated. All Serious Adverse Events (SAEs) were recorded up to 30 days after the last dose of trial drug, presumably CT, CT+BV or bevacizumab alone. All SAEs considered having a causal relationship to these treatments (as considered by the investigator) were recorded, regardless of time elapsed since last dose, even if study has stopped, including SAEs related to trial (study) procedures. After 4 weeks following the last study drug intake or administration, AEs (grades 2–5) were followed up every 2 months.
- Adverse events, graded using NCI CTCAE, Version 3.0, were coded using the most recent version of the MedDRA. Only adverse events ≥Grade 2 were recorded in the eCRF in this study. The proportion of patients experiencing at least one adverse event was reported by preferred term and treatment arm. Patients were classified by system organ and preferred toxicity term according to the maximum reported severity.
- AEs of particular interest were those known to be associated with bevacizumab treatment and were subjected to a separate analysis. Specifically, the events analysed as stated in the protocol were all Grade 2 or greater Reversible Posterior Leuokoencephalopathy Syndrome (RPLS or PRES), ATE (arterial thromboembolic event), CNS bleeding, GI perforation, fistula or abscess, and febrile neutropenia; and Grade 3 or greater hypertension (HTN), proteinuria, wound healing complication, non-CNS bleeding, venous thromboembolic event (VTE), CHF, and peripheral sensory neuropathy. Adverse events of special interest were presented as categories, each of which consists of multiple MedDRA preferred terms (e.g., 'hypertension' includes blood pressure increased, HTN, and malignant HTN).
- Laboratory tests, including hematology, serum chemistry, and urinalysis were performed by local laboratories per local standard of care. These data were not included in the clinical database for this CSR.

8.1.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.1.3. Dose-response and non-pivotal efficacy studies

Not applicable.

8.1.4. Other studies evaluable for safety only

No other studies provided safety data in the present application.

8.1.5. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.2. Patient exposure

Exposure to treatment drugs in the CT and the CT+BV arms were evaluated and compared and the median number of cycles and dose intensity for each chemotherapy agent evaluated. Dose intensity indicated the actual amount of chemotherapy that a patient received compared with the expected dose relative to the length of time the patient was on study chemotherapy.

For the CT and CT+BV arms, the median duration of treatment was 10.3 and 19.9 weeks respectively, and the median number of cycles 3.0 and 6.0.

For paclitaxel, the median number of cycles was 4.0 and 6.0 cycles in the CT and CT+BV arms, respectively. The percentage of patients who received 7 cycles or more was lower in the CT arm (12.7%) than in the CT+BV arm (33.3%). The median total paclitaxel dose was 2055.0 mg in the CT arm compared with 2794.0 mg in the CT+BV arm. The median dose intensity was 91.8% in the CT arm compared with 87.8% in the CT+BV arm.

For topotecan, the median number of cycles was twice as high in the CT+BV arm as compared with the CT arm (CT: 3.0 cycles vs. CT+BV: 6.0 cycles). The median total topotecan dose was also twice as high in the CT+BV arm as compared with the CT arm (CT: 43.2 mg vs. CT+BV: 87.7 mg). The median dose intensity was 75.0% in the CT arm compared with 84.0% in the CT+BV arm.

For PLD, the median number of cycles was 3.0 and 4.0 cycles in the CT and CT+BV arms, respectively. The median total PLD dose was 230.0 mg in the CT arm and 277.0 mg in the CT+BV arm. The median dose intensity was similar between treatment arms (CT: 100% vs. CT+BV: 99.5%).

Bevacizumab Exposure: Only patients in the CT+BV arm received bevacizumab prior to disease progression. The median number of treatment cycles was 6.0 cycles (range: 1–32). The median duration of bevacizumab treatment was 22.1 weeks, and the median dose intensity was 94.4%. The median total dose of bevacizumab was 6750.0 mg.

Of 72 patients in the CT arm who received crossover bevacizumab monotherapy after documented disease progression (optional cross-over phase), the median number of cycles received was 4.5 cycles (range: 1–19). The median duration of bevacizumab treatment was 11.6 weeks, and the median total dose of bevacizumab was 4194.0 mg.

Comment: Dose-intensity (DI) was not provided for the latter group.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Pivotal study

Only Grade 2–5 adverse events were recorded in this study. A total of 158 patients (87.3%) in the CT arm and 163 patients (91.1%) in the CT+BV arm experienced Grade 2–5 adverse events.

8.3.1.1.1. Most frequent adverse events (AEs) by system organ class (SOC)

1. Before Cross-over Treatment: The SOCs most frequently reported (i.e., in ≥ 25% of patients in either treatment arm) were:
    a. Blood and Lymphatic System Disorders (CT: 45.9% vs. CT+BV: 43.6%)

b. Gastrointestinal Disorders (CT: 40.9% vs. CT+BV: 47.5%)

c. General Disorders and Administration Site Conditions (CT: 40.9% vs. CT+BV: 42.5%)

d. Infections and Infestations (CT: 23.2% vs. CT+BV: 34.6%)

e. Skin and Subcutaneous Tissue Disorders (CT: 17.7% vs. CT+BV: 35.8%), Vascular Disorders (CT: 9.9% vs. CT+BV: 25.7%).

2. After Cross-over Treatment (Bevacizumab monotherapy): During bevacizumab monotherapy, a total of 42 of 72 patients (58.3%) experienced Grade 2–5 adverse events, the majority of which were Grade 2. The most frequently reported SOCs occurring in ≥10% of patients were Infections and Infestations (16.7%), Vascular Disorders (16.7%), General Disorders and Site Administration Conditions (13.9%), Gastrointestinal Disorders (13.9%), and Musculoskeletal and Connective Tissue Disorders (11.1%).

8.3.1.1.2. Most frequent AE by preferred term

1. Before Cross-over Treatment: The most frequently reported adverse events occurring in ≥20% of patients in either arm were fatigue (CT: 26.5% vs. CT+BV: 27.4%), anemia (CT: 26.5% vs. CT+BV: 19.6%), and neutropenia (CT: 25.4% vs. CT+BV: 30.7%).

2. After Cross-over Treatment: The most commonly reported Grade 2–5 adverse events were HTN (12.5%) and fatigue (11.1%).

8.3.1.1.3. Differences in the incidence of Gd2-5 AEs in the two arms of the trial by preferred terms

Grade 2–5 adverse events showing at least 10% greater difference in incidence in the CT+BV arm than the CT arm were hypertension (CT: 5.5% vs. CT+BV: 19.0%), proteinuria (CT: 0.6% vs. CT+BV: 12.3%), and peripheral sensory neuropathy (CT: 7.2% vs. CT+BV: 17.9%).

Grade 2–5 adverse events that showed a difference of at least 5% higher incidence in the CT+BV arm were mucosal inflammation (CT: 5.5% vs. CT+BV: 12.8%), infection (CT: 4.4% vs. CT+BV: 10.6%), palmar-plantar erythrodysaesthesia syndrome (CT: 5.0% vs. CT+BV: 10.6%), neutropenia (CT: 25.4% vs. CT+BV: 30.7%), and epistaxis (CT: 0 vs. CT+BV: 5.0%).

The only Grade 2–5 adverse event that showed a difference of at least 5% higher incidence in the CT arm was anemia (CT: 26.5% vs. CT+BV: 19.6%).

8.3.1.1.4. Grade 3-5 AEs

1. Before Cross-over Treatment: The incidence of Grade 3–5 adverse events was 59.2% in the CT+BV arm compared with 53.0% in the CT arm.

   Grade 3–5 adverse events for which the incidence was ≥2% higher in the CT+BV arm were hypertension, palmar-plantar erythrodysaesthesia syndrome, and general physical health deterioration. Grade 3–5 adverse events for which the incidence was ≥2% higher in the CT arm were leukopenia, abdominal pain, ascites, vomiting, fatigue, and dyspnea.

2. After Cross-over Treatment: During crossover bevacizumab monotherapy, Grade 3–5 adverse events occurred in 19 of 72 patients (26.4%). Sixteen patients (22.2%) experienced Grade 3 adverse events; events that occurred in > 1 patient included fatigue (3 patients), HTN (3 patients), abdominal pain (2 patients), diarrhea (2 patients), and pleural effusion (2 patients). Two patients (2.8%) experienced Grade 4 adverse events (transient ischemic attack and PRES.

8.3.1.1.5. Grade 5 AEs

1. Before Cross-over Treatment: Grade 5 adverse events represent deaths that occurred due to an adverse event within 30 days of last protocol treatment (safety follow-up). A total of 5

patients (2.8%) in the CT arm and 6 patients (3.4%) in the CT+BV arm had Grade 5 adverse events.

In the CT arm, the following Grade 5 adverse events were reported: multi-organ failure, cardiac failure, peritonitis, septic shock and sepsis.

In the CT+BV arm, the following Grade 5 adverse events were reported: 2 patients with pneumonia aspiration, and one patient each with cardiac arrest, general physical health deterioration, sepsis and shock. A listing of these events and patient narratives were provided.

2. After Cross-Over Treatment: During bevacizumab monotherapy, one patient (1.4%) experienced a Grade 5 GI haemorrhage. The event that was considered possibly related to bevacizumab treatment occurred in an [information redacted] old patient.

8.3.1.2. Other studies

Not applicable.

8.3.2. Treatment-related adverse events (adverse drug reactions)

8.3.2.1. Pivotal study

Comment:

No assessment of treatment-related adverse events as such was provided in the present application in the CSR, the Clinical Overview, the Summary of Clinical Safety and the SAP Amendment 2. The sponsor is asked to give reasons for this omission. The wording in Section 5.3, Overall Adverse Events, Clinical Overview, however indicates that the AEs reported (as in the CSR) were to be taken as treatment-related, and will be considered as such. It is noted that Listing 709, CSR, in 80 pages of tables lists the AEs for each patients and the relationship to treatment drugs and that causal relationships were provided for the AEs of special interest.

8.3.2.2. Other studies

Not applicable.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Pivotal study

Deaths

1. **Full trial period:** As of the data cut-off date (25 January 2013), a total of 136 patients (74.7%) in the CT arm and 128 patients (71.5%) in the CT+BV arm had died. The majority of these deaths were due to ovarian cancer and disease progression; 130 patients (71.4%) in the CT arm died due to ovarian cancer and disease progression compared with 119 patients (66.5%) in the CT+BV arm.

   A total of 15 patients (6 in the CT arm and 9 in the CT+BV arm) died due to adverse events, which occurred at any point during the study-follow-up period and these included the treatment-emergent Grade 5 adverse events reported up to safety follow-up. For on-treatment Grade 5 adverse events reported up to safety follow-up, see above.

