London, 26 June 2014
EMA/CHMP/347790/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Avastin

International non-proprietary name: BEVACIZUMAB

Procedure No. EMEA/H/C/000582/II/0063

Note

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

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List of abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ATE	Arterial Thromboembolic Event
AURELIA	Avastin Use in platinum-Resistant EpitheLIal ovarian cAncer
BV	Bevacizumab
CA-125	Cancer Antigen 125
CHF	Congestive Heart Failure
CNS	Central Nervous System
CT	Chemotherapy
eCRF	electronic Case Report Form
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire
EORTC QLQ-OV28	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire ovarian cancer 28
EOC	Epithelial Ovarian Cancer
ECOG	Eastern Cooperative Oncology Group
FIGO	Féderation Internationale de Gynécologie et d'Obstétrique
FTC	Fallopian Tube Cancer
GCIG	Gynecologic Cancer InterGroup
GI	Gastro-Intestinal
HR	Hazard Ratio
HRQoL	Health-related Quality of Life
HTN	Hypertension
iDMC	Independent Data Monitoring Committee
IRC	Independent Review Committee
ITT	Intent-to-treat
MAH	Marketing Authorisation Holder
NPT	Non-Protocol-Specified Anti-Cancer Therapy
PFI	Platinum Free Interval
PLD	Pegylated Liposomal Doxorubicin
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PFI	Platinum-free Interval
PFS	Progression Free Survival
PK	Pharmacokinetic
PK-DDI	Pharmacokinetic- drug-drug-interaction
PP	Per Protocol
PPC	Primary Peritoneal Cancer
PPE	Palmar-plantar Erythrodysesthesia Syndrome
PS	Performance Status
q2w	Every 2 weeks
q3w	Every 3 weeks
RECIST	Response Evaluation Criteria for Solid Tumors
RMP	Risk Management Plan
RPLS/PRES	Reversible Posterior Leukoencephalopathy Syndrome / Posterior Reversible Leukoencephalopathy Syndrome

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOC	Standard of Care
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
VTE	Venous Thromboembolic Event

1. Backgrou nd information on the procedure

1.1. Type I I variation

Pursuant to Article 16 variation of Commission Regulation (EC) No 1234/2008, Roche Registration Ltd submitted to the European Medicines Agency on 4 September 2013 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Avastin	BEVACIZUMAB	See Annex A

The following variation was requested:

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

Extension of indication to include the use of Avastin in combination with chemotherapy (paclitaxel, topotecan or pegylated liposomal doxorubicin) in patients with recurrent, platinum-resistant epithelial ovarian, primary peritoneal, or fallopian tube carcinoma based on the results of study MO22224 (AURELIA).

The variation proposed amendments to the SmPC and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/63/2010 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jens Ersboll Co-Rapporteur: Ingunn Hagen Westgaard

Submission date:	4 September 2013
Start of procedure:	20 September 2013
PRAC Rapporteur preliminary RMP assessment report circulated on:	12 November 2013
CoRapporteur's preliminary assessment report circulated on:	14 November 2013
Rapporteur's preliminary assessment report circulated on:	13 November 2013
PRAC Rapporteur updated RMP assessment report circulated on:	29 November 2013
PRAC RMP advice and assessment overview adopted by PRAC	5 December 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	19 December 2013
MAH's responses submitted to the CHMP on:	20 March 2014
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	23 April 2014
PRAC Rapporteur response RMP assessment report circulated on:	23 April 2014
PRAC RMP advice and assessment overview adopted by PRAC	8 May 2014
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	22 May 2014
MAH's responses submitted to the CHMP on:	28 May 2014
PRAC Rapporteur response RMP assessment report circulated on:	4 June 2014
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	5 June 2014
PRAC RMP advice and assessment overview adopted by PRAC	12 June 2014
CHMP Opinion	26 June 2014
CHMP assessment report on similarity	26 June 2014

2. Scientific discussion

2.1. Introduction

Ovarian cancer (cancer that arises in the epithelium including epithelial ovarian cancer [EOC], fallopian tube cancer [FTC], and primary peritoneal cancer [PPC]) 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 each year. It has the highest mortality rate of all gynaecological cancers (WHO 2011, ACS 2011). In 2008, with an incidence of approximately 65,600 women, there were 41,448 deaths due to ovarian cancer across Europe, accounting for 5.5% of all female cancer deaths. Europeans have the highest incidence of ovarian cancer and it is the fifth most commonly diagnosed female cancer in Europe.

Recurrent disease is classified as platinum-resistant or platinum-sensitive, depending on whether the disease recurs < or ≥ 6 months following previous platinum therapy, respectively; this classification is highly prognostic and is important in determining treatment options. Eventually, all recurrent ovarian cancer patients develop platinum-resistant disease for which there are few effective treatment options currently available. Patients with platinum-resistant disease are usually treated with single-agent, non-platinum chemotherapeutic agents. Overall, the prognosis for platinum-resistant recurrence is dismal, 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 (Gordon 2001, Naumann 2011).

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

Avastin (bevacizumab) was approved in the European Union (EU) on 12 January 2005 for the first-line treatment of patients with metastatic cancer of the colon or rectum (mCRC) in combination with fluoropyrimidine-based chemotherapy.

The indication was subsequently extended to include treatment of locally recurrent and metastatic breast cancer in combination with paclitaxel or capecitabine, for Non-Small Cell Lung Cancer (NSCLC) in addition to platinum-based chemotherapy, the first-line treatment of Renal Cell Cancer (RCC) in combination with interferon alfa-2a, treatment of advanced (FIGO stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with carboplatin and paclitaxel and treatment of first recurrence of platinum-sensitive epithelian ovarian, fallopian tube or primary peritoneal cancer in combination with carboplatin and gemcitabine.

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

‘‘Bevacizumab in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin is indicated for the treatment of adult patients with recurrence of platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens’’.

The final indication approved by the CHMP is as follows:

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

Consequently, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated to reflect the change in the indication accordingly. The PL has been updated accordingly.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

The MAH did not submit an ERA since bevacizumab is a monoclonal antibody (protein), and is therefore exempt from the need for an ERA.

2.2.2. Discussion and conclusion on non-clinical aspects

The MAH has submitted a justification for not supplying an ERA assessment for this extension of indication application.

The EMA 2006 Guideline on Environmental Risk Assessment (ERA) for Non-GMO Human Medicinal Products (EMEA/CHMP/SWP/4447/00) specifically lists amino acids, peptides and proteins among those active pharmaceutical ingredients which do not need an ERA for registration or variations in the European Union. The active ingredient of Avastin (Bevacizumab) is a monoclonal antibody that is a recombinant humanised immunoglobulin of isotype IgG1. As a protein, bevacizumab is exempt from the need for an ERA.

Therefore the MAH's justification for not providing an ERA with this application is acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

2.3.2. Pharmacokinetics

One Phase III clinical trial, Study MO22224 (AURELIA), assessed the efficacy and safety of bevacizumab given in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin (PLD) for the treatment of women with recurrent, platinum-resistant epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC).

Bevacizumab is already approved for, in combination with carboplatin and paclitaxel, front-line treatment of adult patients with advanced (International Federation of Gynecology and Obstetrics (FIGO) stages III B, III C and IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer and in combination with carboplatin and gemcitabine, first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.

The pharmacokinetics of bevacizumab in patients with these gynecological cancers has not been characterized in the target population, but the PK of bevacizumab is not expected to differ in these patients compared to other solid tumours.

The volume of distribution ranged from 2.5 – 3.6 L. No protein binding is expected for this monoclonal antibody. The volume of distribution in patients with mRCC and NSCLC was comparable to the values obtained in other oncology settings. For patients with mPC the median and mean volume of distribution was slightly higher than the reference population, however this was due to a difference in the covariate distribution (male/female ratio was higher than in the reference population). A half-life of 20 days in patients with mRCC, NSCLC and metastatic PC patients was comparable to the reference popPK analyses where the half-life was app. 20 days (range 11-50 days). Clearance was approximately 0.23 L/day (range 0,178 – 0,270) which is also similar to the values seen in the 3 studies in patients with mRCC, NSCLC and metastatic PC.

The pharmacokinetics of bevacizumab was linear (dose independent) and exposure was dose proportional at doses of >1 mg/kg (1.5-10 mg/kg/wk). Body weight, sex and albumin levels are important covariates that explain 40% of the inter-patient variance of clearance. Male patients had a 26% faster clearance than female patients (weight corrected) and lower albumin levels (< 29 g/L) was associated with a 20% lower clearance than for patients with albumin of 37 g/L.

There are no data on drug-drug interactions (DDIs) with bevacizumab in combination with topotecan and pegylated liposomal doxorubicin. Few data on co-administration of bevacizumab and paclitaxel exist. In 3 of 8 patients receiving both bevacizumab and paclitaxel, paclitaxel was found in lower concentrations than at day 0 of the study, compared to the paclitaxel concentrations in patients treated only with paclitaxel. However, these data are limited and is not expected to influence the dosing. No DDIs have been observed between bevacizumab and various chemotherapeutic agents.

The pharmacokinetics of bevacizumab was not described in the target population of women with recurrent platinum-resistant epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC) or fallopian tube cancer (FTC). As the PK of bevacizumab was shown to be similar in a variety of oncology indications, the PK of bevacizumab is expected to have the same PK profile in these gynaecological cancers.

2.3.3. Discussion and conclusion on clinical pharmacology

Bevacizumab PK was not evaluated in patients with gynaecological cancers. However as the bevacizumab PK has been shown to be similar in patients with various solid tumours it can be inferred that this also applies to recurrent, platinum-resistant EOC, PPC and FTC.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response studies have been submitted with bevacizumab for the treatment of recurrent platinum resistant EOC, FTC or PPC. 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 tumour 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). 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, 15 mg/kg q3w is the currently approved dose in the front-line and recurrent platinum-sensitive ovarian cancer settings based on a demonstrated benefit in Phase III trials.

2.4.2. Main study

Study MO22224

Study MO22224 was 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.

Methods

Study participants

The Key inclusion and exclusion criteria are described in Table 1 below.

Table 1. Key inclusion and exclusion criteria

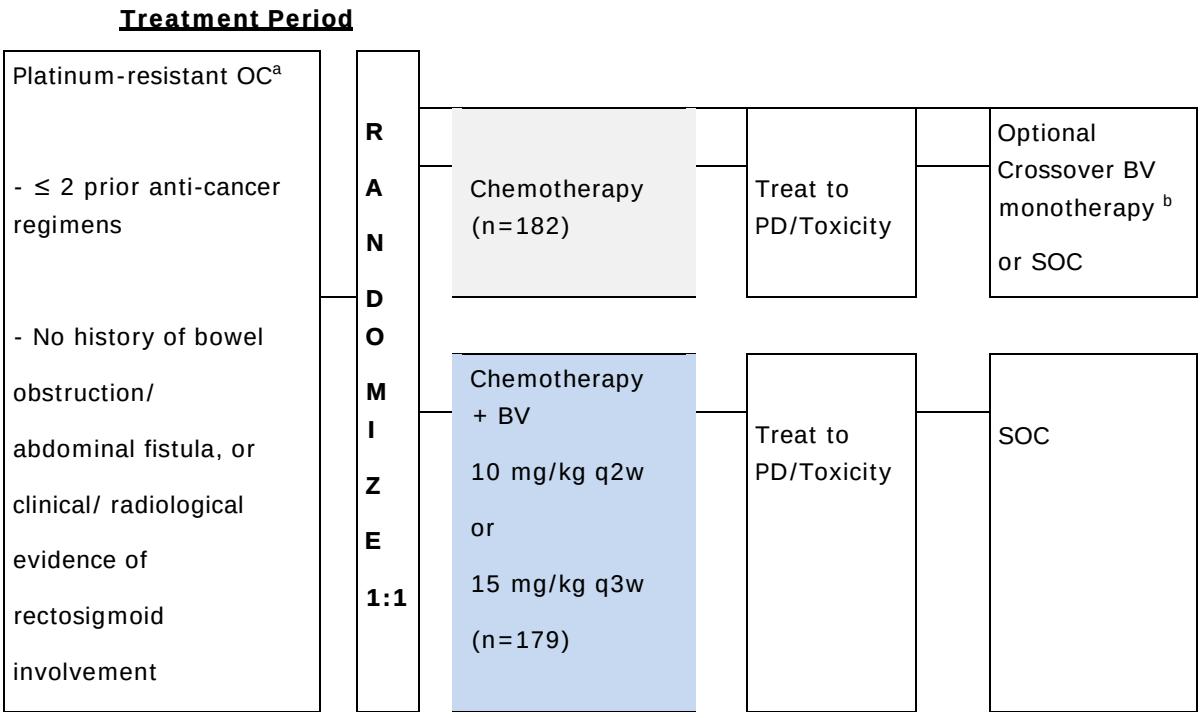
Inclusion criteria	Exclusion criteria
Histologically documented platinum resistant EOC, FTC, or PPC of the following types: adenocarcinoma not otherwise specified (NOS), clear cell adenocarcinoma, endometriod adenocarcinoma, malignant Brenner's tumor, mixed epithelial carcinoma, mucinous adenocarcinoma, serous adenocarcinoma, transitional cell carcinoma and undifferentiated carcinoma	Previous treatment with > 2 anti-cancer regimens.
Progression within 6 months from completion of a minimum of 4 platinum therapy cycles	Patients whose disease was refractory to their previous platinum treatment. (Refractory disease was defined as those patients who progressed during the preceding platinum treatment.)
Measurable disease according to RECIST 1.0 or assessable according to Gynecologic Cancer Intergroup (GCIG) CA-125 criteria and required chemotherapy treatment.	Ovarian tumors with low malignant potential (i.e. borderline tumors).
Patients ≥ 18 years of age	Any prior radiotherapy to the pelvis or abdomen.
Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2.	Surgery within 4 weeks prior to study start
Life expectancy ≥12 weeks	Inadequate bone marrow function, coagulation parameters, liver or renal function.
	Other safety-related exclusion criteria included the following: central nervous system (CNS) disease unrelated to cancer, symptomatic CNS metastasis, pre-existing neuropathy ≥ CTC Grade 2 for those in the paclitaxel group, history or evidence of thrombotic or hemorrhagic disorder, uncontrolled hypertension; left ventricular

	ejection fraction below the institutional lower limit of normal (for patients intended to be treated with PLD), history of bowel obstruction, including sub-occlusive disease, related to the underlying disease and history of abdominal fistula, gastrointestinal (GI) perforation, or intra-abdominal abscess, non-healing wound, ulcer, or bone fracture, serious active infection requiring IV antibiotics or hospitalization, or both, at study entry

Treatments

The study design is presented in Figure 1.

Figure 1. M022224 Study Design



In both arms chemotherapy consisted of one of the following regimens:

- Paclitaxel 80 mg/m^2 as a 1-hour IV infusion on Days 1, 8, 15, and 22 q4w.
- Topotecan 4 mg/m^2 as a 30 minute IV infusion on Days 1, 8, and 15 q4w. Alternatively, a 1.25 mg/m^2 dose could be administered over 30 minutes on Days 1–5 q3w.
- PLD 40 mg/m^2 as a 1 mg/min IV infusion.

In the CT+BV 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/m^2 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.

Upon clear evidence of disease progression (PD per RECIST 1.0), patients in the CT arm were given the opportunity to crossover to bevacizumab monotherapy, and the treatment was continued until disease progression, unacceptable adverse events, or patient request for discontinuation.

Study treatment continued until progressive disease (PD), unacceptable toxicity, or patient request for withdrawal. In addition, any Grade 4 non-hematologic adverse event led to the withdrawal of the patient from the study 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. Bevacizumab dose reductions were not allowed. With treatment related toxicities, chemotherapy doses could be reduced using individual schedules for each chemotherapy drug. No dose re-escalations were planned following dose reduction for toxicity for any of the study treatments.

Response assessment

Patients were assessed for disease response or progression every 8 or 9 weeks, throughout the study until PD, depending on the chemotherapy schedule, using the same imaging method used during screening (CT scan or MRI or plain X-ray). Tumour assessments were only performed post-study treatment in the absence of confirmation of disease progression, at 8-week intervals. Patients were followed up with tumour assessments for a minimum of 6 months unless disease progression occurred earlier. Survival follow-up continued at least until the last patient had completed a minimum of 12 months after the end of treatment.

Objectives

The primary objective of the pivotal study M022224 was to compare the efficacy (progression free survival, PFS) of bevacizumab plus chemotherapy (CT+BV) versus chemotherapy (CT) alone. The key secondary objectives included the evaluation of efficacy by objective response rate (ORR), overall survival (OS) and duration of response and the evaluation of the safety profile of CT+BV vs. CT alone.

Outcomes/endpoints

The primary endpoint of the pivotal study was PFS, defined as the time from randomization to investigator-assessed disease progression or death from any cause, whichever occurred first. Disease progression was determined by the investigator according to RECIST 1.0 or by symptomatic deterioration, whichever occurred first. Progression was not declared based on rising CA-125 levels alone.

The key secondary endpoints were the following:

Objective response rate (ORR) defined as confirmed complete response (CR) or partial response (PR) determined by investigators according to RECIST, in patients with measurable disease at baseline.

Duration of objective response, defined as the time from first occurrence of confirmed PR or CR (whichever occurred first) until disease progression determined by investigators according to RECIST; or death.

Overall survival (OS), defined as the time from randomization to death from any cause.

Abdominal or GI Symptom Scale in QLQ-OV28: The primary patient-reported outcome (PRO) measure is the proportion of patients who have experienced a clinically meaningful improvement at Week 8 or 9 in an ovarian cancer−related abdominal/GI symptom as manifested in the abdominal/GI symptom scale of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) ovarian cancer 28 (OV28) at week 8 or 9.

Exploratory endpoints included ORR by CA-125 response criteria only (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), time to biological progression on the basis of a progressive serial elevation of serum CA-125 alone, other measures of health-related quality of life (HRQoL) and frequency of paracentesis.

Sample size

On the basis of a two-sided test at an α level of 0.05 for the comparison of primary endpoint PFS between the two treatment arms, about 247 PFS events in the two treatment arms combined would be required to achieve 80% power to detect an HR of 0.70. Under the exponential assumption, the corresponding improvement of median PFS is from 4.0 months in the CT arm to 5.7 months in the CT+BV arm. The corresponding sample size was 332 patients. In January 2011, when approximately 300 patients were enrolled, the sample size was increased to 360 patients per the recommendation of the independent Data Monitoring Committee.

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 for the upper limit of the 95% confidence interval (CI) for the HR to be 1.

Randomisation

Patients were randomized 1:1 to CT+BV or CT alone and were stratified by the following three factors:

- Selected chemotherapy cohort (paclitaxel versus topotecan [daily for 5 days versus weekly administration] versus PLD)
- Previous anti-angiogenic therapy (yes or no)
- Platinum-free interval (PFI) (<3 months versus 3–6 months from the last administered dose of platinum therapy to subsequent disease progression).

Blinding (masking)

The study was open-labelled.

Statistical methods

The primary efficacy analysis was the comparison of the PFS survivor functions between the two treatment arms using a two-sided stratified log-rank test. The null hypothesis for the primary efficacy analysis was that there would be no difference in the PFS survivor functions between the two treatment arms. The primary efficacy analysis was performed in the ITT population (all patients who were randomised to one of the two treatment arms) and was planned to be repeated using the Per Protocol (PP) population (subset of ITT population who have received at least one study treatment cycle and had no major violation of the protocol inclusion and exclusion criteria to confirm overall study results).

The Kaplan–Meier method was used to estimate median PFS for each treatment arm. The Brookmeyer–Crowley method was used to construct the 95% CI for the median PFS for each treatment arm. Further, the HR was estimated using a stratified Cox regression model with the same three stratification factors used in the stratified log-rank test in order to assess the magnitude of the

treatment effect. The analysis using the Cox-regression model was also performed in a non-stratified manner.

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 tumour assessment on or before the clinical cut-off date (or at day 1 otherwise), regardless of the initiation of non−protocol-specified anti-cancer therapy (NPT) or crossover of patients in the CT arm to bevacizumab monotherapy.

The following sensitivity analyses were performed using the same statistical methods applied in the primary analysis of PFS: effect of discontinuation because of toxicity; effect of NPT and bevacizumab monotherapy; backdating progressive disease date in the CT+BV arm; backdating PFS event date in the CT+BV arm; accounting for missing data; accounting for the initiation of NPT and bevacizumab monotherapy; and accounting for CA-125 PD.

Computer simulations were performed to generate hypothetical IRC tumor assessment data. The primary analysis approach was performed on each simulated dataset. Stratified HRs and log-rank p-values were summarized for each scenario.

In the first set of simulations, the IRC tumor assessment data were simulated 10,000 times under each of the following scenarios based on the assumption of the concordance rate observed in a phase II study in 44 platinum resistant EOC/PPC patients AVF 4095g:

1. Investigator-determined PD events were not confirmed by IRC (in both arms 20% of PD events not considered as PD events by IRC)
2. Investigator-determined PD events were earlier per IRC: 20% of PD events backdated to the last tumor assessment date before the PD date in both arms. Another random subset of 20% was backdated to the second last tumor assessment.
3. Investigator-determined PD events were not confirmed or were earlier per IRC by combining the above two scenarios.

Second set of simulations with more conservative assumptions:

4. Investigator-determined PD events were not confirmed by IRC: in the CT arm, the investigator-determined PD events were lost at the same rate of 20% as in scenario 1. In the CT+BV arm, a random subset of only 1% of PD events was not considered as PD events by IRC.
5. Investigator-determined PD events were earlier per IRC: in the CT+BV arm, the investigator-determined PD events were backdated at the same rate as in scenario 2. In the CT arm, a random subset of only 10% of PD events was backdated to the last tumor assessment date before the PD date. And another random subset of 10% of PD events was backdated to the second to last tumor assessment dates before the PD dates.
6. Investigator-determined PD events were not confirmed or earlier per IRC: by combining scenarios 4 and 5.

Subgroup analysis

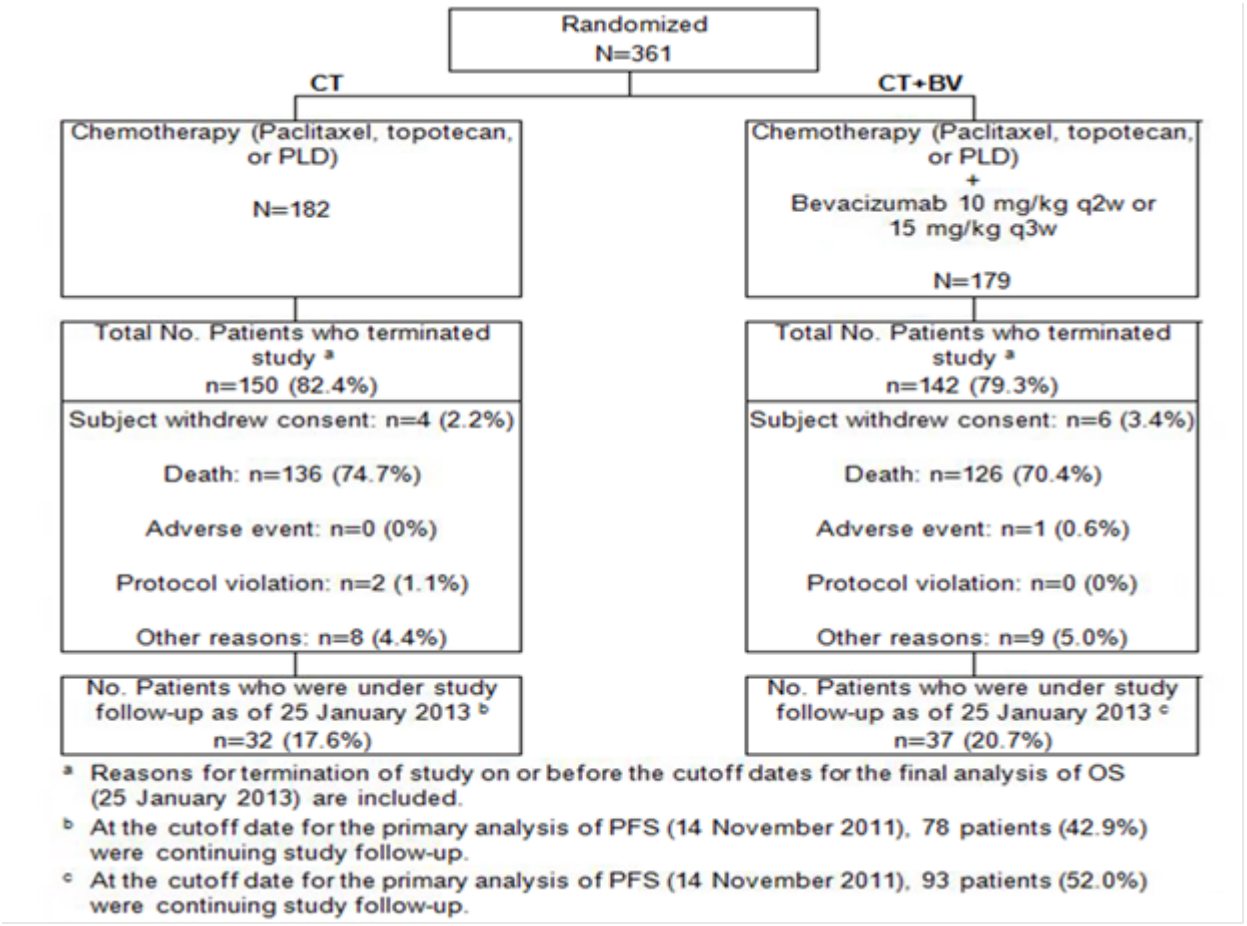
Kaplan-Meier estimates of the median time to event, the unstratified HR, and its 95% confidence interval (CI) of PFS were produced for several demographic and baseline prognostic characteristics.

Results

Participant flow

The disposition of patients is presented in Figure 2.

Figure 2. Disposition of Patients



Recruitment

The first patient was randomized on 29 October 2009 and the last on 14 November 2011. A total of 361 patients were randomized at 96 sites in Europe.

Conduct of the study

The protocol for Study MO22224 was finalized on 4 May 2009 and was subsequently amended three times.

The first amendment was finalized on 24 November 2009, by which date 6 patients were randomized and the following clarifications and changes were provided:

• The definition of platinum resistance was made more specific to define platinum resistance as progression within < 6 months from completion of a minimum of 4 platinum therapy cycles, with the date calculated from the last administered dose of platinum therapy.

• The definition of prior therapies was clarified to include all previous anti-cancer therapy, including those received in the front-line or recurrent settings.

• To clarify that it was not a requirement in RECIST for the same investigator to evaluate the patient at each assessment.

• The statistical analysis for the primary endpoint was updated from a one- to a two-sided log-rank test. The sample size and statistical assumptions were updated accordingly, such that a total of 282 patients were needed to observe 247 events which would be sufficient to yield 80% power for a two-sided log rank test at an alpha level of 5%. Taking into consideration a potential patient drop bevacizumab out, the sample size was adjusted by approximately 15% and therefore a total of 332 patients were enrolled into the study, with 166 patients randomized to either treatment arm.

• The numbers of patients randomized to chemotherapy cohorts was amended because of statistical changes to include 120 patients per chemotherapy cohort.

• The timing of QoL assessments was amended so that it was more suited to the scheduling of cycle visits, the timing of the 3 worst symptom questionnaire was collected at baseline only, and the use of the 3 worst symptom questionnaire methodology was described in more detail.

• The protocol was updated so that all Grade 2 adverse events were collected. Previously, it was only necessary to collect Grade 3–5 adverse events and clinically significant Grade 2 adverse events only.