   In the CT arm, two patients had septic shock. The remaining four deaths were: cardiac failure, multi-organ failure, peritonitis, and GI hemorrhage (this patient died after she switched to bevacizumab monotherapy).

   Of the 9 deaths not reported as ovarian cancer or PD in the CT+BV arm, pneumonia aspiration and sepsis were reported in 2 patients each. The remaining five deaths were: cardiac arrest, cardiopulmonary failure, gastrointestinal disorder, general physical health deterioration, and Shock.

2. **After Cross-Over Treatment:** There were no deaths additional to that reported above as a Grade 5 AE (GI haemorrhage).

Serious Adverse Events

The incidence of Grade 2–5 serious adverse events was 31.1% in the CT+BV arm compared with 27.1% in the CT arm. All Grade 5 adverse events were serious and were described above.

1. **Before Cross-Over Treatment:** Grade 2–5 serious adverse events that occurred in ≥ 2% of patients in either treatment arm were vomiting (CT: 3.9% vs. CT+BV: 0), sub-ileus (CT: 3.3% vs. CT+BV: 2.2%), abdominal pain (CT: 2.8% vs. CT+BV: 2.2%), dyspnea (CT: 2.8% vs. CT+BV: 2.2%), pulmonary embolism (2.8% vs. 1.1%), ileus (CT: 1.1% vs. CT+BV: 2.2%), and HTN (CT: 0 vs. CT+BV: 2.2%).

   In the CT arm, vomiting occurred with an incidence ≥2% compared with the CT+BV arm, and in the CT+BV arm, HTN occurred with an incidence ≥2% compared with the CT arm.

2. **After Cross-Over Treatment:** During bevacizumab monotherapy, 12/ 72 patients (16.7%) experienced Grade 2–5 serious adverse events. Six patients (8.3%) had Grade 3 serious adverse events, and 2 patients (2.8%) had Grade 4 events (transient ischemic attack and PRES). One patient (1.4%) experienced a Grade 5 serious adverse event of GI haemorrhage.

8.3.3.2. Other studies

Not applicable.

8.3.4. Discontinuation due to adverse events

8.3.4.1. Pivotal study

A higher percentage of patients in the CT+BV arm (43.6%) than in the CT arm (8.8%) experienced Grade 2–5 adverse events that led to withdrawal of study treatment with chemotherapy or bevacizumab. The most common (i.e., occurring in ≥2% of patients in either arm) Grade 2–5 adverse events that led to study treatment discontinuation were peripheral sensory neuropathy (CT: 1.7% vs. CT+BV: 4.5%), palmar-plantar erythrodysaesthesia syndrome (CT: 0.6% vs. CT+BV:

3.4%), fatigue (CT: 0% vs. CT+BV: 3.4%), HTN (CT: 0% vs. CT+BV: 2.8%), neutropenia (CT: 0% vs. CT+BV: 2.2%), and proteinuria (CT: 0% vs. CT+BV: 2.2%).

Grade 2–5 adverse events that led to discontinuation of treatment by chemotherapy regimen (paclitaxel, topotecan, or PLD) were:

- Paclitaxel: CT 9(16.4%), CT+BV 27(45%). Greater percentage in CT+BV = 29%
- Topotecan: CT 5(7.9%), CT+BV 12(21%). Greater percentage in CT+BV= 13%
- PLD: CT 2(3.2%), 13(21%). Greater percentage in CT+BV= 18%

The number of specific adverse events whose frequency was 5% or more greater in the CT+BV arm than in the CT arm were as follows for each of the three drugs:

- Paclitaxel – neutropenia (+5%), fatigue (+6.7%), peripheral sensory neuropathy (+6.2%), nail disorders [3 terms] (+11.6%)
- Topotecan - 0
- PLD - Palmar-Plantar Erythrodysaesthesia Syndrome (+6.5%).

Grade 2–5 adverse events that led to discontinuation of bevacizumab treatment were reported in 49 (27.4%) patients. The most common SOCs and specific events respectively were gastrointestinal (n=15, 8.4%; ileus and subileus n=6, abdominal pain n=5,), vascular disorders (n=11, 6.1%; HTN and HTN crisis n=6), and renal and urinary disorders (n=8, 4.5%; proteinuria n=4).

8.3.4.2. Other studies

Not applicable.

8.4. Laboratory tests

Laboratory measurements, including hematology, serum chemistry, and urinalysis, were performed by local laboratories per local standard of care. These data were not included in the clinical database for this CSR.

Comment:

No results for laboratory tests were presented. However the listing of AEs (Listing 709, CSR) included the preferred terms that are defined from laboratory tests, such as neutropenia, and Grade 3 GGT increase. Presumably the investigators used their local data to define such events and then reported them as AEs, with causality. To assess the risk-benefit of the proposed treatment in this group of patients, the AEs related to haematology, liver function and renal function needs to be considered. These data will be requested from the sponsor (see response, Section 11.1.3.3 Absence of Assessments of Laboratory Tests).

8.4.1. Liver function

8.4.1.1. Pivotal study

Information not provided – see above.

8.4.1.2. Other studies

Not applicable.

8.4.2. Kidney function

8.4.2.1. Pivotal study

Information not provided –see above.

8.4.2.2. Other studies

Not applicable.

8.4.3. Other clinical chemistry

8.4.3.1. Pivotal study

Information not provided.

8.4.3.2. Other studies

Not applicable.

8.4.4. Haematology

8.4.4.1. Pivotal study

Information not provided (see above) except for haematological AEs of special interest – bleeding and febrile neutropenia (see Sections 8.5.4 and 8.6.1.4).

8.4.4.2. Other studies

Not applicable.

8.5. Adverse events of special interest - pivotal study

A listing and the narratives of patients who experienced any adverse events of special interest of Grade ≥ 2, Grade ≥ 3, or Grade ≥ 4 were provided in the CSR, in addition to the following assessment.

8.5.1. Before cross-over treatment

8.5.1.1. Arterial thromboembolic events

Grade 2–5 ATEs were reported in one patient (0.6%) in the CT arm and 3 patients (1.7%) in the CT+BV arm. In the CT arm, a patient experienced a Grade 3 pulmonary artery thrombosis event possibly related to topotecan and was ongoing at the clinical cut-off. In the CT+BV arm, ATEs were a Grade 4 ischemic stroke, considered possibly related to bevacizumab treatment and unrelated to PLD; a Grade 3 arterial occlusive disease event reported as possibly related to both topotecan and bevacizumab, that resolved with sequelae; and a Grade 3 arterial embolism event considered possibly related to bevacizumab treatment, and unrelated to topotecan treatment and which resolved.

8.5.1.2. Bleeding

No patients experienced CNS bleeding.

Grade 3–5 non-CNS bleeding events were reported in 2 patients (1.1%) in each treatment arm - in the CT arm, a Grade 3 GI hemorrhage assessed as unrelated to PLD, and a Grade 3 vaginal hemorrhage assessed as unrelated to paclitaxel, and resolved; in the CT+BV arm, a Grade 4 GI hemorrhage assessed as possibly related to bevacizumab and unrelated to PLD, and was ongoing at the time of death on Day 57, and a Grade 3 hemorrhagic ascites assessed as possibly related to bevacizumab and unrelated to topotecan.

Comment:

> [information redacted] was the patient with the Grade 4 GI haemorrhage (Section 6.9.2, 'Bleeding' in the CSR). The event is not listed in the Listings or Narratives of Grade 5 Events (Patient Deaths), but is in Listing 715, CSR, in which the Primary Cause of Death is given as 'Ovarian cancer progression' with the MedDRA term 'Ovarian Cancer'. The sponsor should be asked why this death should not be classified as Grade 5, resulting from the AE of GI bleeding [see response Section 11.1.3.6 Why was a Grade 4 event (GI haemorrhage) not classified as a Grade 5 event?].

8.5.1.3. Congestive cardiac failure

Grade 3–5 CHF was reported in one patient (0.6%) in each treatment arm - in the CT arm, a Grade 5 cardiac failure event assessed as unrelated to PLD chemotherapy, and in the CT+BV arm, Grade 3 left ventricular dysfunction that was considered unrelated to bevacizumab and probably related to PLD; this event resolved.

8.5.1.4. Febrile neutropenia

Grade 2–5 febrile neutropenia was reported in one patient in each treatment arm - in the CT arm, a Grade 4 event of febrile neutropenia that was assessed as probably related to paclitaxel treatment and was ongoing at the time of the clinical cut-off, and in the CT+BV arm, a Grade 3 event of febrile neutropenia that was assessed as unlikely related to bevacizumab treatment, probably related to PLD treatment, and resolved.

8.5.1.5. Fistula and abscess

Grade 2–5 fistula and abscess events were reported in no patients in the CT arm and 4 patients (2.2%) in the CT+BV arm as follows:

- A [information redacted] patient developed a Grade 2 female genital tract fistula that was unrelated to bevacizumab or topotecan treatment, occurred after 212 days from start of treatment, and resolved
- A [information redacted] patient developed a Grade 2 vesical fistula that occurred 7 days after the start of treatment and that was unrelated to bevacizumab or paclitaxel treatment, and was ongoing at the time of the clinical cut-off
- A [information redacted] patient developed a Grade 3 vesical fistula that occurred 169 days after start of treatment, was assessed as probably related to bevacizumab treatment and unrelated to paclitaxel treatment, and was ongoing at the time of the clinical cut-off
- A [information redacted] patient developed a Grade 4 female genital tract fistula that occurred 34 days after start of treatment, was assessed as possibly related to bevacizumab treatment and unrelated to paclitaxel treatment, and resolved; the patient withdrew from study treatment.

No Grade 5 fistulae or abscesses were reported.

Comment:

The difference in incidence between the two arms is striking for an AE known to be associated with bevacizumab treatment. Two of the events were assessed by investigators as unrelated to bevacizumab treatment. The lack of relationship to bevacizumab would be more convincing if information were given whether the patients were receiving treatment at the time of first occurrence of the AE, what the chemotherapy agent(s) was, and whether the patients' disease was responding, stable or progressing. This question will be asked of the sponsor (see response Section 11.1.3.4 Adverse Event of Special Interest – Abscess and Fistula).

8.5.1.6. Gastrointestinal perforation

During the treatment period, one patient (0.6%) in the CT arm and 3 patients (1.7%) in the CT+BV arm experienced Grade 2–5 GI perforations as follows:

- In the CT arm, a [information redacted] patient experienced Grade 5 peritonitis that occurred after 160 days on treatment and was assessed as possibly related to PLD chemotherapy treatment
- In the CT+BV arm, a [information redacted] patient experienced a Grade 4 intestinal perforation that occurred 89 days after start of treatment and was assessed as probably related to bevacizumab and unrelated to topotecan; the event resolved
- In the CT+BV arm, a [information redacted] patient had a Grade 3 ileal perforation event that occurred 94 days after start of treatment and was assessed as possibly related to bevacizumab and possibly related to topotecan; the event was ongoing at the time of the clinical cut-off. This patient also experienced a Grade 3 arterial embolism event
- In the CT+BV arm, a [information redacted] patient had a non-serious Grade 2 anal fistula event that was assessed as possibly related to bevacizumab and unlikely related to paclitaxel. The event occurred 57 days after start of treatment and as of the clinical cut-off, the event was resolved.