• Clarification of how a patient who had been previously enrolled in a blinded study with an anti-angiogenic was to be stratified.

• The frequency of CA-125 assessments was corrected to be performed every cycle and not at every visit.

• A window of flexibility was permitted for cycle visits (± 3 days). This flexibility was also applied to follow-up visits to allow for public holidays/clinic scheduling.

• The end-of-treatment assessment was corrected to be calculated from the last dose of study medication.

• Clarification that the previously described “optional post-study phase” for patients randomized to the CT arm was for the CT arm patients only and that bevacizumab was to be given as part of the study to those patients who opted to receive crossover bevacizumab monotherapy.

• Additional safety guidance to clarify the management of bevacizumab in the event of CNS bleeding, proteinuria management, and hypersensitivity with paclitaxel.

• The definition of residual disease was amended based on the presence or absence of macroscopic disease.

•One of the definitions of progression for patients with measurable disease at randomization was further described and specified that every effort would be made to document progressive disease objectively and the definition of progression for patients with non-measurable disease at randomization was further detailed and corrected.

The protocol for Study MO22224 was amended a second time on 28 October 2010, by which date 236 patients were randomized, and the following key clarifications and changes were provided:

• Clarification regarding the exclusion criteria for platinum refractory disease, peripheral neuropathy, and previous malignancies.

• Addition of LVEF assessments every fourth cycle for patients receiving PLD.

• Additional requirement to capture certain concomitant medication in the eCRF, particularly supportive medication prescribed for the treatment of cancer-related symptoms or potential side effects of chemotherapy.

• Clarification that only serious adverse events caused by protocol-mandated interventions needed to be collected prior to initiation of study medication and that all serious adverse events needed to be collected before, during, and after study drug dosing.

• Guidance on dose modification to reflect the bevacizumab safety profile.

• Clarification to ensure that only those patients who experienced disease progression on chemotherapy alone were able to subsequently receive bevacizumab on the bevacizumab crossover option.

The protocol for Study MO22224 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).

Baseline data

The baseline demographic and disease characteristics are presented in Tables 2 and 3.

Table 2. Demographic and Baseline Characteristics: Randomized Patients

	CT (n=182)	CT+BV (n=179)	All Patients (n=361)
Age (yr)			
n	182	179	361
Mean (SD)	60.7 (9.8)	60.0 (11.1)	60.3 (10.4)
Median	61.0	62.0	61.0
25th and 75th percentiles	55.0 - 67.0	55.0 - 68.0	55.0 - 67.0
Min-Max	25 - 84	25 - 80	25 - 84
Age Group (yr)			
n	182	179	361
< 65	119 (65.4%)	109 (60.9%)	228 (63.2%)
>= 65	63 (34.6%)	70 (39.1%)	133 (36.8%)
Race			
n	51	55	106
Asian	1 (2.0%)	(0.0%)	1 (0.9%)
Other (Spanish)	1 (2.0%)	(0.0%)	1 (0.9%)
White	49 (96.1%)	55 (100.0%)	104 (98.1%)
ECOG performance status at baseline			
n	181	178	359
0	102 (56.4%)	109 (61.2%)	211 (58.8%)
1	70 (38.7%)	53 (29.8%)	123 (34.3%)
2	8 (4.4%)	16 (9.0%)	24 (6.7%)
3	1 (0.6%)	(0.0%)	1 (0.3%)

Table 3. Baseline Disease Characteristics: Randomized Patients

	CT (n=182)	CT+BV (n=179)	All Patients (n=361)
Origin of cancer [1]			
n	181	179	360
Fallopian tube	6 (3.3%)	2 (1.1%)	8 (2.2%)
Ovary	154 (85.1%)	164 (91.6%)	318 (88.3%)
Ovary, Fallopian tube	1 (0.6%)	(0.0%)	1 (0.3%)
Ovary, Primary peritoneal	2 (1.1%)	3 (1.7%)	5 (1.4%)
Primary peritoneal	18 (9.9%)	10 (5.6%)	28 (7.8%)
Histological grade			
n	162	157	319
Grade 1 - Well differentiated	9 (5.6%)	10 (6.4%)	19 (6.0%)
Grade 2 - Moderately differentiated	48 (29.6%)	53 (33.8%)	101 (31.7%)
Grade 3 - Poorly differentiated	105 (64.8%)	94 (59.9%)	199 (62.4%)
Measurable disease at baseline			
n	182	179	361
NO	38 (20.9%)	37 (20.7%)	75 (20.8%)
YES	144 (79.1%)	142 (79.3%)	286 (79.2%)
Baseline SLD of target lesions (mm)			
n	144	143	287
Mean (SD)	76.8 (69.7)	76.5 (72.1)	76.7 (70.7)
Median	56.5	52.0	54.0
25th and 75th percentiles	27.0 - 98.0	26.0 - 95.0	27.0 - 97.0
Min-Max	10 - 370	0 - 493	0 - 493
Any non-target lesions at baseline			
n	182	179	361
YES	134 (73.6%)	134 (74.9%)	268 (74.2%)
Ascites at baseline			
n	182	179	361
YES	54 (29.7%)	59 (33.0%)	113 (31.3%)
Baseline CA-125 within 14 days before first protocol treatment			
n	176	171	347
<2*ULN	26 (14.8%)	19 (11.1%)	45 (13.0%)
>=2*ULN	150 (85.2%)	152 (88.9%)	302 (87.0%)
PFI (months)			
n	182	179	361
3-6 mon	135 (74.2%)	127 (70.9%)	262 (72.6%)
<3 mon	47 (25.8%)	52 (29.1%)	99 (27.4%)

Prior treatment for ovarian cancer

Prior treatment for ovarian cancer is presented in Table 4.

Table 4. Prior Treatment for Ovarian Cancer

	CT (n=182)	CT+BV (n=179)	All Patients (n=361)
Any prior treatment			
Yes	182 (100.0%)	179 (100.0%)	361 (100.0%)
Initial surgical management of ovarian cancer			
No	10 (5.5%)	14 (7.8%)	24 (6.6%)
Yes	159 (87.4%)	156 (87.2%)	315 (87.3%)
Missing	13 (7.1%)	9 (5.0%)	22 (6.1%)
Received any first line chemotherapy			
Yes	182 (100.0%)	179 (100.0%)	361 (100.0%)
First line platinum-based regimen			
Yes	182 (100.0%)	179 (100.0%)	361 (100.0%)
Received any second line chemotherapy			
n	182	179	361
No	104 (57.1%)	107 (59.8%)	211 (58.4%)
Yes	78 (42.9%)	72 (40.2%)	150 (41.6%)
Second line platinum-based regimen			
n	78	72	150
No	7 (9.0%)	11 (15.3%)	18 (12.0%)
Yes	71 (91.0%)	61 (84.7%)	132 (88.0%)
Second line chemotherapy regimen			
Yes	78	72	150
Paclitaxel	25 (32.1%)	26 (36.1%)	51 (34.0%)
PLD	34 (43.6%)	35 (48.6%)	69 (46.0%)
Topotecan	4 (5.1%)	2 (2.8%)	6 (4.0%)
Other	66 (84.6%)	55 (76.4%)	121 (80.7%)
Any previous anti-angiogenic therapy			
n	182	179	361
No	167 (91.8%)	167 (93.3%)	334 (92.5%)
Yes	15 (8.2%)	12 (6.7%)	27 (7.5%)

Numbers analysed

A total of 361 patients (182 patients in the CT group and 179 patients in the CT+BV) were included in the ITT population.

A total of 294 patients (158 patients in the CT group and 136 patients in the CT+BV) were included in the PP population.

Outcomes and estimation

Primary endpoint

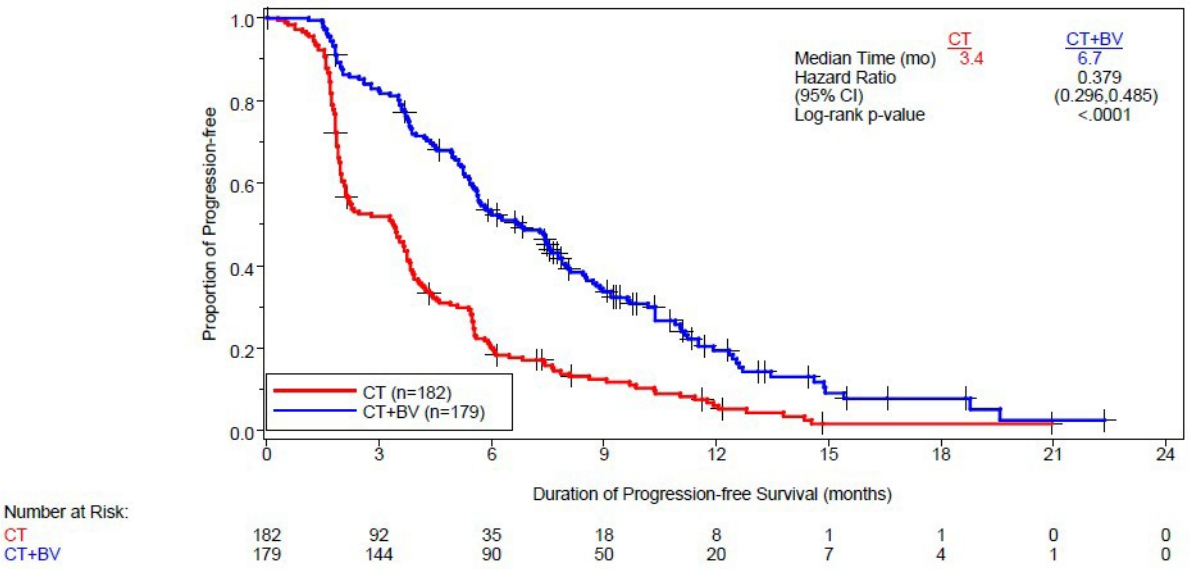
Progression-Free Survival (Investigator-Assessed)

The efficacy results in terms of the primary endpoint of PFS and for the primary analysis of 14 November 2011 are summarised in the following table and figure.

Table 5. Progression-Free Survival-Stratified analysis- cut-off 14 November 2011 (Randomised patients)

	CT	CT+ BV
Patients randomised	182	179
Progressive disease or died	168 (92.3%)	141 (78.8%)
Censored	14 (7.7%)	38 (21.2%)
Progression-free survival (months)		
Median (95% CI)	3.4 (2.10, 3.75)	6.7 (5.62, 7.79)
log-rank p-value (stratified)	< 0.0001	
Hazard ratio (95% CI)	0.379 (0.296, 0.485)	

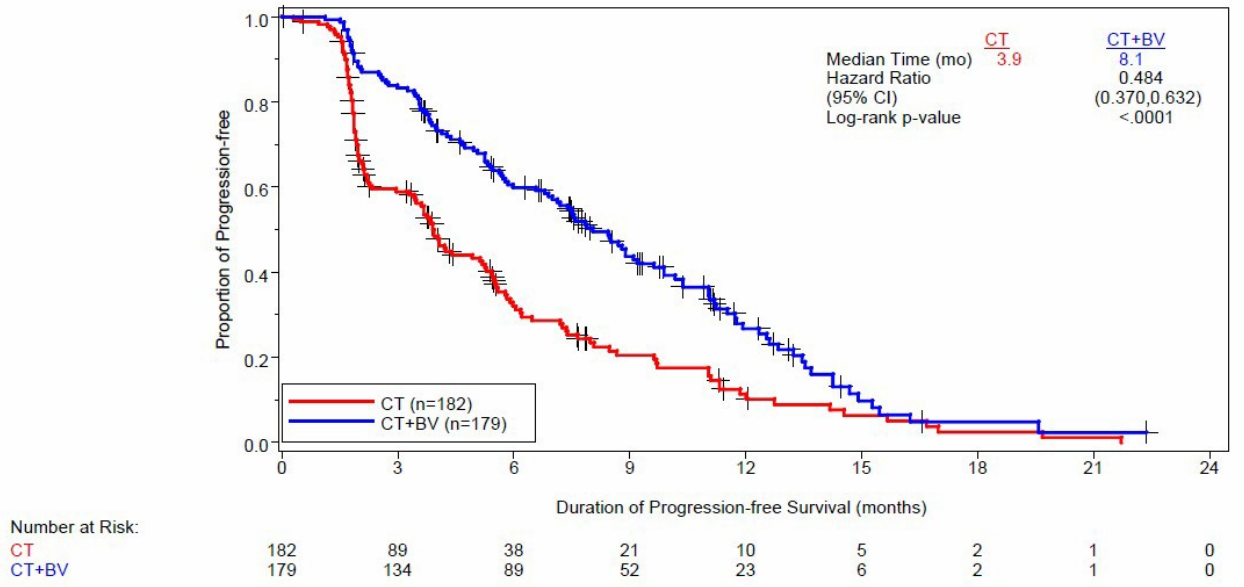
Figure 3. Kaplan-Meier plot of Progression Free Survival (Randomised patients)



BV = bevacizumab; CT = chemotherapy.

The MAH provided an analysis of PFS by IRC upon request. The results are presented in the following figure.

Figure 4. Kaplan-Meier Plot of PFS as Determined by the IRC



+ = censored value; BV = bevacizumab; CI = confidence interval; CT = chemotherapy.

Sensitivity and exploratory analyses of PFS

An overview of the results of the sensitivity analyses of PFS is presented in Table 7.