In addition, a [information redacted] patient in the CT+BV arm developed a Grade 4 GI perforation that occurred > 30 days after the last doses of paclitaxel and bevacizumab ; the event occurred 349 days after start of treatment and after documentation of PD and > 30 days after start of treatment with doxorubicin. The investigator assessed the event as related to bevacizumab and unrelated to paclitaxel. The sponsor stated that 'additional data indicated that other possible etiological factor for the event included ovarian cancer.'

Comment:

> The narrative history of this patient ([information redacted]) shows the patient developed a large pelvic mass and peritoneal 'carcinosis', and was assessed as having PD. Whether the mass was an abscess or malignant was not investigated. At the time she had been off treatment with bevacizumab for 13 days (24 Dec 2010-6 Jan 2011). On 28 Jan 2011, she developed 'neoplastic fever' and 'pelvic necrosis'. The causal relationship for the AE assigned by the investigator to bevacizumab treatment in not in the sponsor's list above. Presumably this is because the sponsor has chosen the second date (35 days post bevacizumab treament) instead of the earlier date (13 days). However some doubt remains about the nature of the pelvic mass first diagnosed (6 Jan 2011), so I consider this more likely to be an 'on trial' AE of bevacizumab (within 30 days of ceasing treatment).
>
> The number of these events causally related to bevacizumab therefore was four.

8.5.1.7. Hypertension

Grade 3–5 HTN events were reported in 1.1% of patients in the CT arm and 7.8% of patients in the CT+BV arm.

In the CT arm, 2 patients experienced Grade 3 HTN events.

In the CT+BV arm, one patient experienced a Grade 3 event of increased blood pressure and 12 patients experienced Grade 3 HTN events. In the CT+BV arm, a [information redacted] patient experienced a Grade 4 hypertensive crisis assessed as probably related to bevacizumab and unrelated to PLD treatment; the event resolved.

Comment:

> The Special Interest AE category of 'Hypertension' includes the MedRA preferred terms 'Blood Pressure Increased' (includes the specific AEs, 'blood pressure increasing', 'increase (sic) blood pressure'); and 'Hypertension' (includes the specific AEs, 'arterial high blood pressure', 'increased arterial hypertension', 'high blood pressure', 'high bloodpressure'(sic), 'hypertension', 'hypertension intermittent', 'hypertension/high blood pressure', 'increase hypertension', and 'increase of arterial hypertension'.

8.5.1.8. Peripheral sensory neuropathy

In the CT arm, Grade 3 peripheral sensory neuropathy adverse events were reported in 5 patients (2.8%) all of whom were in the paclitaxel chemotherapy cohort.

In the CT+BV arm, Grade 3 peripheral sensory neuropathy adverse events were reported in 8 patients (4.5%); 7 of whom were in the paclitaxel chemotherapy cohort and one patient who was in the PLD chemotherapy cohort.

In all but one patient, the adverse event was considered possibly or probably related to chemotherapy treatment. In all cases, bevacizumab treatment was considered unrelated or unlikely. As of the clinical cut-off, 7 patients (2 patients in the CT arm and 5 patients in the CT+BV arm) had peripheral sensory neuropathy events ongoing.

No patient in either arm experienced Grade 4 or Grade 5 peripheral sensory neuropathy events.

8.5.1.9. Proteinuria

Grade 3–5 proteinuria events were reported in no patients in the CT arm and 4 patients (2.2%) in the CT+BV arm. Of the 4 patients in the CT+BV arm, a 71-year-old patient (0.6%) developed Grade 4 nephrotic syndrome assessed as probably related to bevacizumab and unlikely related to PLD, and resolved. The 3 other patients experienced Grade 3 proteinuria events. No patient experienced Grade 5 proteinuria.

8.5.1.10. Reversible posterior leukoencephalopathy syndrome or posterior reversible encephalopathy syndrome

No patient in the CT arm and one patient (0.6%) in the CT+BV arm experienced PRES/RPLS. A [information redacted] patient experienced Grade 3 PRES/RPLS on Study Day 58 that resolved without sequelae and was considered possibly related to bevacizumab treatment.

8.5.1.11. Venous thromboembolic events

Grade 3–5 VTEs were reported in 7 patients (3.9%) in the CT arm and 6 patients (3.4%) in the CT+BV arm. In the CT arm, one patient experienced Grade 3 deep vein thrombosis, 5 patients experienced Grade 4 pulmonary embolism, and one patient developed a Grade 4 venous embolism.

In the CT+BV arm, two patients experienced Grade 3 venous embolism, one patient had Grade 3 pulmonary embolism, one patient had Grade 3 venous thrombosis, and two patients experienced Grade 4 pulmonary embolism.

No patients experienced Grade 5 VTEs.

8.5.1.12. Wound healing complication

Grade 3–5 wound healing complication events were reported in 2 patients (1.1%) in the CT+BV arm. One patient developed a Grade 3 catheter site necrosis and one patient developed a Grade 3 postoperative wound infection. No patients in the CT arm experienced any wound healing complication events.

8.5.2. After cross-over treatment

Of the 72 patients who received crossover bevacizumab monotherapy, 7 patients (9.7%) experienced Grade 3–5 adverse events of special interest: one patient had a Grade 4 transient ischemic attack event and a Grade 3 HTN event, one patient had a Grade 4 RPLS/PRES, two patients had Grade 3 and 5 hemorrhage (non-CNS bleeding), one patient had Grade 3 proteinuria, and two patients had Grade 3 HTN.

8.5.3. Summary and conclusions AEs of special interest

Before Cross-over Treatment: In the CT arm, a total of 5.1% of patients experienced an AE of special interest and 21.8% in the CT+BV arm.

Adverse events of special interest were observed at a higher rate in bevacizumab treated patients by the percentage shown for the following categories:

- Grade 2 or greater - GI perforation (+1.1%), fistula and abscess (+2.2%), RPLS/ PRES (+0.6%)[one patient in the CT+BV arm; 0 in the CT]
- Grade 3 or greater - HTN (+6.7%), peripheral sensory neuropathy (+1.7%), proteinuria (+2.2%), ATE (+1.1%), and wound healing complications (+1.1%).

After Cross-over Treatment: Of the 72 patients who received monotherapy with bevacizumab after disease progression, the frequency of special interest AEs was less that the in the Before Cross-Over group, except for RPLS/PRES with a frequency of 4.2% (n=1).

For bevacizumab, results reported in the Precautions section of the Australian PI were:

- GI perforation and Fistula and Abcess – In metastatic GI and ovarian cancer, serious cases were reported in up to 2% patients
- RPLS/PRES - Two confirmed cases (0.8%) of Posterior Reversible Encephalopathy Syndrome (PRES) were reported in Study AVF4095g (OCEANS).

HTN - 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.

Peripheral Sensory Neuropathy – Not included

Proteinuria - In clinical trials, proteinuria has been reported within the range of 0.7% to 38% of patients receiving AVASTIN.

ATE - 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.

Wound Healing Complications – In a variety of clinical situations, wound healing complications ranged from 1.1% to 20%.

Comment:

The conclusion in the CSR is correct that the incidence of AEs of special interest was consistent with that reported for bevacizumab previously. Nevertheless the AEs described are serious and potentially life-threatening.

8.6. Gd 2-5 serious adverse events in sub-groups

Serious adverse events in two sub-groups were assessed in the CSR, the first by age (less than 65 years and 65 years or over) and the second by type of chemotherapy (paclitaxel, topotecan or PLD).

Age: In patients less than 65 years, serious AEs occurred in the CT and CT+BV arms in 26.3% and 26.6% of patients respectively and in those 65 or more, 28.6% and 38.6% respectively.

Chemotherapy: The frequency of serious AEs in each of the chemotherapy sub-groups was:

- Paclitaxel – CT 20%, CT+BV 28.3%; topotecan – CT 30.2%, CT+BV 28.1%; PLD – CT 30.2%, CT+BV 37.1%. The serious AEs by preferred term that occurred with a frequency of 5% or more in the CT+BV arm than in the CT arm were for paclitaxel, pyrexia (+5%); for topotecan, none; and for PLD.

Comment:

Addition of bevacizumab to paclitaxel and PLD increased the frequency of serious AEs by approximately 8%.

No assessment of the frequency of serious AEs in the subgroup of patients with ascites was reported. This is important since 31.3% of patients had ascites when receiving chemotherapy and no pharmacokinetic studies were done on these patients to determine whether the PK parameters of bevacixumab were altered, especially whether the ascites formed a third space with prolongation of drug clearance. This assessment will be requested from the sponsor (see response in Section 12.1.3.5 Adverse Events in the Sub group of Patients with Ascites).

8.7. Post-marketing experience

The Clinical Overview states 'Periodic Safety Update Report (PSUR)/Recent Periodic Benefit-Risk Evaluation Report (PBRER) data are consistent with the SmPC and previous PSURs/PBRERs. The post-marketing reports are provided in Module 5.3.6 Post-Marketing Experience.'

Comment:

Module 5.3.6 stated that Reports of Post Marketing Experience were not applicable (NA). Section 6 of the Summary of Clinical Safety (SCS) has a review of the Post-marketing experience as follows.

The post–marketing experience with bevacizumab was based on safety data contained in nine previously scheduled Periodic Safety Update Reports (PSURs). The total number of patients exposed to bevacizumab in the post-marketing setting or in clinical trials over the 8-year period covered by the PSURs is estimated to be approximately 1,339,560 patients.

During the 9-year period from 26 February 2004 to 25 February 2012, a total of 53,586 AEs, of which 44,427 were serious, were reported in 28,252 patients (2.1%). In 3,411 cases (0.3%), the outcome was fatal. Overall, the incidence of patients reporting AEs, the proportion of AEs considered serious, and the incidence of patients with AEs leading to death has remained stable over this period.

The most frequently reported serious adverse events in patients treated with bevacizumab during the reporting period 26 February 2011 to 25 February 2012 were GI disorders (19.0%), general disorders and administration site conditions (10.5%), infections and infestations (9.2%), vascular disorders (7.8%), and nervous system disorders (7.3%).

Comment:

The above tables do not identify AEs by preferred terms, but by SOCs. It is important to know the frequency of the drug-related AE by preferred terms in the SOCs GI disorders, vascular disorders and nervous system disorders so that a comparison can be made with the frequency of these AEs in the pivotal trial. The sponsor will be asked to provide this (See response in Section 11.1.3.7 Frequency of the preferred terms in the following SOC-GI disorders, vascular disorders and nervous system disorders). The post-marketing information given in the current PI lists mainly rarely reported AEs and AEs of unknown frequency.

8.8. Safety issues with the potential for major regulatory impact

The main safety issue with the potential for rejecting this application is the absence of safety data needed to arrive at a conclusion on risk-benefit, especially since the proposed treatment did not demonstrate an increase in OS nor an improvement in quality of life. The missing data have been requested in Section 12 Clinical Questions and will not be listed again here.

8.9. Evaluator's overall conclusions on clinical safety

Drug exposure in the pivotal study:

- Patients in the CT+BV arm received treatment for twice as long and received twice as many cycles as those in the CT arm, except for those receiving PLD.
- The median number of treatment cycles of bevacizumab before cross-over treatment was 6, and after cross-over, 4.5. Dose-intensity after cross-over was not provided.

Adverse events:

- The overall incidence of adverse events (Grade 2–5 collected) was 87.3% in the CT arm compared with 91.1% in the CT+BV arm. The incidence of Grade 3–5 adverse events was 53.0% in the CT arm compared with 59.2% in the CT+BV arm before cross-over and 26.4% from bevacizumab treatment after cross-over. The incidence of patients who experienced serious adverse events was 27.1% in the CT arm compared with 31.3% in the CT+BV arm before cross-over, and 16.7% from bevacizumab treatment after cross-over
- Grade 2–5 adverse events showing at least 10% higher incidence in the CT+BV arm than the CT arm were hypertension (CT: 5.5% vs. CT+BV: 19.0%), proteinuria (CT: 0.6% vs. CT+BV: 12.3%), and peripheral sensory neuropathy (CT: 7.2% vs. CT+BV: 17.9%). Those showing at least 5% higher incidence in the CT+BV arm than the CT arm were mucosal inflammation (CT: 5.5% vs. CT+BV: 12.8%), infection (CT: 4.4% vs. CT+BV: 10.6%), palmar-plantar

erythrodysaesthesia syndrome (CT: 5.0% vs. CT+BV: 10.6%), neutropenia (CT: 25.4% vs. CT+BV: 30.7%), and epistaxis (CT: 0 vs. CT+BV: 5.0%). The only Grade 2–5 adverse event that showed a difference of at least 5% higher incidence in the CT arm was anemia (CT: 26.5% vs. CT+BV: 19.6%)

- Grade 5 adverse events occurred in 5 patients (2.8%) in the CT arm and 6 patients (3.4%) in the CT+BV arm before cross-over and in one patient (1.4%) after cross-over. A total of 6 patients in the CT arm and 9 in the CT+BV arm died due to adverse events. The difference was that Grade 5 AEs were limited to the study period up to 30 days after last treatment whereas the total number included patients in the study follow-up
- The incidence of adverse events leading to withdrawal of study treatment was 8.8% in the CT arm compared with 43.6% in the CT+BV arm. The most frequently occurring adverse events leading to withdrawal of study treatment with chemotherapy or bevacizumab were peripheral sensory neuropathy, palmar-plantar erythrodysesthesia syndrome, fatigue, proteinuria and neutropenia
- More patients discontinued treatment in the paclitaxel plus bevaciamab compared to the paclitaxel arm (16% v CT+BV 45%) than with topotecan and PLD chemotherapy
- The incidences of adverse events of special interest were higher in the CT+BV arm (21.8%) as compared to the CT arm (5.1%). Individual AEs of special interest are summarized in Section Adverse events of special interest-Pivotal study. The incidence of GI perforations was 1.7% (n=3) in the CT+BV arm. One patient in the CT arm developed a fatal peritonitis. One patient experienced PRES in the CT+BV arm and another possible before cross-over, and a third after cross-over treatment with bevacizumab.

Comment:

The figure of 3 patients in the CT+BV arm (SCS and CSR) should be 4, if a probable case in included (see Comment, Section 8.6.1.6 Gastrointestinal Perforation).

- The incidence of serious adverse events reported were higher in the CT+BV arm for patients ≥ 65 years of age (38.6%), compared to those 65 or less (26.6%). These included fatigue, alopecia, mucosal inflammation, peripheral sensory neuropathy, and hypertension
- Addition of bevacizumab to paclitaxel and PLD increased the frequency of serious AEs by approximately 8%. Peripheral sensory neuropathy was more frequently reported in the paclitaxel cohort and palmar-plantar erythrodysesthesia syndrome in the PLD cohort
- The safety of bevacizumab in combination with chemotherapy could not be assessed in patients with ascites, since this sub-group was not separately assessed for safety
- Although a comparison of the incidence of AEs, particularly those of special interest, showed a similar incidence in the pivotal study and in other reported clinical trials of different tumor types, a comparison with the incidence in post-marketing reports could not be made as these data were not provided.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefit of bevacizumab in the proposed usage was:

- A clinically important prolongation of Progression Free Survival (PFS) and a significant increase in the overall response rate in this patient population.

However

- No significant clinical benefit was demonstrated in Overall Survival (OS) in the CT+BV treatment arm compared to the CT arm
- No improvement in the QOL was demonstrated in any of the parameters assessed, although a benefit was demonstrated in the frequency of paracenteses of malignant ascites in the CT+BV group.

Why was OS not increased when the PFS was prolonged? A detailed discussion on this issue is beyond the scope of this evaluation, as the possible reasons remain speculative. In brief it is noted that:

- Survival of the 72 patients progressing on the CT arm may have benefited in terms of survival after cross-over treatment with bevacizumab, so that the OS of the CT group approached that of the CT+BV group. No response data for this group was provided to support this effect
- Patients received greater exposure (more cycles) of chemotherapy when administered with bevacizumab compared to chemotherapy alone. Administration of bevacizumab may have therefore allowed the delivery of longer treatment, although the dose intensity was similar to that seen from chemotherapy alone.

One outstanding question is whether PFS was an appropriate end-point under international guidelines for a study of this type. The CHMP Guideline on the Evaluation of Anticancer Medicinal Products in Man Dec 2005, page 17, states 'If major differences in toxicity are expected in favour of the control regimen, OS should normally be selected as the most appropriate primary endpoint. Similarly, if there are no evidence based next line therapies available and if the period of time from disease progression to death is expected to be short, OS is considered to be the most appropriate endpoint; in most cases even if crossover is foreseen according to protocol. In cases where alternative endpoints are considered to adequately capture patient benefit, the choice has to be justified and scientific advice is recommended. PFS is an acceptable endpoint in situations where it is expected that further lines of treatment with effect on OS may importantly hamper the detection of a relevant treatment effect on OS.' Regarding the latter point, no evidence is available indicating bevacizumab has activity in ovarian cancer that has progressed after treatment with bevacizumab combination therapy.

9.2. First round assessment of risks

- The risks of increased frequency, more severe and more serious AEs in the usage of bevacizumab in combination with chemotherapy for the requested indication were confirmed in the pivotal study. The incidence was as reported in previous studies in different tumour types. The incidence of patients experiencing Grade 2-5 AEs was similar in the CT and the CT+BV groups of patients, but those receiving chemotherapy plus bevacizumab experienced an 6.2% more severe (Gd3-5) AEs. As well, 50% more patients died of the effects of AEs in the CT+BV group (n=9) than in the CT group (n=6)
- The number of withdrawals due to AEs was very much larger (43.6%) in the CT+BV group than in the CT group (8.8%). Reasons may include the longer time of treatment with bevacizumab (twice, on average), and the continuing treatment with bevacizumab after disease progression. After cross-over, the incidence of AEs from patients receiving bevacizumab was less than before cross-over, but after cross-over additional chemotherapy was not given with bevacizumab
- The incidence of peripheral sensory neuropathy and of palmar-plantar erythrodysesthesia syndrome was increased by the addition of bevacizumab to placlitaxel and PLD chemotherapy respectively

- Older patients (over 65 years) were a greater risk of adverse effects of bevaciuzmab and chemotherapy.

Patients with ascites (one-third of the patient population) are at potential risk of experiencing a greater incidence of severe and serious AEs as no safety data and no PK studies were provided in this sub-group.

Addendum: Data provided by the sponsor in its S31 responses (see Section 11.1.3.5Adverse Events in the Sub-group of Patients with Ascites) showed this was not the case.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of bevacizumab used in combination with chemotherapy for the indication requested needs to take into account the following considerations:

- the PFS with CT +BV alone was 6.8 months – that is the additional treatment with BV doubled the PFS of 3.4 months found in the CT group
- the duration of OS with CT+BV was 16.6 mths; during this time patients received CT+BV treatment for a median duration of 5 months, a treatment with serious and potentially life threatening consequences
- no significant increase in OS and no significant improvement in the QOL was demonstrated for patients receiving CT+BV compared to CT alone
- missing data that the sponsor has been asked to provide (see Section 11) requires assessment to reach a conclusion about the benefit-risk balance.

10. First round recommendation regarding authorisation

A recommendation regarding authorisation can only be made after the information requested in Section 11 has been evaluated in the context of the present evaluation.

11. Clinical questions

11.1. Clinical questions

11.1.1. Pharmacokinetics

11.1.1.1. Justification for not providing PK data in the present evaluation

Two main arguments were presented to justify the lack of PK data in the patient population to be treated in this new indication for AVASTIN.

1. The PK parameters of bevacizumab found in a variety of solid tumors were similar and would be expected to apply to the present clinical population.

   However about one-third of subjects in the pivotal study in this application had ascites at base-line. Ascites would be still present when bevacizumab was administered, raising the question whether this would alter the PKs of bevacizumab by creating a third-space from which bevacizumab could slowly re-enter the systemic circulation or penetrate more directly the gastrointestinal tract, increasing the risk of toxicity.

Question 1.1: Please justify the absence of data on the PK of bevacizumab in patients with malignant ascites, and give reasons why ascites as a third pharmacological space would not be a safety risk in such patients when treated with AVASTIN.

Response 1.1: The sponsor responded as follows:

a. Two references were provided that reported the beneficial treatment of ascites with bevacizumab

b. The concentration of bevacizumab in the blood to which patients would be exposed if bevacizumab diffused back from ascites into the systemic circulation would be low compared to therapeutic levels of the drug which persist for a long time given the half-life of 20-28 days and the duration of treatment

c. Although the incidence of SAEs was higher in patients who had ascites at baseline (CT 44.4%, CT+BV 39%) than in patients without ascites (CT 27.1%, CT+BV 31.3%), the SAE rate in the CT+BV arm was not higher than that in the CT arm, although the both rates in this subpopulation were numerically higher than in the overall safety population. The incidence of AEs of special interest was greater in the CT+BV arm compared to the CT arm but of similar increases in the total population and the subpopulation with ascites.