Table 6. Progression Free Survival: Sensitivity analysis

	Median PFS (months)		Stratified Analysis		
PFS Analysis	**CT**	**CT+BV**	**Hazard Ratio**	**(95% CI)**	**log-rank p-value**
Primary stratified analysis	3.4	6.8	0.384	(0.300, 0.491)	< 0.0001
Accounting for missing scans in both arms [a]	3.4	6.6	0.391	(0.307, 0.498)	< 0.0001
Accounting for missing scans in the CT+BV arm only [b]	3.4	6.6	0.398	(0.312, 0.509)	< 0.0001
Censoring at discontinuation due to toxicity [c]	3.4	7.8	0.304	(0.231, 0.401)	< 0.0001
Censoring at NPT and crossover BV monotherapy [d]	3.4	6.8	0.378	(0.294, 0.487)	< 0.0001
Accounting for initiation of crossover to BV monotherapy or NPT [e]	2.5	6.3	0.384	(0.300, 0.490)	< 0.0001
Backdating PD date in the CT+BV arm [f]	3.4	4.8	0.541	(0.427, 0.685)	< 0.0001
Backdating PD or death date in the CT+BV arm [g]	3.4	4.6	0.603	(0.476, 0.764)	< 0.0001
RECIST PD/biological progression by CA-125 symptomatic deterioration/death [h]	3.3	5.6	0.392	(0.306, 0.501)	< 0.0001

Subgroup analysis of PFS

The results of the subgroup analyses are presented below.

Table 7. Progression Free survival by baseline risk factor

Baseline Characteristic	Total n	Total Events	CT (n=182) # of Events	CT (n=182) Median (month)	CT+BV (n=179) # of Events	CT+BV (n=179) Median (month)	Hazard Ratio	(95% CI)
All Patients	361	309	168	3.4	141	6.7	0.46	(0.37 - 0.58)
Age (years)								
< 65	228	200	111	3.3	89	6.0	0.46	(0.35 - 0.61)
>= 65	133	109	57	3.6	52	7.8	0.45	(0.31 - 0.67)
Baseline ECOG performance status								
0	211	171	93	3.5	78	8.5	0.34	(0.25 - 0.46)
1	123	112	65	3.3	47	5.0	0.70	(0.48 - 1.03)
>=2	25	24	9	3.3	15	5.2	0.64	(0.27 - 1.51)
Platinum therapy free interval (month)								
<3	99	91	45	2.0	46	5.4	0.50	(0.33 - 0.75)
3-6	262	218	123	3.6	95	7.6	0.42	(0.32 - 0.56)
Measurable disease at baseline								
No	75	64	35	3.7	29	8.0	0.43	(0.26 - 0.71)
Yes	286	245	133	2.8	112	6.2	0.46	(0.36 - 0.59)
Baseline SLD of target lesions (mm)								
<= Median (54.0)	144	123	63	3.3	60	6.9	0.52	(0.36 - 0.75)
> Median	143	123	70	2.2	53	6.0	0.41	(0.28 - 0.59)
Ascites at baseline								
No	248	208	116	3.5	92	7.6	0.47	(0.35 - 0.62)
Yes	113	101	52	2.5	49	5.4	0.38	(0.25 - 0.58)
Chemotherapy selected at randomization								
Paclitaxel	115	89	50	3.9	39	9.2	0.47	(0.31 - 0.72)
PLD	126	118	61	3.5	57	5.1	0.53	(0.36 - 0.77)
Topotecan	120	102	57	2.1	45	6.2	0.28	(0.18 - 0.44)
Previous anti-angiogenic therapy								
No	334	287	156	3.4	131	6.9	0.43	(0.34 - 0.54)
Yes	27	22	12	4.3	10	5.4	1.11	(0.46 - 2.69)

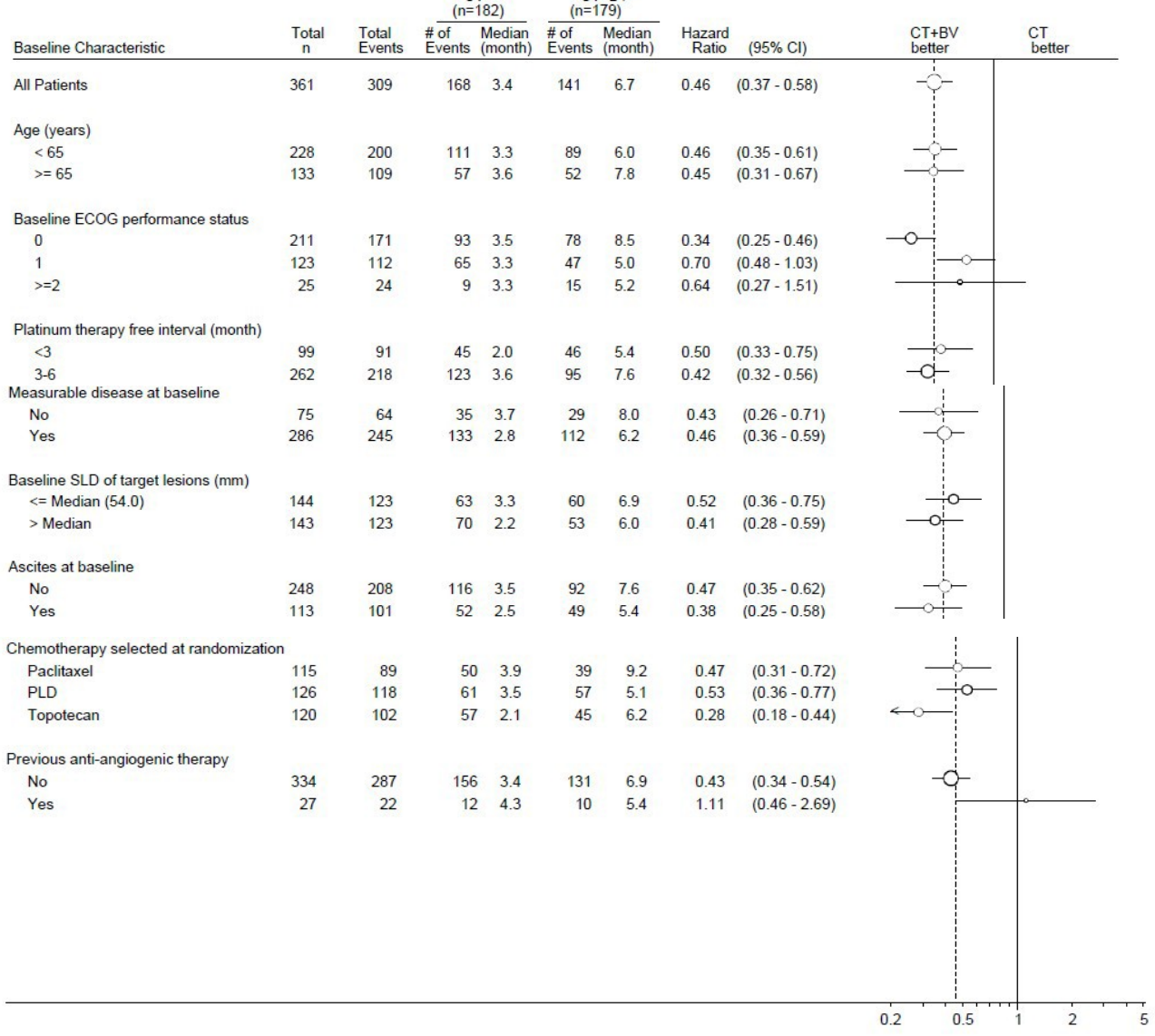
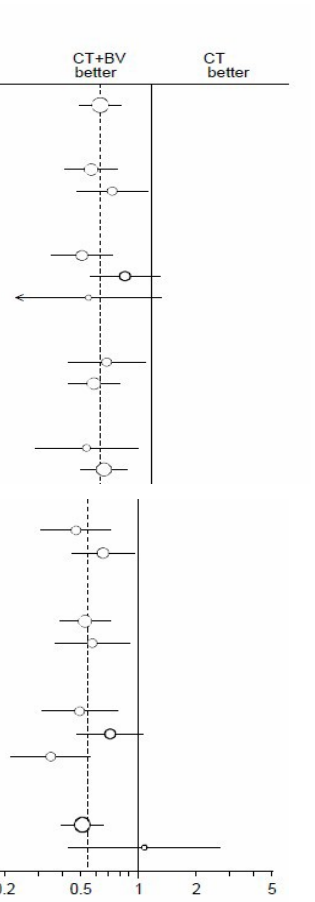


Table 8. PFS as Determined by the IRC by Baseline Risk Factor: Randomized Patients

Baseline Characteristic	Total n	Total Events	CT (n=182) # of Events	CT (n=182) Median (month)	CT+BV (n=179) # of Events	CT+BV (n=179) Median (month)	Hazard Ratio	(95% CI)
All Patients	361	251	134	3.9	117	8.1	0.54	(0.42 - 0.70)
Age (years)								
< 65	228	162	90	3.6	72	7.5	0.49	(0.36 - 0.67)
>= 65	133	89	44	5.3	45	9.2	0.63	(0.41 - 0.96)
Baseline ECOG performance status								
0	211	128	68	4.1	60	10.2	0.44	(0.31 - 0.62)
1	123	97	56	3.9	41	5.9	0.73	(0.48 - 1.11)
>=2	25	24	9	1.8	15	3.9	0.47	(0.20 - 1.13)
Platinum therapy free interval (month)								
<3	99	77	36	3.5	41	5.4	0.59	(0.37 - 0.94)
3-6	262	174	98	4.0	76	9.2	0.50	(0.37 - 0.68)
Measurable disease at baseline								
No	75	45	26	4.1	19	8.8	0.46	(0.25 - 0.85)
Yes	286	206	108	3.8	98	7.6	0.57	(0.43 - 0.75)
Baseline SLD of target lesions (mm)								
<= Median (54.0)	144	91	45	4.1	46	8.9	0.47	(0.31 - 0.72)
> Median	143	115	63	3.7	52	5.6	0.66	(0.45 - 0.95)
Ascites at baseline								
No	248	172	92	3.7	80	8.5	0.53	(0.39 - 0.72)
Yes	113	79	42	4.1	37	7.0	0.58	(0.37 - 0.91)
Chemotherapy selected at randomization								
Paclitaxel	115	76	40	4.2	36	9.6	0.50	(0.31 - 0.78)
PLD	126	100	51	3.9	49	7.5	0.71	(0.48 - 1.06)
Topotecan	120	75	43	2.3	32	7.1	0.35	(0.22 - 0.56)
Previous anti-angiogenic therapy								
No	334	230	122	3.9	108	8.1	0.51	(0.39 - 0.66)
Yes	27	21	12	5.6	9	9.6	1.08	(0.43 - 2.68)



Simulation analysis

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. In the second set of simulations, more conservative assumptions were made in favor of the CT arm. 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 indicated 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 (data not shown).

Secondary endpoints

Objective Response Rate (ORR) per RECIST

The results of the ORR are presented in the following table:

Table 9. ORR: Randomised Patients with Measurable Disease at Baseline

	CT	CT+ BV
Patients randomised	144	142
Patients with objective response	18 (12.5%)	40 (28.2%[1])
Complete response	5 (3.5%)	5 (3.5%)
Partial Response	13 (9%)	35 (24.6%)
Difference in objective response rate (95% CI)	15.7 (6.5, 24.8)	
p-value (stratified)	0.0007	

Duration of Objective Response

The analysis of duration of objective response included only randomized patients with an objective response. 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 tumour assessment. 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 in the CT arm and 9.4 months in the CT+BV arm (data not shown).

Overall Survival

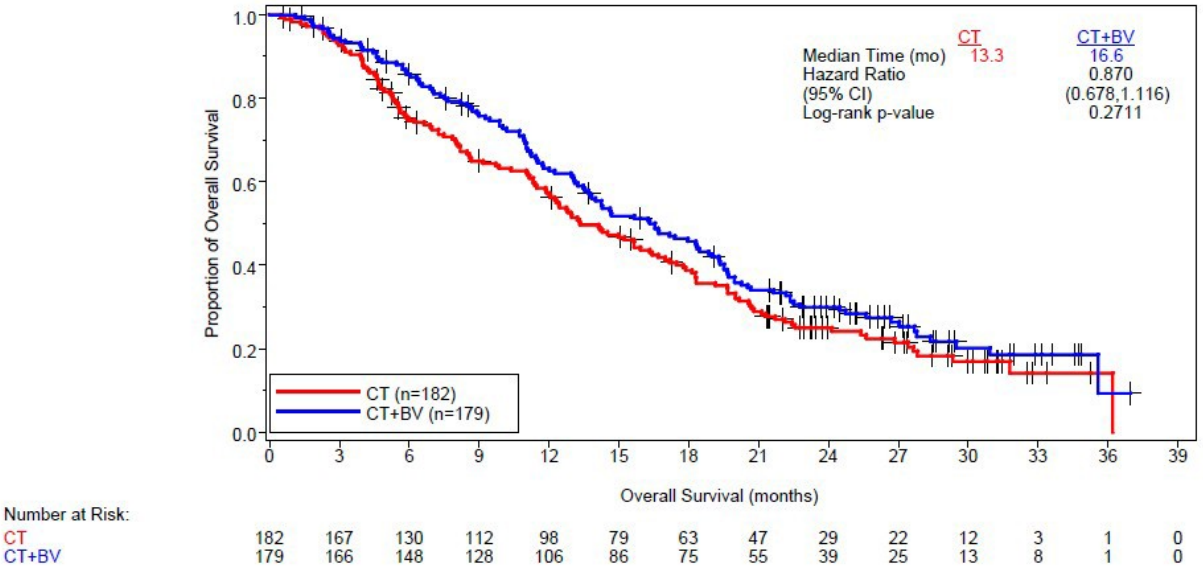
The results of the final analysis of OS (cut-off date 25 January 2013) are summarised in the following tables and figure.

Table 10. Overall Survival- Stratified analysis - cut-off date 25 January 2013

	CT	CT+BV
Patients randomised	182	179
Death	138 (75.8%)	128 (71.5%)
Censored	44 (24.2%)	51 (28.5%)
Overall Survival (months)		
Median (95% CI)	13.3 (11.89, 16.43)	16.6 (13.70, 18.99)
Log-rank p-value (stratified)	0.2711	
Hazard ratio (95% CI)	0.870 (0.678, 1.116)	

[1] Correction, figure 18.2% changed to 28.2%

Figure 4. Kaplan Meier plot of Overall Survival: Final analysis

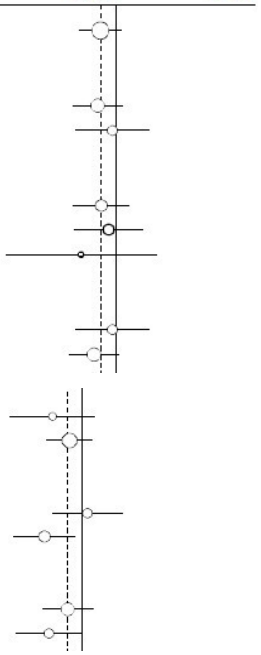


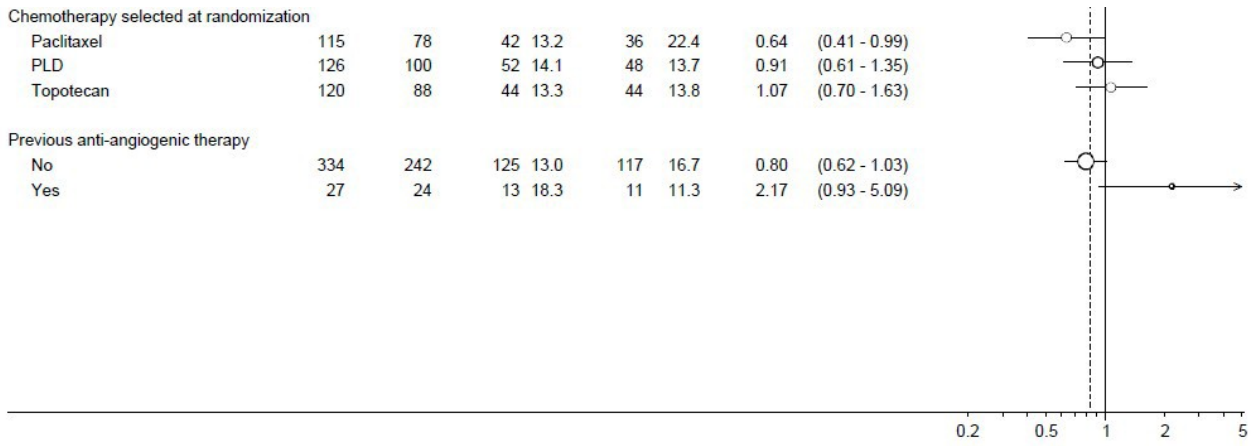
BV = bevacizumab; CT= chemotherapy.

Exploratory subgroup analyses of final OS

Table 11.Overall Survival by baseline risk factor: Final analysis

Baseline Characteristic	Total n	Total Events	CT (n=182) # of Events	CT (n=182) Median (month)	CT+BV (n=179) # of Events	CT+BV (n=179) Median (month)	Hazard Ratio	(95% CI)
All Patients	361	266	138	13.3	128	16.6	0.83	(0.65 - 1.06)
Age (years)								
< 65	228	180	98	12.9	82	14.7	0.80	(0.60 - 1.08)
>= 65	133	86	40	16.7	46	18.3	0.95	(0.62 - 1.46)
Baseline ECOG performance status								
0	211	138	68	17.8	70	19.7	0.84	(0.60 - 1.17)
1	123	102	60	11.9	42	11.8	0.91	(0.62 - 1.36)
>=2	25	24	9	7.0	15	6.4	0.66	(0.28 - 1.58)
Platinum therapy free interval (month)								
<3	99	83	40	11.9	43	11.0	0.95	(0.62 - 1.47)
3-6	262	183	98	15.7	85	18.4	0.77	(0.58 - 1.03)
Measurable disease at baseline								
No	75	60	31	13.0	29	18.3	0.70	(0.42 - 1.17)
Yes	286	206	107	14.1	99	14.7	0.86	(0.65 - 1.13)
Baseline SLD of target lesions (mm)								
<= Median (54.0)	144	87	43	20.2	44	17.4	1.07	(0.70 - 1.63)
> Median	143	119	64	10.4	55	14.3	0.63	(0.44 - 0.91)
Ascites at baseline								
No	248	168	90	17.0	78	19.3	0.84	(0.62 - 1.13)
Yes	113	98	48	7.9	50	11.7	0.67	(0.45 - 0.99)





Abdominal/GI Symptom Scale in EORTC QLQ-OV28

The QLQ-OV28 assessment was completed at baseline by 162 of 182 (89.0%) and 158 of 179 (88.3%) randomized patients in the CT and CT+BV arms, respectively. The CT+BV arm showed improvement at all assessment time points. In comparison, the CT arm showed worsening at Weeks 8/9, 16/18, and 24, but not at Week 30. In the CT+BV arm, the mean abdominal/GI symptom scale gradually decreased from baseline indicating that as a group, there was an improvement from baseline levels in the mean scores in abdominal/GI symptoms. In contrast, the CT arm showed worsening abdominal/GI symptoms from baseline over the study treatment period.

Repeated measure mixed-effect model analysis, with baseline score as a covariate, was implemented for the absolute abdominal/GI symptom scale Overall, the mean difference between treatment arms was 6.1 points (95% CI: 1.1, 11.2; p = 0.0181) favoring CT+BV. The data showed neither a statistically significant temporal effect nor a statistically significant interaction between time and treatment (data not shown).

Ancillary analyses

PFS and OS analyses by chemotherapy cohort

The PFS and OS analyses by chemotherapy cohort are presented in the table below.

Table 12: Exploratory PFS and OS analyses by chemotherapy cohort

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

ORR by CA-125 response criteria only

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) (data not shown).

Time to biological progression on the basis of a progressive serial elevation of serum CA-125 alone

Table 13. Time to biological progression by CA-125: Randomised patients

	CT	**CT+BV**
Patients randomised	182	179
Patients progressed by CA-125	51 (28%)	70 (39.1%)
Censored	131 (72%)	109 (60.9%)
Time to progression by CA-125 (months)		
Median (95% CI)	7.1 (6.01, 9.49)	8.5 (7.49, 11.27)
Log-rank p-value (stratified)	0.0233	
Hazard ratio (95% CI)	0.640 (0.434, 0.944)	

The Kaplan-Meier curves began to separate after 5 months (data not shown).

Frequency of paracentesis

Among patients in the CT arm, 8 patients required a total of 15 post-dosing procedures of paracentesis during the protocol treatment periods (cycles) 1 through 8 on the basis of the data captured on the CRF. In the CT+BV arm, one patient required one post-dosing procedure of paracentesis, which occurred during treatment cycle 1 (data not shown).

Other measures of health-related quality of life (HRQoL)

Compliance rate

The primary HRQoL endpoint (abdominal/GI scale) was based on the QLQ-OV28 module. The compliance rates for QLQ-C30 were slightly higher than the compliance rates for QLQ-OV28. The compliance rates for FOSI and HADS were similar to the rates seen for the QLQ-OV28.

Global health status/quality of life in EORTC QLQ-C30

A responder analysis of GHS/QoL was performed by identifying those patients with an occurrence of improvement in each arm based on an increase in the QLQ-C30 GHS/QoL scale of ≥10 points from baseline score. Across all time points, the CT+BV arm consistently showed higher response rates than the CT arm. Meanwhile, the mean change from baseline in the GHS/QoL in the CT+BV arm consistently indicated an improvement. These results demonstrate that a greater proportion of patients in the CT+BV arm improved in meaningful levels of GHS/QoL, and as a group, the mean level of GHS/QoL was numerically improved during treatment in the CT+BV arm.

Functional scales in EORTC QLQ-OV28 and QLQ-C30

Mean score changes from baseline indicated that physical function for the CT+BV arm was generally worse over time than at baseline, but not consistently worse than the CT arm in terms of responder rate. Cognitive function was consistently worse in the CT+BV arm than in the CT arm in terms of response rate. In both treatment arms, the cognitive function was worsened over time compared with the respective baseline values, suggesting that the cognitive function of patients, no matter which protocol-specified treatment they received, worsened over time.

Symptom scales in EORTC QLQ-OV28 and QLQ-C30

The CT+BV arm showed advantages compared with the CT arm in the following symptoms: frequent urination, fatigue, and peripheral neuropathy. Of the remaining symptom scales, diarrhea and hearing were worse in the CT+BV arm. Other symptoms did not show differences between the two arms. However, there were some notable changes in symptoms. In both arms, there were improvements in insomnia, and symptom worsening in skin problems, taste disturbance, and hair loss.

FOSI and HADS

Planned analyses were conducted on both FOSI and HADS. No evidence of treatment effect was demonstrated by these two instruments.

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 14. Summary of efficacy for trial MO22224

Title: A two-arm phase 3, multicenter, open-label, randomised, trial of bevacizumab plus chemotherapy versus chemotherapy alone in patients with platinum-resistant, epithelial ovarian, fallopian tube or primary peritoneal cancer.			
Study identifier	MO22224		
Design	multicenter, randomized, open-label, two-arm		
	Duration of main phase:		Until disease progression or unacceptable toxicity
Hypothesis	Superiority		
Treatments groups	Chemotherapy (CT)		• Paclitaxel 80 mg/m^2 as a 1-hour IV infusion on Days 1, 8, 15, and 22 q4w OR • Topotecan 4 mg/m^2 as a 30 minute IV infusion on Days 1, 8, and 15 q4w. Alternatively, a 1.25 mg/m^2 dose could be administered over 30 minutes on Days 1−5 q3w OR • Pegylated liposomal doxorubicin (PLD) 40 mg/m^2 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.
	Bevacizumab (Bv)+ Chemotherapy (CT)		• Paclitaxel 80 mg/m^2 as a 1-hour IV infusion on Days 1, 8, 15, and 22 q4w+ bevacizumab 10 mg/kg IV q2w. • Topotecan 4 mg/m^2 as a 30 minute IV infusion on Days 1, 8, and 15 q4w + bevacizumab 10 mg/kg IV q2w. Alternatively, a 1.25 mg/m^2 dose could be administered over 30 minutes on Days 1−5 q3w+ bevacizumab 15 mg/kg q3w. • PLD 40 mg/m^2 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+ bevacizumab 10 mg/kg IV q2w.
Endpoints and definitions	Primary endpoint	Progression free survival (PFS)	Time from randomization to investigator-assessed disease progression or death from any cause, whichever occurs first.
	Secondary endpoint	Objective Response Rate (ORR) per RECIST	Rate of patients with an observed tumour response. ORR will be evaluated for three types of responders: -Patients who have a response as defined per RECIST and as defined using the 50% response criteria for CA-125 by and assessed according to the GCIG criteria (“responders”) -Patients who have a response as defined per RECIST but no response as defined using the 50% response criteria for CA-125 (“RECIST responders”) - Patients who do not have a response as defined per RECIST but who do have a response as defined using the 50% response criteria for CA-125 (“CA-125 responders”)

	Secondary endpoint	Overall Survival (OS)	Time between randomization and death due to any cause
Database lock	14//11/2011		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat population (includes all patients randomized into the study, 14/11/2011 (167 events had occurred)		
Descriptive statistics and estimate variability	Treatment group	CT	Bv+CT
	Number of subject	182	179
	PFS (median, in months)	3.4	6.7
	95% CI	(2.10, 3.75)	(5.62, 7.79)
	ORR	12.5%	28.2%
	95% CI	(7.1%, 17.9%)	(20.8%, 35.6%)
	OS (median, in months)	13.0	14.6
	95% CI	(11.33, 15.67)	(13.11, 19.32)
Effect estimate per comparison	Primary endpoint (PFS)	Comparison groups	CT vs Bv+CT
		HR	0.379
		95% CI	(0.296, 0.485)
		Stratified log-rank p-value	<0.0001
	Key Secondary endpoint (ORR)	Comparison groups	CT vs Bv+CT
		Difference in ORR	15.7 %
		95% CI	(6.5, 24.8)
		Stratified p-value	0.0007
	Secondary endpoint (OS) (interim analysis)	Comparison groups	CT vs Bv+CT
		HR	0.730
		95% CI	(0.534, 0.999)
		Stratified log-rank p-value	0. 0.047
Notes	Stratification factors for the primary analysis (log-rank): selected chemotherapy cohort, previous anti-angiogenic therapy, and PFI.		
Analysis description	**Final Analysis**		
Analysis population and time point description	Intent to treat population 25 January 2013 (264 events had occurred)		
Descriptive statistics and	Treatment group	CT	Bv+CT

estimate variability	Number of subject	182	179
	OS (median, in months)	13.3	16.6
	95% CI	(11.89, 16.43)	(13.70, 18.99)
Effect estimate per comparison	Overall Survival	Comparison groups HR	CT vs Bv+CT 0.870
		95% CI	(0.678, 1.116)
		Stratified log-rank p-value	0.2711

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

N/A

Clinical studies in special populations

No studies in special populations were submitted.

Supportive study

N/A

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The open-label design of study MO22224 could have led to bias with regard to PFS and OS. However, an independent review of data (PFS by IRC) support the PFS by INV.

There is a difference in the timing of imaging between the two treatment arm, and the INV and IRC. However, sensitivity analysis, where backdating of PD dates only in the CT+Bv arm, supported the primary estimate. Thus, there are no major implications of the differences. The robustness of the overall PFS estimate was addressed in a computer simulated IRC analysis and in several sensitivity analyses.

Patients in the topotecan+Bv group seem to respond better to treatment compared to PLD+Bv or paclitaxel+Bv when looking at PFS. However, when looking at the OS subgroup analyses, it seems that patients in the topetecan+Bv have a poorer OS compared to the other cohorts. This could be a chance finding. Post-progression therapy may have confounded the OS estimate, but no data has been collected.

There were only 16 patients over 75 years included in this study. Therefore no definitive conclusions can be drawn regarding efficacy results in this group. Section 5.1 of the SmPC has been updated to reflect it.

Information on race is lacking due to the fact that the ethics committee in some countries do not allow collection of such data. Section 5.1 of the SmPC has been updated to reflect it. The missing data on prior surgery in 6% of the patients is explained with a potentially long time-span from surgery to inclusion.