Comment:

There is no evidence that the presence of ascites contributes to greater toxicity in patients receiving bevacizumab for ovarian cancer.

2. Pharmacokinetic studies in the present population of patients were claimed to be unnecessary because the PK parameters of bevacizumab had been shown to be similar in a variety of other cancers as shown in the Population PK Analysis of Bevazicumab, Report 1031769 and confirmed for pancreatic cancer in Population PK Analysis BO17706.

   However this claim of similar PK parameters of bevacizumab in different cancers in patients with different covariates is not supported by a number of conclusions in the up-dated Report 1031796. The possible clinical effects of covariates on PK parameters such as clearance rates of bevacizumab (see Section 4, Discussion and Conclusions, Population PK Analysis Report 1031796) are an example. It is possible that the dose of bevacizumab may need to be reduced to decrease the risk of serious adverse effects in patients who receive the drugs named above, co-administered with bevacizumab.

Question 2.1: Please explain why the conclusions of Report 1031796 as stated above differ from the statements in the Clinical Overview, that states 'A population PK assessment for the influence of combination therapy on bevacizumab disposition has been reported for various chemotherapies and other anti-cancer agents (e.g., erlotinib, trastuzumab, and rituximab). Results show that there were no differences in CL observed between patients treated with single-agent bevacizumab and patients treated with bevacizumab co-administered with chemotherapies (including paclitaxel) or other anti-cancer agents, suggesting that chemotherapies and anti-cancer agents do not alter bevacizumab PK when coadministered with bevacizumab.' , and also on page 18, Section 3.1, dot point 7 that states 'The cumulative PK-DDI data to date for bevacizumab given in combination with various chemotherapy and other anti-cancer agents across tumor types do not suggest a potential for a PK-DDI between bevacizumab and chemotherapy or other anti-cancer agents.'

Similarly, the Summary of Clinical Pharmacological Studies, Module 2.7.2, are wrong in their conclusions, claiming a 17% increase in half-life of bevacizumab with named anti-cancer drugs, instead of the correct 40%. Was this because the earlier Population PK model was used and not that in Report 1031796? It is noted that Report 1031796 is part of the justification for not providing PK data in this patient population.

Response 2.1: The sponsor correctly pointed out that in the Population PK Analysis of Bevacizumab, 2008, the significant covariates, in order of decreasing influence on the Between Subject Variance for the parameter, were: (i) CL – baseline body weight (WTB), albumin, tumor burden (BURD) and sex; (ii) V1(central volume of distribution) – WTB, sex, BURD and protein;

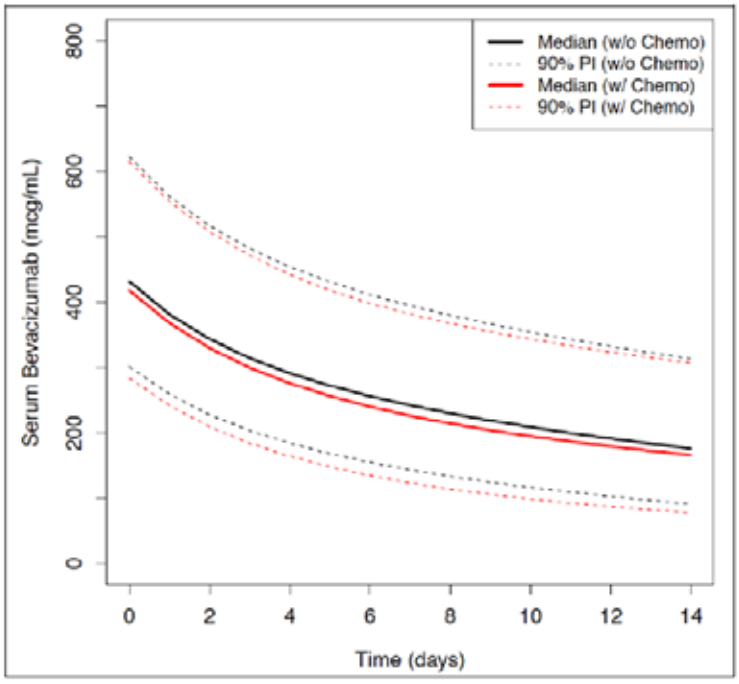
(iii) V2 (peripheral volume of distribution– the effect of concomitant chemotherapies and sex, so that chemotherapy was not shown to be a covariate affecting CL, only of V2.

Question 2.2: On the basis of the findings of a 40% increase in the half-life of bevacizumab, should the initial dose of bevacizumab be less than your recommended dose in patients who are to be co-administered carboplatin, gemcitabine, paclitaxel, topotecan or doxorubicin (pegylated liposomal)?

Response 2.2: The Sponsor stated that 'The updated PPK model (Report #1031796) derives half-life for a Typical Patient using point estimates of the primary PK parameters for clearance (CL and Q) and volume of distribution (V1 and V2). This estimation method calculates a bevacizumab half-life of 20 days when administered as a single-agent, and a half-life of 28 days when administered in combination with the chemotherapies that were evaluated. This is an apparent 40% increase in half-life when bevacizumab is administered in combination with chemotherapy.'

To assess the effect of this 40% increase, simulations were done from the updated PPK model for median bevacizumab steady-state concentrations, with 90% prediction intervals (90% PI), using a bevacizumab dose of 10 mg/kg administered every 2 weeks for both single-agent bevacizumab and in combination with chemotherapy. The results are shown in the following Figure 5.

Figure 5: Simulated Concentrations of Bevacizumab at Steady-State concentrations (median and 90% PI) at 10 mg/kg (q2 week) with and without chemotherapy.



As shown in the Figure, the median bevacizumab concentrations are similar between the two groups, with the 90% PI for each group showing substantial overlap. These results show that the systemic exposure of bevacizumab between the two groups is similar when bevacizumab is administered as a single-agent or in combination with chemotherapy.

Comment:

I accept that chemotherapies do not alter bevacizumab serum concentrations when co-administered with bevacizumab in this modelling outcome. Therefore, a decrease in dose is not warranted due to the apparent increase of 40% in the half-life estimates for bevacizumab, as systemic exposure is not altered in the presence of chemotherapy. The

caveat applies however that the value for the CL, and these results on the effect of that increase are all produced by modelling and not by clinical data in PK studies.

11.1.2. Efficacy

11.1.2.1. Continuing treatment with bevacizumab after disease progression

The reasons for selecting the dosage of bevacizumab in the pivotal trial B022224 are given in the Module 2.7.3, Summary of Clinical Efficacy, Section 4, except for the following: 'Bevacizumab should be administered in combination with chemotherapy until PD or unacceptable toxicity. Bevacizumab may be continued as a single agent if chemotherapy is discontinued earlier.'

The first usage is acceptable, but the second is ambiguous since the wording allows bevacizumab to be continued if the patient were receiving chemotherapy plus bevacizumab, and then the chemotherapy was stopped early, say for toxicity. The CSR on the other hand specifically stated that only patients in the chemotherapy alone arm were to cross over on disease progression to receive monotherapy with bevacizumab.

Please confirm that only patients with PD in the chemotherapy alone arm crossed-over to receive bevacizumab monotherapy. IF patients who were randomised to the CT+BV arm had the CT discontinued early and received BV, please indicate the how many of the 72 patients were in this group. Also provide the assessment of response for all patients (n=72) who received monotherapy, in total and in the two groups previous CT only and previous CT+BV if such was the case.

Response 3: The Sponsor confirmed that only patients in the chemotherapy alone arm could receive study treatment after disease progression by crossing over to bevacizumab monotherapy. A total of 72 patients, randomized to the CT alone arm, had crossed over to optional bevacizumab monotherapy at the time of OS cut-off (25Jan2013). Patients in the CT + BV arm, who discontinued chemotherapy but continued bevacizumab therapy until toxicity or PD, were not regarded as cross-over patients and were not part of the patient subset of 72 patients.

Response assessment for patients in the CT arm who received optional bevacizumab monotherapy following disease progression was not part of the protocol objective, thus the tumor assessment requirements were not designed to support such analysis. Investigator's assessed response throughout the study compared to the patient disease assessment at baseline, with no 're-baselining' performed at the time of crossover, therefore the response assessments recorded during crossover are not meaningful.

Comment:

From this response, I conclude that 72 patients received BV monotherapy after previous CT alone when they developed toxicity or PD, and would be recorded as such in the data analysis. Some patients apparently continued BV even though they were in the CT+BV arm, but the response does not state how these patients' data were handled.

11.1.2.2. The use of CA 125 to assess response

The use of CA 125 in the pivotal trial as described in the CSR and the trial protocol followed the guidelines of the Gynaecological Cancer Group (Rustin GJS, Vergote I, Eisenhauer E et al, Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG): Int J Gynecol Cancer 2011;21: 419-423), except that, as stated in the CSR in assessing PFS, Ca 125 was not used to determine progressive disease.

The following is in the abstract of that paper 'The criteria for defining progression are now acceptable in clinical trials of recurrent disease as they have since been validated ([information redacted] personal communication, 2010). The GCIG requests that data from all clinical trials using these definitions are made available to GCIG trial centers so that continual validation and

improvement can be accomplished. These definitions were developed from analyzing patients receiving cytotoxic chemotherapy and have not yet been validated in patients receiving molecular targeting agents' (my emphasis).

Please address the questions (1) whether the definitions have since been validated in patients receiving molecular targeting agents and (2) whether the personal communication from [information redacted] referred to in the paper has been published in a peer-reviewed journal. If neither or either is the case, justification for the use of these guidelines is needed.

Response 4: The response was:

1. Ca125 concentrations were not used to assess PD in the trial.
2. The use of Ca125 in patients receiving combination therapy with a molecular targeting agent has not been validated as an indicator of progressive disease. Further, some reports of patients so treated have shown no increase in Ca125 with PD, and in other cases a steady rise in Ca125 for up to 8 months before PD occurred as shown by RECIST criteria.
3. The personal communication from [information redacted] referred to in the article by Rustin et al. has not been published in a peer-reviewed journal at the current time.

11.1.2.3. Acceptability of statistical analysis plan (SAP) amendment 2

The reason given for SAP Amendment 2 by the applicant (CSR) is that 'The plan emphasizes analyses that would meet the expectations of Regulatory Agencies in their review processes for approval of the new indication.'

The amendment was made 11 months after the close of the clinical data-base of the trial. Until this time, the SAP had been the same in all the amended protocols, and assessments of the various endpoints would have been made by the investigators following these trial protocols up to closure of the clinical data-base. It is therefore possible that results or early impressions of these assessments may have led to the SAP Amendment 2, which was not part of the original study design. Therefore selection bias in the changes to the SAP cannot be excluded.

In all the trial protocols, Quality of Life (QOL) was to be assessed by investigators during the course of the trial using multiple HRQoL instruments, including the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ) ovarian cancer module with 28 items (OV28). Such assessments would have been completed at the time of clinical data-base cut-off (25 Jan 2013), after which no more assessments for QOL were done. The above changes to the SAP (Amendment 2) were made 11 months (CORRECTION from S31 response – to read 1 month) later on 19th Dec 2013 (CORRECTION from S31 response – to read 19th Dec 2012). In that period, the results of the investigators' assessments of trial patients' QOL using all instruments would have been in whole or in part or potentially available for scrutiny. For the sponsor then to decide that the results from all instruments were no longer to be part of the secondary objectives as pre-defined in the protocols and used throughout, and to regard these outcomes as exploratory only rather than secondary objectives, then to select only the Quality of Life Questionnaire-OV28 abdominal/ (GI) symptom scale to be a secondary objective for QOL introduces the strong possibility of data selection and bias.

I therefore conclude that it would be unsafe to accept this change, and I intend to evaluate QOL as determined by all instruments as a secondary objective of the trial as planned, and as stated in the trial protocols.

If the sponsor does not agree with this decision, please give reasons.

Response 5: The sponsor corrected dates in the CER that were in error. These have been corrected (pp 21-23). The corrections reduced the time in question from 11 to 1 month.

The sponsor did not address the point of the question, but justified at length with references and data the validity of using the QOL questionnaire, QOL-OV28 to assess the PRO for abdominal and GI symptoms.

Comment:

This was not the issue. The issue was that the Trial Protocol in Section 2.2, listed all the QOL instruments as secondary objectives of the study. After the study had been running for 2 years and 3 months (from the first patient randomised on 29th Oct 2009 until 13 Jan 2012,when the first amendment was made to the Statistical Analysis Plan), investigators were assessing QOL by all instruments AS A SECONDARY OBJECTIVE of the trial. The amendment changed this to make only QOL-OV28 a secondary objective and the other instruments exploratory only. The response provided no justification for this except that QOL-OV28 gave the best result so because the other QOL results are not adequately considered, my original objection stands, and the QOL assessment should be based on all instruments as in the original study design (see next question and response).

11.1.2.4. Need for further information on QOL

Insufficient information has been provided on the assessment of the QOL in this study. Given the failure to show an increase in overall survival in patients treated with bevacizumab, the assessment of QOL is of vital importance in determining patient benefit if any from treatment with bevacizumab. Please provide the following information on QOL:

1. What was the proportion of evaluable patients who completed QoL questionnaires over the course of the treatment (ie longitudinal data) for both arms.

   Response 6 (1): The sponsor provided various tables from the CSR for Study B22224 that provided information of which the following shown the figures for baseline and week 30 assessments.

   a. Global Health status: The proportion of evaluable patients in the CT and CT+BV groups were 94.5% and 93.9% respectively at baseline falling to 42.4% and 62.2% at Week 30 (Table 110, p507 CSR).

   b. QOL-OV28: The compliance rate for the CT and CT+BV groups were 89.0% and 88.3% respectively at baseline falling to 42.4% and 54.9% at Week 30 (Table 110, p507 CSR).

   c. FOSI: A similar percentage (87%) of patients in each arm completed this questionnaire at baseline. At week 30, 42.4% in the CT arm and 52.4% in the CT+BV arm had completed the questionnaire.

   d. HADS: A similar percentage (92.3% in the CT arm and 91.1% in the CT+BV arm) of patients completed this questionnaire at baseline. At week 30, 42.4% in the CT arm and 61.0% in the CT+BV arm had completed the questionnaire.

2. Please fill in the table below to demonstrate the number of patients with evaluable QoL questionnaires for the following groups.

Response 6(2): The sponsor provided the requested information for only one of the questionnaires QOL--OV28, although this was just one of 4 secondary endpoints for QOL(see Comment on Response 5 above). The sponsor did not complete the table provided as requested – this has been done by the evaluator.

Note: A table was provided by the sponsor and headed 'Table 6. Summary of Adverse Events: Patients Evaluable for the Abdominal/GI Symptom Scale at Baseline and Follow–up'. However the data provided were the figures for Week 8/9 only not at Baseline.

Comment:

The 8/9 week time may have been chosen to allow time for AEs to have occurred. The figures are therefore for one time point in the continuum of the study. As stated above, at baseline, evaluable QOL-OV28 questionnaires were obtained from 162 of 182 (89%) of patients in the CT arm and from 158 of 179 (88.3%) in the CT+BV arm. This sampling is balanced and acceptable.

2.1 The proportions of patients with evaluable baseline and follow-up QoL questionnaire outcomes of those patients.

a. experiencing adverse events on bevacizumab compared with those who had an AE in the control arm?

b. experiencing adverse events on bevacizumab compared with those who were on bevacizumab who did not experience an AE leading to discontinuation?

	Bevacizumab/chemo Evaluable QoL (n, %)	**Chemotherapy alone Evaluable QoL (n, %)**
All patients at 8/9 weeks	117	135
Patients no AE	11(8.1%)	9 (7.7%)
Patients with any grade AE	124(91.9%)	108 (92.3%)
Patients with Grade 3 or 4 AE	82(62.7%)	73(62.4%)
Patients with AE leading to discontinuation	62(45.9%)	22(18.8%)

Comment:

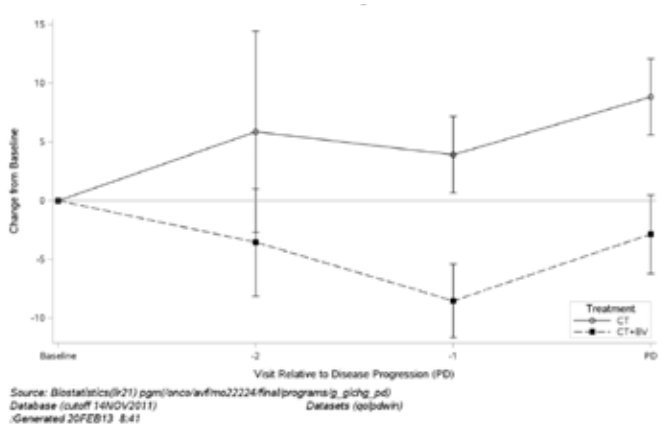
The one significant difference in the above figures for the two arms is for patients with AEs leading to discontinuation. The high figure for CT+BV (46%) reflects the higher overall incidence (43.6%; n=78) of patients discontinuing the study due to AEs from BV, compared to those discontinuing due to CT alone (8.8%; n=16)[Table 38, CSR MO22224]. We do not know how many patients discontinued the study due to AEs by the 8/9week time point (as above), compared to the 62 who discontinued AND completed an evaluable questionnaire. A further confounding factor is the 8/9 week data above show 22 patients in the CT arm discontinued due to AEs, but the CSR as stated cited the total number of patients discontinuing the study due to AEs was 16 (from Table 38, CSR MO22224).

In assessing QOL, if the AEs that lead to discontinuation of the study negatively affect QOL as is likely, the larger number in the CT+BV arm could be a negative influence on QOL of patients in that arm of the study, and would not bias an analysis towards a benefit for the CT+BV treatment arm.

2.2 Please provide the QoL outcomes for all those on bevacizumab at the last time point prior to progression compared with those in the control arm at the last time point prior to progression?

Response 6 (2.2): Again the sponsor has chosen one (QOL-OV28) of the 4 instruments used and provided a chart from the CSR (Figure 6 following from page 126, CSR).

Figure 6: EORTC QlQ-OV28 Abdominal/GI Symptom Score Change prior o and around the disease progression: Randomised patients



The sponsor states within a 6-week window around PD (-1 to PD), the abdominal/GI symptom scale increased from the previous assessment point for both the CT + BV and CT arms. This indicates that the symptom progression was correlated with PD and independent of treatment.

Comment:

> In the figure, negative values indicate improvement. Of note is that none of the points reach 10, defined in the analysis as the minimum clinically effective value for either benefit or deterioration.

2.3 Did any of the QoL tools measure symptom burden?

Response 6 (2.3): The sponsor replied that symptom burden was assessed through the severity, functional and the global health status/quality of life items of the EORTC and FOSI. The EORTC and the FOSI, which were designed to assess the concept of severity, did not directly use the concept of 'burden' in the symptom-related items. Both disease- and treatment-related symptoms were captured in a comprehensive way by the different HRQoL measures.

Comment:

> As stated in this evaluation (Quality of Life Assessments), none of the instruments used to assess QOL (QOL-C30, QOL-OV28, FOSI, HADS) showed that the addition of BV to the chemotherapy improved the quality of life in a statistically significant way. Note especially that this was true of the QOL-OV28 instrument that showed no statistically significant benefit in spite of a trend to higher values with CT+BV (Table 103.3 CSR and this evaluation).

11.1.2.5. Obscure meaning of captions on two tables

The captions of Table 114 CSR, (Patient Disposition and Reason for End of Treatment - Chemotherapy Alone: by November 14, 2011 Randomized Patients - Paclitaxel Assigned at Randomization) and that of Table 111, CSR (Patient Disposition and Reason for End of Treatment - Chemotherapy (Paclitaxel): by November 14, 2011 Randomized Patients - Paclitaxel Assigned at Randomization) are confusing. Please explain the meaning of these captions.

Response 7: The sponsor stated that the caption to Table 114 was wrong and should read 'Patient Disposition and Reason for End of Treatment - Chemotherapy Alone: by November 14, 2011 Randomized Patients'.

Comment:

This mistake has been corrected in the text of this evaluation (and in Table 9 Patient Disposition and Reason for End of Treatment Chemotherapy Alone by November 14, 2011 All Randomized Patients).

11.1.2.6. Assessment of response of malignant ascites to treatment

Frequency of paracenteses performed on patients while on-study was summarized by treatment period for patients with ascites at baseline, as well as patients without ascites at baseline. No formal statistical analysis was performed, but the frequency of paracentesis was substantially reduced among patients treated with CT+BV.

A foot-note to Table 26, p135 CSR, states that one patient had multiple paracenteses, but the number of paracenteses was not given. In assessing these data, it is important to know how many paracentesis procedures were performed on each patient throughout the study.

Please provide this information.

Response 8: The sponsor provided two tables showing that at baseline, 54 patients in the CT arm and 59 in the CT+BV arm had ascites, and that 12 patients in the CT arm and one patient in the CT+BV arm had subsequent paracentesis procedures. A total of 6 patients in the CT arm and one patient in the CT+BV arm had more than one paracentesis procedure.

Comment:

The response confirms that the frequency of paracentesis was substantially reduced among patients treated with CT+BV. Further support for this effect was given in two references provided by the sponsor.