The MAH stated that the decision to include only the abdominal/GI symptom scale of the QLQ-OV28 as a secondary endpoint was proclaimed in Amendment 1. However, the time point of the final analysis has been decided almost a year after the database locks. This is considered questionable as there is a good chance that this decision has been data-driven. Consequently the reliability of this analysis is in question and cannot be credited in the benefit-risk evaluation. Over the last few years a number of papers have been published aiming at identifying signatures or individual biomarkers predictive of response to bevacizumab. The MAH will submit an updated biomarker report to the EMA in June 2014 as part of the annual reports of the Annex II condition.

Efficacy data and additional analyses

Results from the study revealed a median progression free survival of 6.7 months for the CT+BV group and 3.4 months for the CT group.

Concerning subgroup analyses of PFS, there was a variation on how well the IRC evaluation supported the INV based PFS estimate, and it was in the paclitaxel cohort it was most convincing. With regard to patients that had received prior anti-angiogenic therapy, there seems to be a negative effect of bevacizumab when added to CT with regard to OS and no effect on PFS. The indication has been revised to include a statement with regard to prior anti-angiogenic treatment in order to reflect it.

The key secondary endpoint (ORR) shows a clear benefit in favour of CT+Bv, and this finding is supported by longer duration of objective response.

No overall detrimental effect of CT+Bv is seen on OS. It was only in the paclitaxel cohort that the improvement in PFS was supported by a numerically similar improvement in OS. Although not statistically significant overall, the OS improvement in the paclitaxel-treated group appears quite substantial in this setting. While the median OS on CT alone is about 13-14 months whatever the CT applied, it is increased to 22 months in the bevacizumab+paclitaxel group (borderline) while no effect at all is observed in the other treatment groups. In section 5.1 of the SmPC the subgroup analyses for all three cohorts should be shown, both for PFS and OS in order to reflect the fact that the outcome in the three chemotherapy cohorts is not the same.

Based on the HRQoL results, the addition bevacizumab to CT has no or little effect (in either direction) on the QoL. However, the clinical relevance of these results is uncertain, and the matter is further complicated by the open-label nature of the MO22224 study.

2.4.4 Conclusions on the clinical efficacy

The pivotal study MO22224 study has demonstrated that bevacizumab in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin resulted in an absolute gain in median PFS of 3.3 months in adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.

This result is considered clinically relevant. A number of sensitivity analyses have confirmed the robustness of the pooled result. A positive effect was seen in the subgroup analyses, however in the individual chemotherapy cohorts, the most robust effect was seen in the paclitaxel cohort.

The result was supported by a marked increase in ORR and a longer duration of objective response. No overall detrimental effect of CT+Bv is seen on OS. Post-progression therapy may have confounded OS

results which may explain why the improvement in PFS was not supported by similar improvement in OS.

2.5. Clinical safety

2.5.1. Introduction

The evaluation of safety information for bevacizumab in combination with chemotherapy in patients with EOC, FTC, or PPC, who were considered to have platinum-resistant disease, is derived from the Phase III Study MO22224.

Safety data up to the data cut-off date of 25 January 2013 were included in the safety analysis. The primary safety analysis was performed on the safety-evaluable population (N=360), which was defined as all randomized patients who received any full or partial dose of bevacizumab or chemotherapy (paclitaxel, topotecan, PLD). Safety was compared according to the treatment actually received (n=181 CT and n=179 CT+BV).

Upon disease progression or toxicity, patients in the CT arm had the option to receive crossover bevacizumab monotherapy. In the CT arm, if the patient had crossed over to receive bevacizumab monotherapy, only data on or prior to the crossover were included in the primary analyses. The data after the crossover for these patients (N=72 for the last analysis period) were summarized separately in order to evaluate the safety parameters for the crossover bevacizumab monotherapy period.

Patient exposure

Chemotherapy exposure

The median duration of chemotherapy was 19.9 weeks in the CT+BV arm versus 10.3 weeks the CT arm.

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 6.0 cycles in the CT+BV arm versus 3.0 cycleswith the CT arm . The median total topotecan dose was 87.7 mg in the CT+BV arm versus 43.2 mg in the CT arm. 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

Duration of safety follow-up

Duration of safety follow-up is calculated from the first dosing date of the study treatment until 30 days after the last dosing date. For the 72 patients in the CT arm who had crossover bevacizumab monotherapy, the treatment period of bevacizumab monotherapy was excluded. The median duration of safety follow-up was nearly twice as long in the CT+BV arm compared with the CT arm (CT: 3.3 months vs. CT+BV: 6.1 months).

Adverse events

An overview of the adverse events is presented in Table 15.

Table 15. Overview of Adverse Events: Safety Evaluable Patients

	CT **(n = 181)**	**CT+BV** **(n = 179)**
Grade 2–5 adverse event [a]	158 (87.3%)	163 (91.1%)
Grade 3–5 adverse event	96 (53.0%)	106 (59.2%)
Grade 2–5 serious adverse event	49 (27.1%)	56 (31.3%)
Grade 3–5 serious adverse event	35 (19.3%)	44 (24.6%)
Grade 2–5 adverse events that led to withdrawal of study treatment	16 (8.8%)	78 (43.6%)
Grade 5 adverse event	5 (2.8%)	6 (3.4%)

[a] Note: Only Grade 2–5 adverse events were collected in Study MO22224.

A summary of Grade 2-5 AEs and Grade 3-5 AEs with an incidence difference of ≥ 5% between the two arms and a summary of Grade 5 AEs are presented in tables 16, 17 and 18 respectively.

Table 16. Grade 2-5 adverse events with an incidence difference of ≥ 5% between two arms: Safety-evaluable patients

System Organ Class Preferred Term	NCI-CTCAE Grade	CT (n=181)	CT+BV (n=179)
- Any adverse events -	- Total -	158 (87.3%)	163 (91.1%)
	5	5 (2.8%)	6 (3.4%)
	4	10 (5.5%)	19 (10.6%)
	3	81 (44.8%)	81 (45.3%)
	2	62 (34.3%)	57 (31.8%)
Blood And Lymphatic System Disorders			
Anaemia	- Total -	48 (26.5%)	35 (19.6%)
	3	4 (2.2%)	3 (1.7%)
	2	44 (24.3%)	32 (17.9%)
Neutropenia	- Total -	46 (25.4%)	55 (30.7%)
	4	3 (1.7%)	8 (4.5%)
	3	27 (14.9%)	21 (11.7%)
	2	16 (8.8%)	26 (14.5%)
General Disorders And Administration Site Conditions			
Mucosal Inflammation	- Total -	10 (5.5%)	23 (12.8%)
	3	1 (0.6%)	3 (1.7%)
	2	9 (5.0%)	20 (11.2%)
Infections And Infestations			
- Overall -	- Total -	42 (23.2%)	62 (34.6%)
	5	3 (1.7%)	1 (0.6%)
	3	8 (4.4%)	10 (5.6%)
	2	31 (17.1%)	51 (28.5%)
Infection	- Total -	8 (4.4%)	19 (10.6%)
	3	3 (1.7%)	1 (0.6%)
	2	5 (2.8%)	18 (10.1%)
Nervous System Disorders			
- Overall -	- Total -	23 (12.7%)	43 (24.0%)
	4	(0.0%)	1 (0.6%)
	3	8 (4.4%)	9 (5.0%)
	2	15 (8.3%)	33 (18.4%)
Peripheral Sensory Neuropathy	- Total -	13 (7.2%)	32 (17.9%)
	3	5 (2.8%)	8 (4.5%)
	2	8 (4.4%)	24 (13.4%)
Renal And Urinary Disorders			
- Overall -	- Total -	9 (5.0%)	27 (15.1%)
	4	1 (0.6%)	1 (0.6%)
	3	2 (1.1%)	4 (2.2%)
	2	6 (3.3%)	22 (12.3%)
Proteinuria	- Total -	1 (0.6%)	22 (12.3%)
	3	(0.0%)	3 (1.7%)
	2	1 (0.6%)	19 (10.6%)
Respiratory, Thoracic And Mediastinal Disorders			
- Overall -	- Total -	19 (10.5%)	35 (19.6%)
	5	(0.0%)	2 (1.1%)
	4	5 (2.8%)	2 (1.1%)
	3	8 (4.4%)	7 (3.9%)
	2	6 (3.3%)	24 (13.4%)
Epistaxis	- Total -	(0.0%)	9 (5.0%)
	2	(0.0%)	9 (5.0%)
Skin And Subcutaneous Tissue Disorders			
- Overall -	- Total -	32 (17.7%)	64 (35.8%)
	3	8 (4.4%)	21 (11.7%)
	2	24 (13.3%)	43 (24.0%)
Palmar-Plantar Erythrodysaesthesia Syndrome	- Total -	9 (5.0%)	19 (10.6%)
	3	3 (1.7%)	8 (4.5%)
	2	6 (3.3%)	11 (6.1%)
Vascular Disorders			
- Overall -	- Total -	18 (9.9%)	46 (25.7%)
	5	(0.0%)	1 (0.6%)
	4	1 (0.6%)	1 (0.6%)
	3	4 (2.2%)	19 (10.6%)
	2	13 (7.2%)	25 (14.0%)
Hypertension	- Total -	10 (5.5%)	34 (19.0%)
	3	2 (1.1%)	12 (6.7%)
	2	8 (4.4%)	22 (12.3%)

Table 17. Grade 3-5 adverse events with an incidence difference of ≥ 5% between two arms: Safety-evaluable patients

System Organ Class Preferred Term	NCI-CTCAE Grade	CT (n=181)	CT+BV (n=179)
- Any adverse events -	- Total -	96 (53.0%)	106 (59.2%)
	5	5 (2.8%)	6 (3.4%)
	4	10 (5.5%)	19 (10.6%)
	3	81 (44.8%)	81 (45.3%)
Blood And Lymphatic System Disorders			
- Overall -	- Total -	37 (20.4%)	33 (18.4%)
	4	6 (3.3%)	8 (4.5%)
	3	31 (17.1%)	25 (14.0%)
Leukopenia	- Total -	12 (6.6%)	8 (4.5%)
	4	1 (0.6%)	(0.0%)
	3	11 (6.1%)	8 (4.5%)
Gastrointestinal Disorders			
- Overall -	- Total -	35 (19.3%)	27 (15.1%)
	4	1 (0.6%)	4 (2.2%)
	3	34 (18.8%)	23 (12.8%)
Abdominal Pain	- Total -	9 (5.0%)	5 (2.8%)
	3	9 (5.0%)	5 (2.8%)
Ascites	- Total -	5 (2.8%)	(0.0%)
	3	5 (2.8%)	(0.0%)
Vomiting	- Total -	9 (5.0%)	2 (1.1%)
	3	9 (5.0%)	2 (1.1%)
General Disorders And Administration Site Conditions			
- Overall -	- Total -	24 (13.3%)	15 (8.4%)
	5	1 (0.6%)	1 (0.6%)
	4	(0.0%)	1 (0.6%)
	3	23 (12.7%)	13 (7.3%)
Fatigue	- Total -	18 (9.9%)	8 (4.5%)
	4	1 (0.6%)	(0.0%)
	3	17 (9.4%)	8 (4.5%)
General Physical Health Deterioration	- Total -	(0.0%)	4 (2.2%)
	5	(0.0%)	1 (0.6%)
	4	(0.0%)	1 (0.6%)
	3	(0.0%)	2 (1.1%)
Respiratory, Thoracic And Mediastinal Disorders			
Dyspnoea	- Total -	7 (3.9%)	3 (1.7%)
	3	7 (3.9%)	3 (1.7%)
Skin And Subcutaneous Tissue Disorders			
- Overall -	- Total -	8 (4.4%)	21 (11.7%)
	3	8 (4.4%)	21 (11.7%)
Palmar-Plantar Erythrodysaesthesia Syndrome	- Total -	3 (1.7%)	8 (4.5%)
	3	3 (1.7%)	8 (4.5%)
Vascular Disorders			
- Overall -	- Total -	5 (2.8%)	21 (11.7%)
	5	(0.0%)	1 (0.6%)
	4	1 (0.6%)	1 (0.6%)
	3	4 (2.2%)	19 (10.6%)
Hypertension	- Total -	2 (1.1%)	12 (6.7%)
	3	2 (1.1%)	12 (6.7%)

Table 18. Grade 5 adverse events: Safety-evaluable patients

System Organ Class Preferred Term	CT (n=181)	CT+BV (n=179)
- Any adverse events -	5 (2.8%)	6 (3.4%)
Cardiac Disorders		
- Overall -	1 (0.6%)	1 (0.6%)
Cardiac Arrest	(0.0%)	1 (0.6%)
Cardiac Failure	1 (0.6%)	(0.0%)
General Disorders And Administration Site Conditions		
- Overall -	1 (0.6%)	1 (0.6%)
General Physical Health Deterioration	(0.0%)	1 (0.6%)
Multi-Organ Failure	1 (0.6%)	(0.0%)
Infections And Infestations		
- Overall -	3 (1.7%)	1 (0.6%)
Peritonitis	1 (0.6%)	(0.0%)
Sepsis	1 (0.6%)	1 (0.6%)
Septic Shock	1 (0.6%)	(0.0%)
Respiratory, Thoracic And Mediastinal Disorders		
- Overall -	(0.0%)	2 (1.1%)
Pneumonia Aspiration	(0.0%)	2 (1.1%)
Vascular Disorders		
- Overall -	(0.0%)	1 (0.6%)
Shock	(0.0%)	1 (0.6%)

Adverse events of special interest

- *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, one patient experienced a Grade 3 pulmonary artery thrombosis adverse event 47 days after start of treatment that was considered possibly related to topotecan and ongoing at the clinical cutoff.

In the CT+BV arm, the following ATEs were reported:

-One patient experienced a Grade 4 ischemic stroke that occurred 62 days after start of treatment and was considered possibly related to bevacizumab treatment and unrelated to PLD, and resolved without sequelae.