11.1.2.7. The effect if any of discontinuation from treatment on progression free survival

Please provide the median and interquartile time to treatment failure for both arms (ie incorporating discontinuations due to adverse events, toxicity, disease progression etc)? Also please provide a K-M curve for PFS for those patients who remained on active treatment up until the time of their disease progression ie taking into account discontinuations due to toxicity and adverse events.

Response 9: The sponsor stated that the median time to treatment failure in the CT arm was 3.4 months (interquartile range 1.8-5.5), and the median time to treatment failure in the CT+BV arm was 5.4 months (interquartile range 3.4-9.3). Based on the stratified analysis, the HR was 0.422 (95% CI: 0.333, 0.536; log-rank p-value < 0.0001).

Comment:

These figures compare with the median values for PFS of 3.4 months for the CT arm and 6.8 months for the CT+BV arm. Note that the median time to treatment failure is shorter in the CT+BV arm but unchanged in the CT arm, probably due to the high discontinuation rate (43.6%) in the CT+BV arm compared to the CT arm (8.8%).

In the K-M curve provided for those patients on treatment until PD, the median PFS for the CT arm was 2.1mths and 5.4mths for the CT+BV arm.

Comment:

In this case, the median value for the PFS in the CT+BV arm was the same, 5.4 mths, as the Time to Treatment Failure in that arm (above), but for the CT arm was shorter (2.1mths v. 3.4mths).

Note that these results differed from those of the sensitivity analysis (Section 3.9.3.1.2, p58, CSR) of PFS when the PFS data for patients who discontinued study treatment due

to toxicity alone were censored at the time of the last tumor assessment prior to the discontinuation. In this case, the median value of PFS was 3.4 mths in the CT and 7.8 mths in the CT+BV arm.

Conclusion: The more realistic situation in oncology practice would be where all events (time from randomization to discontinuation of treatment for any reason, including progressive disease or death or withdrawal of treatment due to adverse events/unacceptable toxicity, withdraw consent, symptomatic deterioration, or other reason considered progressive) that define time to treatment failure can occur, so that the duration of PFS of 5.4 mths found for the CT+BV arm in that analysis would be more relevant to clinical oncology practice. The 2 months increase on the PFS with the addition of BV was statistically significant compared to CT alone, but less than the 3.4 mths increase seen in the primary analysis.

11.1.2.8. The number of patients who received prior anti-angiogeneic therapy

Please explain the difference between the IVRE and eCRF recorded numbers for those who had received prior anti-angiogenic therapy, and justify which is more likely to be accurate? In what percentage was the prior treatment unknown due to blinding from the previous trial?

Response 10: The sponsor replied that eligible patients were registered in the study via an interactive voice response system (IVRS). The investigator was required to telephone the automated system and enter the patients' details, including whether or not the patient had received prior anti-angiogenic therapy. This information was used for the stratification of the patient, and was not changed in the IVRS system even if it was identified that the investigator had made a mistake.

The stratification data on the eCRF required 100% source document verification (SDV) by the monitor according to the SDV plan, and data could be changed if mistakes were identified. Therefore the eCRF contains the data most likely to be an accurate representation of the patient status at baseline.

According to the eCRF data, previous anti-angiogenic treatment was unknown, due to previous trial blinding, in 33.3% of the cases (in 9 out of 27 patients).

Comment:

The less accurate IVRS system was used for stratification and the more accurate eCRF for the data analysis. The 9 unknown cases were considered as having received anti-angiogenic therapy. In the event, of the 27 patients in the group, 15 (8.2% of patients in that arm) were in the CT arm and 12 (6.7%) were in the CT+BV arm. The distribution in each arm was acceptable.

11.1.2.9. PFS in subgroups of patients

1. Was there an improvement in PFS with bevacizumab/PDL cf PDL alone?

Response 11(1): The sponsor provided corrected data from Table 315 in the CSR that showed the median PFS in the PDL arm was 3.5 mths compared to 5.1 mths in the PDL+BV arm. The HR was 0.53 with a 95%CI of 0.36-0.77.

2. Was there an improvement in PFS for those with ascites at baseline with addition of bevacizumab to treatment?

Response 11(2): The sponsor provided corrected data from Table 315 in the CSR that showed patients with and without ascites responded similarly to CT+BV. Patients without ascites at baseline (n=248) had a PFS of 3.5 mths in the CT arm compared to 7.6 in the CT+BV arm, while patients with ascites at baseline (n=113) had a PFS of 2.5 mths and 5.4 mths respectively.

Comment:

Although both groups respond better to CT+BV than to CT alone, the increase in the PFS is shorter (2.9 mths) in patients with ascites than in those without ascites (4.1 mths) at baseline.

11.1.2.10. Independent review of scans

Please clarify whether an independent review of scans was undertaken as specified in the protocol amendment, and if not, provide a justification for this not being done.

Response 12: The sponsor replied that it had conducted a retrospective, blinded, central review of radiographic data in Study MO22224 as specified in the protocol amendment.

Comment:

The study report of the review was undated, but the graphs have a sub-date of Dec 2013, while the original submission was being evaluated. It is not clear to this evaluator why the sponsor choose to submit the application with only the investigators' assessments, rather than wait for the results of the independent radiological review.

The clinically meaningful and statistically significant improvement observed in investigator-assessed PFS was confirmed by the Independent Review Committee (IRC).

Comment:

Review summary

Design: This retrospective IRC review was performed after the study MO22224 had reached the clinical cut-off date for analysis of study endpoints, and used as much radiographic data as possible for each patient before or on 14 November 2011 (the clinical cut-off date). The blinded IRC review was performed for all patients enrolled in this study for whom at least the baseline and one postbaseline tumor assessment were available and evaluable. Radiographic data were provided to BioClinica (this group was performing the study for Roche) in a blinded fashion such that patient treatment (CT or CT+BV) and the date the data were obtained were unknown to the assessors.

Radiographic data were reviewed by the IRC based on modified RECIST version 1.0. The radiographs were initially reviewed independently by two IRC radiologists. Adjudication by a third radiologist was required when the dates of progression assessed by the two readers were different or when only one of the two radiologists assessed disease progression (PD). The adjudicator could either agree with one of the original radiologists or provide a third assessment that would be considered the final result. Error! Reference source not found.

Concordance and Discordance Rates: For patients with RECIST PD determined by both investigator and IRC, a summary was provided of percentages of patients with a PD determined by IRC in comparison to that determined by the investigators on an earlier, later, or the same date, and also on a date that was 9 weeks earlier or later (which indicated a discordance in PD at more than one consecutive radiographic assessment). This analysis was also performed for concordance on PFS status and timing of the PFS events for the ITT population.

The discrepancy rates for each arm and their differential discordance rates were calculated as described by Amit et al 2011. The early discrepancy rate (EDR) quantifies the frequency with which the investigators declare PD earlier than the IRC among all patients with investigator-assessed PD. The late discrepancy rate (LDR) quantifies the frequency with which the investigators declare PD later than the IRC among all patients with discrepant PFS assessment by the investigators and the IRC. The differential discordances for EDR and LDR were calculated as the differences in EDR and LDR, respectively, between the two arms. These differential discordances estimate the evaluation bias regardless of data maturity.

Results: Completeness -The IRC received radiographs from 14 countries and from 91 of 96 study sites corresponding to 333 of 361 (92.2%) randomized patients. Of these, only 35 patients were not included in the IRC-evaluable population due to missing or non-evaluable baseline and/or post-baseline radiographic exams. The remaining 298 patients (82.5%) were IRC-evaluable; these were balanced between the treatment arms: 153 (84.1%) in the CT arm and 145 (81.0%) in the CT+BV arm.

Adjudication: Overall, 113 of 298 patients (37.9%) in the IRC-evaluable population required adjudication (CT: 34.6% vs. CT+BV: 41.4%)

Primary Analysis: A total of 134 (73.6%) PFS events occurred in the CT arm and 117 (65.4%) in the CT+BV arm. There was a statistically significant difference in PFS duration between the treatment arms, with a median PFS of 3.9 months (95% CI: 3.4, 5.2) in the CT arm and 8.1 months (95% CI: 6.9, 9.6) in the CT+BV arm, HR = 0.484 (95% CI: 0.370, 0.632; log-rank p-value < 0.0001). The Kaplan-Meier plot was similar to that observed for investigator-assessed PFS in the Study MO22224 Primary CSR.

Comment:

The values of 3.9 mths (CT) and 8.1 mths (CT+BV) compare with 3.4 (CT) and 6.8 mths (CT+BV) for the investigator assessed PFS.

Subgroup analyses: The IRC's analysis of PFS compared to the same analyses using investigators' assessments of PFS in the original application show that in the latter, a significant benefit was shown for the subgroup of patients receiving PD chemotherapy with BV but in the IRC assessment, no benefit was shown (CI for the HR 0.46-1.06). In this case the patient **numbers were adequate for analysis (51 events CT and 49 CT+BV).**

Concordance: The concordance rate, defined as agreement between investigator and IRC on progression status (yes/yes or no/no), was 69.1% overall and was comparable between treatment arms (CT: 69.9% vs. CT+BV: 68.2%).

When comparing IRC and investigator PFS for all randomized patients, the concordance rate (agreement between investigator and IRC) in PFS was 78.7% overall (CT: 76.9% vs. CT+BV: 80.4%).

Discordance: The discordance rate in PD date on more than one consecutive assessment, as indicated by a difference of more than 9 weeks in the PD dates assessed by the IRC and investigators, was 16.8% overall (CT: 17.5% vs. CT+BV: 15.6%).

Comment:

The concordance and discordance rates are acceptable in this type of comparison.

Conclusion:

I agree that the results of the retrospective IRC evaluation support the conclusions of Study MO22224 that used assessments by the investigators, except in the one case of a subgroup analysis referred to above.

11.1.3. Safety

11.1.3.1. Absence of data on the relationship of trial drug administration to the occurrence of adverse events

While causal relationship was provided for AEs of special interest, this information was not provided for AEs as a whole in the CSR, the Clinical Overview, the Summary of Clinical Safety and the SAP Amendment 2. The wording in Section 5.3, Overall Adverse Events however indicates that all AEs reported as above (as in the CSR) were to be taken as treatment-related.

Please give reasons for this omission.

Response 13: The sponsor does not explain the omission, rather indicating that causality of all AEs by investigators was listed in the 81 pages of Listing 709, p539 of the MO22224 CSR.

Comment:

Apparently the sponsor was not prepared to summarize these data. In the absence of such a summary by the sponsor, this evaluator will take the conservative position, and consider all AEs as a whole to be treatment related.