- One patient experienced a Grade 3 arterial occlusive disease event that occurred 61 days after start of treatment and was reported as possibly related to both topotecan and bevacizumab, and resolved with sequelae.

- One patient experienced a Grade 3 arterial embolism event 36 days after start of treatment that was considered possibly related to bevacizumab treatment, unrelated to topotecan treatment, and resolved.

- *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, one patient experienced a Grade 3 GI hemorrhage that occurred 22 days after start of treatment and was assessed as unrelated to PLD; and one patient experienced a Grade 3 vaginal hemorrhage that occurred 42 days after start of treatment, was assessed as unrelated to paclitaxel, and resolved.

In the CT+BV arm, one patient experienced a Grade 4 GI hemorrhage that occurred 44 days after start of treatment, was assessed as possibly related to bevacizumab and unrelated to PLD, and was ongoing at the time of death on Day 57; and one patient experienced a Grade 3 hemorrhagic ascites that occurred 65 days after start of treatment, was assessed as possibly related to bevacizumab and unrelated to topotecan, with additional data indicating that other possible factors for the event included pre-existing underlying disease – malignancy, and the event resolved.

- *Congestive Heart 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 occurred in one patient after 71 days of treatment and was assessed as unrelated to PLD chemotherapy. In the CT+BV arm, a 50-year-old patient experienced Grade 3 left ventricular dysfunction that was considered unrelated to bevacizumab and probably related to PLD with onset 151 days after start of treatment; this event resolved.

- *Febrile Neutropenia*

Grade 2–5 febrile neutropenia was reported in one patient in each treatment arm. In the CT arm, one patient (0.6%) experienced 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 cutoff. In the CT+BV arm, one patient (0.6%) experienced a Grade 3 event of febrile neutropenia that was assessed as unlikely related to bevacizumab treatment, probably related to PLD treatment, and resolved.

- *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.

- One 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.

- One 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 cutoff.

- One 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 cutoff.

- One 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.

• *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.

- In the CT arm, one 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, one 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, one 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 cutoff. This patient also experienced a Grade 3 arterial embolism event.

- In the CT+BV arm, one 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 cutoff, the event was resolved. In addition, one 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, and additional data indicated that other possible etiological factor for the event included ovarian cancer.

• *Hypertension (HTN)*

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, one patient experienced a Grade 4 hypertensive crisis that occurred 71 days after treatment start and was assessed as probably related to bevacizumab and unrelated to PLD treatment; the event resolved.

• *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 cutoff, 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.

- *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, one patient (0.6%) developed Grade 4 nephrotic syndrome that occurred 71 days after start of treatment, was assessed by the investigator 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.

- *Reversible Posterior Leukoencephalopathy*

Syndrome/Posterior Reversible Encephalopathy Syndrome

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

- *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.

- *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.

Serious adverse event / deaths / other significant events

Deaths

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 (Table 22). 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.

Table 19. Death and Primary Cause of Death: Randomized Patients

	CT (n=182)	CT+BV (n=179)
Deaths	136 (74.7%)	128 (71.5%)
Primary Cause of Death		
Ovarian Cancer/PD	130 (71.4%)	119 (66.5%)
Disease Progression	31 (17.0%)	21 (11.7%)
Malignant Peritoneal Neoplasm	1 (0.5%)	1 (0.6%)
Metastatic Neoplasm	1 (0.5%) [1]	(0.0%)
Ovarian Cancer	95 (52.2%)	94 (52.5%)
Ovarian Cancer Metastatic	1 (0.5%)	2 (1.1%)
Ovarian Cancer Recurrent	(0.0%)	1 (0.6%)
Ovarian Epithelial Cancer	1 (0.5%)	(0.0%)
Adverse Event	6 (3.3%)	9 (5.0%)
Cardiac Arrest	(0.0%)	1 (0.6%)
Cardiac Failure	1 (0.5%)	(0.0%)
Cardiopulmonary Failure	(0.0%)	1 (0.6%)
Gastrointestinal Disorder	(0.0%)	1 (0.6%)
Gastrointestinal Haemorrhage	1 (0.5%) [2]	(0.0%)
General Physical Health Deterioration	(0.0%)	1 (0.6%)
Multi-Organ Failure	1 (0.5%)	(0.0%)
Peritonitis	1 (0.5%)	(0.0%)
Pneumonia Aspiration	(0.0%)	2 (1.1%)
Sepsis	(0.0%)	2 (1.1%)
Septic Shock	2 (1.1%)	(0.0%)
Shock	(0.0%)	1 (0.6%)

[1] This patient had disease progression per RECIST in May 2012 and died June 2012. There was no AE reported.

[2] The adverse event occurred after switching to the bevacizumab monotherapy.

Other Serious Adverse Events (SAEs)

The incidence of Grade 2–5 SAEs was 31.3% in the CT+BV arm compared with 27.1% in the CT arm. Grade 2–5 SAEs that occurred in greater than one patient in either treatment arm (Table 20).

Table 20. Grade 2–5 Serious Adverse Events Occurring in Greater than One Patient in Either Treatment Arm: Safety-Evaluable Patients

	CT (n=181)	CT+BV (n=179)
Any serious adverse events		
Total	49 (27.1%)	56 (31.3%)
Grade 5	5 (2.8%)	6 (3.4%)
Grade 4	6 (3.3%)	10 (5.6%)
Grade 3	24 (13.3%)	28 (15.6%)
Grade 2	14 (7.7%)	12 (6.7%)
Blood and Lymphatic System Disorders		
Neutropenia	3 (1.7%)	1 (0.6%)
Anemia	2 (1.1%)	0
Gastrointestinal Disorders		
Abdominal pain	5 (2.8%)	4 (2.2%)
Ileus	2 (1.1%)	4 (2.2%)
Subileus	6 (3.3%)	4 (2.2%)
Constipation	2 (1.1%)	3 (1.7%)
Small intestinal obstruction	0	2 (1.1%)
Ascites	3 (1.7%)	0
Diarrhea	2 (1.1%)	0
Vomiting	7 (3.9%)	0
General Disorders And Administration Site Conditions		
General physical health deterioration	1 (0.6%)	3 (1.7%)
Pyrexia	3 (1.7%)	3 (1.7%)
Fatigue	2 (1.1%)	0
Infections and Infestations		
Device related infection	1 (0.6%)	2 (1.1%)
Infection	2 (1.1%)	1 (0.6%)
Pneumonia	2 (1.1%)	0
Metabolism and Nutrition Disorders		
Dehydration	1 (0.6%)	2 (1.1%)
Renal and Urinary Disorders		
Vesical fistula	0	2 (1.1%)
Reproductive System and Breast Disorders		
Female genital tract fistula	0	2 (1.1%)
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	5 (2.8%)	4 (2.2%)
Pleural effusion	1 (0.6%)	2 (1.1%)
Pneumonia aspiration	0	2 (1.1%)
Pulmonary embolism	5 (2.8%)	2 (1.1%)
Vascular Disorders		
Hypertension	0	4 (2.2%)

Serious Adverse Events that Occurred in ≥ 2% of Patients in Either Treatment Arm

Grade 2–5 serious adverse events that occurred in ≥ 2% of patients in either treatment arm were vomiting (CT: 3.9% versus CT+BV: 0), subileus (CT: 3.3% versus CT+BV: 2.2%), abdominal pain (CT: 2.8% versus CT+BV: 2.2%), dyspnea (CT: 2.8% versus CT+BV: 2.2%), pulmonary embolism (CT: 2.8% versus CT+BV: 1.1%), ileus (CT: 1.1% versus CT+BV: 2.2%), and HTN (CT: 0 versus 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.

Laboratory findings

No laboratory findings data were submitted by the MAH.

Safety in special populations

Intrinsic factors

Age group

The majority of patients were <65 years old (65.4% CT and 60.9% CT+BV). Consistent with the overall study population, in both age subgroups, the majority of patients in both treatment arms (85.7% to 91.4%) experienced at least one Grade 2–5 adverse event. Consistent with the overall study population, Grade 2–5 adverse events with a 10% difference in incidence between the CT arm and the CT+BV arm were HTN (< 65 years: 1.7% versus 12.8%; ≥ 65 years: 12.7% versus 28.6%), peripheral sensory neuropathy (< 65 years: 8.5% versus 13.8%; ≥ 65 years: 4.8% versus 24.3%), and proteinuria (< 65 years: 0 versus 10.1%; ≥ 65 years: 1.6% versus 15.7%; see Table 16).

Certain other adverse events had a higher incidence in the CT+BV arm in those ≥ 65 years. Comparing the rates of adverse events within the CT+BV arm only for the < 65 versus ≥ 65 years subgroups, the rates of Grade 3 adverse events were 45% and 45.7%, the rates of Grade 4 adverse events were
9.2% and 12.9%, and the rates of Grade 5 events were 1.8% (2 patients) and 5.7% (4 patients). The adverse events with a 5% difference in incidence difference in the CT+BV arm for the subgroup < 65 versus ≥ 65 years include: fatigue (< 65 years: 22.0% versus ≥ 65 years: 35.7%); mucosal inflammation (< 65 years: 10.1% versus ≥ 65 years: 17.1%); peripheral sensory neuropathy (< 65 years: 13.8% versus ≥ 65 years: 24.3%); alopecia (< 65 years: 4.6% versus ≥ 65 years: 14.3%); proteinuria (< 65 years: 10.1% versus ≥ 65 years: 15.7%); and palmar-plantar erythrodysesthesia (< 65 years: 9.2% versus ≥ 65 years: 12.9%).

Extrinsic factors

Chemotherapy cohort

The number of patients in each chemotherapy cohort was similar among treatment arms (55 CT and 60 CT+BV received paclitaxel; 63 CT and 62 CT+BV received PLD, and 63 CT and 57 CT+BV received topotecan).

The incidence of Grade 2–5 adverse events was 90.9% CT and 95.0% CT+BV for paclitaxel, 85.7% CT and 90.3% CT+BV for PLD, and 85.7% CT and 87.7% CT+BV for topotecan. Of note, Grade 2–5 adverse events of peripheral sensory neuropathy (12 patients [21.8%] in the CT arm versus 22 patients [36.7%] in the CT+BV arm) and palmar-plantar erythrodysaesthesia syndrome (8 patients

[12.7%] in the CT arm versus 17 patients [27.4%] in the CT+BV arm) were reported with a higher incidence for the paclitaxel and PLD chemotherapy-containing regimens, respectively.

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

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.≥ 2% of patients in either arm) Grade 2–5 adverse events that led to study treatment discontinuation were (in decreasing order of frequency in the CT+BV arm); peripheral sensory neuropathy (CT: 1.7% versus CT+BV: 4.5%), palmar plantar erythrodysesthesia syndrome (CT: 0.6% versus CT+BV: 3.4%), fatigue (CT: 0 versus CT+BV: 3.4%), HTN (CT: 0 versus CT+BV: 2.8%), neutropenia (CT: 0 versus CT+BV: 2.2%) and proteinuria (CT: 0% versus CT+BV: 2.2%).

Post marketing experience

The post–marketing experience with bevacizumab is based on safety data contained in nine Periodic Safety Update Reports (PSURs) covering the period from February 26, 2004, to February 25, 2012. The total number of patients exposed to bevacizumab in the post-marketing setting or in clinical trials in this 8-year period covered by the PSURs is estimated to be approximately 1,339,560 patients.

In the last reporting period (Feb-2011 to Feb-2012), a total of 11131 adverse events were reported, of which 9420 were serious. During the 8-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 3411 cases (0.3%), the outcome was fatal.

2.5.2. Discussion on clinical safety

Overall, there are more AEs in the CT+Bv arm, which is expected. Major differences are seen with regard to hypertension, PPES, peripheral sensory neuropathy, infections and infestations, and subcutaneous disorders. Higher event rates are observed for the following AEs: fatigue, mucosal inflammation, peripheral sensory neuropathy, alopecia, proteinuria, PPES, infections and hypertension. Section 4.8 of the SmPC has been updated to reflect it.

As expected from previous bevacizumab studies, the majority of patients experienced one or more AE of any grade, but, as grade 1 AEs are not collected in this study, the exact incidence is not known. However, a total of 91.1% in the CT+BV arm and 87.3% in the CT arm and experienced Grade 2–5 adverse events, and for grade 3-5 the reported frequencies were 59.2% and 53.0%, respectively. The total incidence of Grade 2–5 serious AEs (SAEs) was 31.3% in the CT+BV arm compared with 27.1% in the CT arm. For Grade 3–5 SAEs the incidences were 24.6% and 19.3%, respectively. Regarding the individual chemotherapy cohorts, the incidence of Grade 2–5 SAEs was 20.0% CT and 28.3% CT+BV for paclitaxel, 30.2% CT and 37.1% CT+BV for PLD, and 30.2% CT and 28.1% CT+BV for topotecan. Only Grade 2-5 AEs in at least 10% of patients in any treatment group between CT cohorts were presented. These data showed some striking differences, which is reflected briefly in the SmPC.

There is a considerable difference in the rate of discontinuations between the two treatment arms, which could be explained by the higher exposure to study treatment in the CT+Bv arm. However, this is a well-known pattern that is seen when bevacizumab combined with different chemotherapies. The majority of discontinuations in the CT+Bv arm are due to Grade 2 and 3 events. The main AEs leading to discontinuation are neutropenia, gastrointestinal disorders, fatigue, neuropathy, pulmonary embolism, PPES, and hypertension. The proportion of patients (43.6%) that discontinue treatment in the CT+Bv arm is high, and the proportion of discontinued patients with unresolved AEs (18.4%) is also high. However, it should also be mentioned that no new safety signals were observed. More importantly, time from discontinuation of chemotherapy (due to AEs) to a PFS event was comparable between the CT arm and the CT + BV arm (median time CT: 4.0 months, CT+BV: 3.9 months).