11.1.3.2. Grouping of grades of AEs

The grades of AEs were grouped as Grades 2-5, Grades 3-5, and Grade 5. Please indicate where the data for the adverse events and serious adverse events for each arm, according to following grading can be found: Grade1-2, Grade3-4, Grade 5. If the data have not been presented in this way, please provide two tables with these data.

Response 14: The sponsor replied that Grade 1 AEs were not required in the study and so these cannot be provided. The request for Grade 2 AEs was not met. Instead a reference was made to the 26 pages of Table 611, CSR, showing Grades 2-5 of all AEs. Grade 3-4 AEs were provided, and Grade 5 AEs in Table 6[1].

Comment:

This request was only partly met, as the separate listing of Grade 2 AEs was not provided. Comparing the data provided with that evaluated previously did not change the evaluator's assessments as stated in Section 8.4.1.1 Pivotal study.

11.1.3.3. Absence of assessments of laboratory tests

No results for laboratory tests were presented. However the listing of AEs (Listing 709, CSR) included the preferred terms that are defined from laboratory tests, such as neutropenia, and Grade 3 GGT increase. Presumably the investigators used their local data to define such events and then reported them as AEs, with causality. To assess the risk-benefit of the proposed treatment in this group of patients, the AEs related to haematology, liver function and renal function needs to be considered. Please provide these data, including possible relationship to bevacizumab administration.

Response 15: The sponsor did not explain why the results of laboratory investigations were not given, as is the standard for reporting clinical trials. Instead the sponsor repeated what was stated above that laboratory abnormalities were only reported as AEs if the laboratory results were abnormal, clinically significant, and treatment-emergent, meeting one or more of the following conditions: accompanied by clinical symptoms, leading to a change in study medication, and/or requiring a change in concomitant therapy.

Comment:

The response is unsatisfactory and the absence of a report of laboratory investigations is another safety concern in this study.

11.1.3.4. Adverse event of special interest – abscess and fistula

The difference in incidence between the two arms, CT and CT+BV, of this AE is striking for an AE known to be associated with bevacizumab treatment. Two of the events were assessed by investigators as unrelated to bevacizumab treatment. The lack of relationship to bevacizumab would be more convincing if information were given whether the patients were receiving treatment at the time of first occurrence of the AE, what the chemotherapy agent(s) was, and whether the patients' disease was responding, stable or progressing.

Please provide this information.

[1] Not shown in this AusPAR

Response 16: The sponsor provided the requested information. The first patient developed the fistula 5 days after starting CT+BV. She had a repeat laparotomy in Oct 2010 (date not given) and had her one and only study treatment on 8 Nov 2010. She died on 31 Dec 2010 with PD.

Comment:

> Because of possible roles of tissue injury and progressive disease, the role of BV in contributing to her fistula is uncertain.

The second patient was receiving study treatment at the time of the occurrence of a rectovaginal fistula. She was documented to have partial response on 12 July 2011. She received her 8th cycle of study treatment with bevacizumab on 09 August 2011 (day 198) and topotecan on 16 August 2011 (day 205), and she was diagnosed with Grade 2 rectovaginal fistula on 23 August 2011 (day 212). Her study treatment was permanently discontinued due to the rectovaginal fistula event. The patient was diagnosed with disease progression on 20 September 2011 (day 240).

Comment:

> The patient was assessed as having a PR, and 6 weeks later developed her fistula. She was assessed a having PD 4 weeks after that. The time to diagnose PD (4 weeks) after the fistula was diagnosed suggests that her fistula may have been related to BV rather than PD.

11.1.3.5. Adverse events in the sub-group of patients with ascites

Addition of bevacizumab to paclitaxel and PLD increased the frequency of serious AEs by approximately 8%.

No assessment of the frequency of serious AEs in the subgroup of patients with ascites was reported. This is important since 31.3% of patients had ascites when receiving chemotherapy and no pharmacokinetic studies were done on these patients to determine whether the PK parameters of bevacixumab were altered, especially whether the ascites formed a third space with prolongation of drug clearance.

Please provide the frequency and nature of the serious AEs in this subgroup of patients

Response 17: This information was provided in an earlier response (see Response 1.1, Point (3)).

11.1.3.6. Why was a Grade 4 event (GI haemorrhage) not classified as a Grade 5 event?

[information redacted] was the patient with the Grade 4 GI haemorrhage (Section 6.9.2,'Bleeding', in the CSR). The event is not listed in the Listings or Narratives of Grade 5 Events (Patient Deaths), but is in Listing 715, CSR, in which the Primary Cause of Death is given as 'Ovarian cancer progression' with the MedDRA term 'Ovarian Cancer'. Please explain why this death should not be classified as Grade 5, resulting from the AE of GI bleeding, and why if GI bleeding was still occurring at the time death, this was not the cause of death rather than 'ovarian cancer'. The arbitrary time of a 30 day cut-off does not change the cause of death.

Response 18: The sponsor stated that the patient experienced Grade 4 GI haemorrhage the day after her second dose of bevacizumab (day 44). On day 47, she was diagnosed with digestive occlusion (diagnostic details not provided). Even though the event of GI haemorrhage was assessed by the investigator to be possibly related to bevacizumab treatment, the GI haemorrhage was also assessed by the investigator as due to tumor progression (reappearance of ascites) and the digestive occlusion.

Comment:

The patient's haemorrhage continued at home, possibly about day study 50 (not stated), and she was diagnosed with PD due to ascites and a rising Ca125 level. The investigator assessed the haemorrhage as due to BV initially then to PD. The cause is uncertain.

11.1.3.7. Frequency of the preferred terms in the following SOC- GI disorders, vascular disorders and nervous system disorders

Table 20, Summary of Adverse Events by System Organ Class in Patients Receiving Bevacizumab: Post-Marketing Data, in the Summary of Clinical Safety, Module 2.7.4, does not give the preferred terms for the AEs reported.

To allow a comparison of frequency of these AEs with that in the pivotal study, please provide the frequency of preferred terms for the following SOCs referred to in the PMD – GI disorders, vascular disorders and nervous system disorders.

Response 19: The sponsor did not answer this question and did not provide the frequency of preferred terms from the PMD as requested. It instead provided the preferred terms from the MO22224 trial, and argued against the validity of any comparison with post-marketing data.

Comment:

It is noted that the percentages in the post-marketing data do not reflect frequency in the population, unlike the clinical trial. Nevertheless, the data do show the frequency of AEs reported. The most frequently reported serious AEs were G-I disorders (19% of AEs reported), General disorders and administration site conditions (10%), Infections and infestations (9.2%), Respiratory, mediastinal and thoracic disorders (8.6%), and Vascular disorders (8.4%). These compared with the most frequent SOCs reported in the trial of Blood and lymphatic system disorder, G-I disorder, General disorders and administration site conditions, Infections and infestations, and Skin and subcutaneous tissue disorders. The SOCs in italics were common to both patient populations.

11.1.3.8. Information on other trials

Aside from those submitted to the TGA with this submission or previous submissions by the Sponsor for bevacizumab in ovarian cancer, is the Sponsor aware of any other trials that have been or are being conducted comparing the addition of bevacizumab to standard treatment in patients with advanced ovarian cancer?

Response 20: The sponsor listed two trials:

1. In the front-line setting, the GOG-0262 trial compares every-3-weeks paclitaxel versus dose dense weekly paclitaxel in combination with carboplatin with or without concurrent and consolidation bevacizumab in the treatment of primary stage II, III, or IV epithelial ovarian cancer. The target accrual of 625 patients has been completed and the results of final OS are expected at the end of 2014.
2. In the recurrent platinum-sensitive setting, GOG-0213 is a phase III randomized controlled trial comparing carboplatin and paclitaxel alone or in combination with bevacizumab, followed by bevacizumab and secondary cytoreductive surgery. The trial is ongoing, having now enrolled 790 out of the 913 target number of patients. The results are expected approximately by end of 2015.

11.1.3.9. PI and CMI

No questions

12. Second round evaluation of clinical data submitted in response to questions

12.1. Second round benefit-risk assessment

12.1.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of bevacizumab in the proposed usage were reduced as follows:

- Time to Treatment Failure (see Section 11.1.2.6 The Effect if any of Discontinuation from Treatment on Progression Free Survival) provided in the responses showed a reduction in benefit when this parameter was compared to the period of Progression Free Survival (PFS)
- The benefit to the PFS of adding bevacizumab to PD chemotherapy, as shown by investigators' assessments was not confirmed by the assessments of the Independent Review Committee.

12.1.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks in the proposed usage of bevacizumab are reduced in the case of patients with ascites at baseline whose safety profile was shown to be the same as for patients without ascites at baseline (see Section 11.1.3.5 Adverse Events in the Sub-group of Patients with Ascites).

12.1.3. Second round assessment of benefit-risk balance

The benefit-risk balance of bevacizumab is unfavourable given the proposed usage, but would become favourable if the changes recommended in Section 14 are adopted.

13. Second round recommendation regarding authorisation

1. The following change to the proposed indication would make the product approvable

   '*AVASTIN (bevacizumab) in combination with paclitaxel or topotecan is indicated for the treatment of patients who present with ascites associated with recurrent, platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens.*'

The recommended change is based on the demonstrated efficacy of the treatment of the one-third of patients with ascites on presentation, and the associated relief of symptoms.

Although the PFS is accepted under International Guidelines as a surrogate measure of efficacy, any associated clinical benefit must be sufficient to provide an acceptable risk benefit ratio. The measure of Time to Treatment Failure (TTF) includes important clinical reasons why patients stop treatment that are not considered in the measure of PFS, and becomes more important when other clinical benefits from the treatment with bevacizumab are in question. Also the TTF appears closer to the situation in real life oncology practice than the PFS. Treatment of all patients did not result in an acceptable risk-benefit because of the short increase of 2 mths in the Time to Treatment Failure, from 3.4 to 5.4 mths, the response rate of 28.2%, and an Overall Survival of 16.6 mths, not significantly different from the 13 months in the chemotherapy alone arm. The toxicity of adding bevacizumab is clearly shown by the much higher frequency of serious adverse events, adverse events unique to the drug, and the high rate of discontinuation from adverse events due to bevacizumab, noting that 72 patients out of every 100 receiving added bevacizumab did not respond to the treatment.

Treatment with pegylated liposomal doxorubicin (PD) is not recommended because of the increased frequency of Palmar-Plantar Erythrodysaesthesia Syndrome with BV (PD arm 12.7%; PD+BV arm 27.4%), the overall high frequency of Gd 5 AEs in the PD+BV arm – 6.3% PD alone; 8.1% PD+BV, and the failure to show any benefit in the PFS for patients treated with bevacizumab added to PD chemotherapy (Independent Review of PFS).

2. Changes to the Product Information as recommended are also required to make the product approvable.

14. References

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