The median time from discontinuation of any study treatment (due to AEs) to PFS event was 4.0 months in the CT arm versus 3.2 months in the CT + BV arm. The MAH stated that the median time of 3.2 months between study treatment discontinuation and PFS event should be considered in the context of longer duration treatment in CT + BV arm and this is endorsed. There are a comparable number of Grade 5 AEs, and with regard to AESI, the most striking difference is seen in the number of hypertension, fistula or abscess, and proteinuria. The majority of events resolved with or without sequelae. In general, the number of events is low, and should be interpreted with caution. However, all these AESI are adequately addressed in section 4.4 of the SmPC.

There are no safety concern with regard to deaths and SAEs. Overall, the difference of SAEs is acceptable and in most SOCs the numbers are small and comparable, except for vomiting and hypertension.

In patients ≥65 years there was a difference with regard to peripheral sensory neuropathy, proteinuria, mucosal inflammation, infections, and Palmar-Plantar Erythrodysaesthesia Syndrome (PPES). The SmPC has been updated to reflect it.

A review of Grade 2-5 AEs by chemotherapy revealed that the Paclitaxel+Bv cohort had slightly more AEs, while the Topotecan+Bv cohort seems to have a better safety profile than the two other cohorts.

It is of concern that the integrated safety analysis could potentially mask higher toxicity of one of the chemotherapy-bevacizumab combinations, especially since more SAEs were reported in the PLD cohort. However, tables of grade 2-5 AEs by chemotherapy cohort showed that among the three chemotherapy cohorts, the paclitaxel cohort had the highest discontinuation rate because of Grade 2-5 AEs. The discontinuation rates in the PLD and topotecan cohorts were similar. The only Grade 2-5 SAEs that occurred with a ≥ 5% incidence difference between the two treatment arms in the paclitaxel cohort was pyrexia. No single Grade 2-5 SAE occurred with a ≥ 5% incidence difference between the two treatment arms in the PLD and topotecan cohorts.

In the pivotal study, patients with a history of bowel obstruction were excluded, which is accepted. It is however unclear if patients who previously experienced bowel resection as part of their initial debulking surgery have a higher risk for GI perforations and fistulae. However, the details of the prior debulking surgery were not collected in this study. Therefore, if patients who previously experienced bowel resection as part of their initial debulking surgery have a higher risk for GI perforations and fistulae is not known at the time being. The current wording in the SmPC (sections 4.4 and 4.8) addresses this issue.

Finally, the MAH didn't collect laboratory findings with the argument that these were performed by local laboratories according to local standards. This is of concern, as the combination of PLD and topotecan with bevacizumab has not been previously analysed in Phase III studies in ovarian cancer. However, according to the protocol, laboratory tests should be performed as per local standards and were only reported on the Adverse Events pages in the eCRF if the laboratory test results ≥ Grade 2, or

fell outside of the laboratory reference range and met the clinical significance criteria (i.e. accompanied by clinical symptoms, leading to a change in study medication and/or requiring a change in concomitant therapy). This is reassuring.

2.5.3. Conclusions on clinical safety

The safety profile was overall in line with the extensive experience with bevacizumab across multiple oncology indications. No unexpected safety signals were seen in this study. The combination of bevacizumab and PLD/topotecan/paclitaxel leads to more AEs, but this is also due to a higher exposure to study treatment in the CT+Bv arm. Overall, the safety profile of CT+Bv is acceptable taking into consideration the nature of the disease.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 14.2, the PRAC considers by consensus that the risk management system for bevacizumab (Avastin) in the treatment of adult patients with recurrence of platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin is acceptable.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Table 21. Summary of the Safety Concerns

Important identified risks	Bleeding / hemorrhage Pulmonary haemorrhage Proteinuria Arterial thromboembolic events (ATE) Hypertension Congestive heart failure Wound healing complications Gastrointestinal perforations Posterior reversible encephalopathy syndrome Neutropenia Venous thromboembolic events (VTE) Fistula (other than gastrointestinal) Thrombotic microangiopathy Pulmonary hypertension Ovarian failure Hypersensitivity reactions / infusion reactions Gall bladder perforation Peripheral sensory neuropathy Cardiac disorders (excluding CHF and ATE) Osteonecrosis of the jaw Infections Necrotizing fasciitis Adverse events following off-label intravitreal use
Important potential risks	Embryo-foetal development disturbance Physeal dysplasia

Missing information	Safety profile of the different treatment combinations in patients with non-squamous NSCLC Long-term effects of bevacizumab when used in the pediatric population Safety and efficacy in patients with renal impairment Safety and efficacy in patients with hepatic impairment Use in pregnancy and lactation

The PRAC agreed.

Pharmacovigilance plans

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Biomarker investigation 1	Identification and selection of a more targeted population of patients most likely to benefit from the combination of Avastin and paclitaxel in the treatment of firstline metastatic breast cancer.	None	Ongoing	Annually
BO17707: ICON 7 1	Study BO17707: submission of results from the pre-specified final analysis for Overall Survival.	All safety concerns	Ongoing	December 2013
BO20924 (BERNIE) 3	Assess safety and efficacy in pediatric patients	Physeal dysplasia Long-term effects of bevacizumab when used in the pediatric population.	Ongoing	CSR Q1 2017
Obtain long term follow up information from studies in the pediatric population after patients complete their 5.5 years of follow up in study BO20924 3	Assess safety in pediatric patients	Long-term effects of bevacizumab when used in the pediatric population.	Planned	Protocol submission Q4 2017
MO18725 (OLIVIA) randomized phase II study 3	To assess safety and resectability in patients treated with bevacizumab who have primarily unresectable liver metastases secondary to colorectal cancer and who are scheduled for standard, first line chemotherapy.	Wound healing complications	Ongoing	Q2 2014.
BO21990 (AVAglio) 3	To investigate the efficacy and safety of bevacizumab, temozolomide, and radiotherapy followed by 6 cycles maintenance with bevacizumab and	Wound healing complications	Ongoing	CSR March 2013

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
	temozolomide as compared to placebo, temozolomide, and radiotherapy followed by 6 cycles maintenance with placebo and temozolomide.			

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 22.Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important identified risks		
Bleeding/ Hemorrhage	Routine. EU SPC section 4.4: Patients treated with Avastin have an increased risk of haemorrhage, especially tumour-associated haemorrhage. Avastin should be discontinued permanently in patients who experience Grade 3 or 4 bleeding during Avastin therapy (NCI-CTCAE v.3) (see section 4.8). Patients with untreated CNS metastases were routinely excluded from clinical trials with Avastin, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS haemorrhage in such patients has not been prospectively evaluated in randomised clinical trials (see section 4.8). Patients should be monitored for signs and symptoms of CNS bleeding, and Avastin treatment discontinued in cases of intracranial bleeding. There is no information on the safety profile of Avastin in patients with congenital bleeding diathesis, acquired coagulopathy or in patients receiving full dose of anticoagulants for the treatment of thromboembolism prior to starting Avastin treatment, as such patients were excluded from clinical trials. Therefore, caution should be exercised before initiating therapy in these patients. However, patients who developed venous thrombosis while receiving therapy did not appear to have an increased rate of Grade 3 or above bleeding when treated with a full dose of warfarin and Avastin concomitantly (NCI-CTCAE v.3). Labelled in section 4.8 of the EU SPC	None proposed
Pulmonary hemorrhage	Routine. EU SPC section 4.4: Patients with non-small cell lung cancer treated with Avastin may be at risk of serious, and in some cases fatal, pulmonary haemorrhage/haemoptysis. Patients with recent pulmonary haemorrhage/ haemoptysis	None proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	(> 2.5 ml of red blood) should not be treated with Avastin.	
Proteinuria	EU SPC section 4.4: Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with Avastin. There is evidence suggesting that all Grade (US National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE (version 3.0)]) proteinuria may be related to the dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy. Therapy should be permanently discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome) (NCI-CTCAE v.3). Labelled in section 4.8 of the EU SPC.	None proposed
Arterial thromboembolic events	Routine. EU SPC section 4.4: In clinical trials, the incidence of arterial thromboembolic reactions including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs) was higher in patients receiving Avastin in combination with chemotherapy compared to those who received chemotherapy alone. Patients receiving Avastin plus chemotherapy, with a history of arterial thromboembolism or age greater than 65 years have an increased risk of developing arterial thromboembolic reactionsduring therapy. Caution should be taken when treating these patients with Avastin. Therapy should be permanently discontinued in patients who develop arterial thromboembolic reactions. Labelled in section 4.8 of the EU SPC.	None proposed
Hypertension	EU SPC section 4.4: An increased incidence of hypertension was observed in Avastin-treated patients. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre existing hypertension should be adequately controlled before starting Avastin treatment. There is no information on the effect of Avastin in patients with uncontrolled hypertension at the time of initiating therapy. Monitoring of blood pressure is generally recommended during therapy. In most cases hypertension was controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. The use of diuretics to manage hypertension is not advised in patients who receive a cisplatin-based chemotherapy regimen. Avastin should be permanently discontinued if medically significant hypertension cannot be adequately controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy. Labelled in section 4.8 of the EU SPC.	None proposed
Congestive heart failure	EU SPC section 4.4: Reactions consistent with CHF were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF,	None proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	requiring treatment or hospitalisation. Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, or congestive heart failure with Avastin. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present. In patients in AVF3694g who received treatment with anthracyclines and who had not received anthracyclines before, no increased incidence of all Grade CHF was observed in the anthracycline + bevacizumab group compared to the treatment with anthracyclines only. CHF Grade 3 or higher reactions were somewhat more frequent among patients receiving bevacizumab in combination with chemotherapy than in patients receiving chemotherapy alone. This is consistent with results in patients in other studies of metastatic breast cancer who did not receive concurrent anthracycline treatment (NCI-CTCAE v.3). Labelled in section 4.8 of the EU SPC.	
Wound healing complications	Routine. EU SPC section 4.4: Avastin may adversely affect the wound healing process. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for elective surgery. Labelled in section 4.8 of the EU SPC. In addition, definition in glioblastoma study protocols of in- and exclusion criteria (e.g. time between surgical procedures or traumatic injury and initiation of bevacizumab therapy), and not permitted concomitant treatment (e.g. craniotomy, intratumoral interstitial therapy, radiosurgery).	None proposed
Gastrointestinal perforations	Routine. EU SPC section 4.4: Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation when treated with Avastin. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation. Labelled in section 4.8 of the EU SPC.	None proposed
Posterior Reversible Encephalopathy Syndrome(PRES)	Routine. EU SPC section 4.4: There have been rare reports of Avastin-treated patients developing signs and symptoms that are consistent with PRES, a rare neurologic disorder, which	None proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of Avastin. The safety of reinitiating Avastin therapy in patients previously experiencing PRES is not known. Labelled in section 4.8 of the EU SPC.	
Neutropenia	Routine. EU SPC section 4.4: Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus Avastin in comparison to chemotherapy alone. This has mainly been seen in combination with platinum- or taxane-based therapies in the treatment of NSCLC and mBC. Labelled in sections 4.5 and 4.8 of the EU SPC.	None proposed
Venous thromboembolic events	Routine. EU SPC section 4.4: Patients may be at risk of developing venous thromboembolic reactions, including pulmonary embolism under Avastin treatment. Avastin should be discontinued in patients with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism (NCI-CTCAE v.3). Patients with thromboembolic reactions ≤ Grade 3 need to be closely monitored (NCI-CTCAE v.3). Labelled in section 4.8 of the EU SPC.	None proposed
Fistula (other than gastrointestinal)	Routine. EU SPC section 4.4: Patients may be at increased risk for the development of fistulae when treated with Avastin. Permanently discontinue Avastin in patients with tracheoesophageal (TE) fistula or any Grade 4 fistula [US National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE v.3)]. Limited information is available on the continued use of Avastin in patients with other fistulae. In cases of internal fistula not arising in the gastrointestinal (GI) tract, discontinuation of Avastin should be considered. Labelled in section 4.8 of the EU SPC.	None proposed
Thrombotic microangiopathy	Routine. Labelled in section 4.8 of the EU SPC.	None proposed
Pulmonary hypertension	Routine. Labelled in section 4.8 of the EU SPC.	None proposed
Ovarian failure	Routine. text in SPC Section 4.4 of the EU SPC states: Avastin may impair female fertility (see sections 4.6 and 4.8). Therefore fertility preservation strategies should be discussed with women of child-bearing potential prior to starting	None proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	treatment with Avastin. Section 4.6 of the EU SPC states: Avastin may impair female fertility (see sections 4.6 and 4.8). Therefore fertility preservation strategies should be discussed with women of child-bearing potential prior to starting treatment with Avastin. Labelled in section 4.8 of the EU SPC.	
Hypersensitivity reactions and Infusion Reactions	Routine. EU SPC section 4.4: Patients may be at risk of developing infusion/hypersensitivity reactions. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanised monoclonal antibody. If a reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted. Labelled in section 4.8 of the EU SPC.	None proposed
Gall Bladder perforations	Routine. EU SPC section 4.4: Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation when treated with Avastin. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation. Labelled in section 4.8 of the EU SPC.	None proposed
Peripheral sensory neuropathy	Routine. Labelled in section 4.8 of the EU SPC.	None proposed
Cardiac disorders (excl. CHF and ATE)	Routine. Supraventricular tachycardia is labelled in section 4.8 of the EU SPC.	None proposed
Osteonecrosis of the Jaw	Routine EU SPC section 4.4 Cases of ONJ have been reported in cancer patients treated with Avastin, the majority of whom had received prior or concomitant treatment with intravenous bisphosphonates, for which ONJ is an identified risk. Caution should be exercised when Avastin and intravenous bisphosphonates are administered simultaneously or sequentially. Invasive dental procedures are also an identified risk factor. A dental examination and appropriate preventive dentistry should be considered prior to starting the treatment with Avastin. In patients who have previously received or are receiving intravenous bisphosphonates invasive dental procedures should be avoided, if possible. Labelled in section 4.8 of the EU SPC.	None proposed
Infection	Labelled as “very common” in section 4.8 of the EU SPC	None proposed
Necrotizing fasciitis	Routine EU SPC section 4.4: Necrotising fasciitis, including fatal cases, has rarely	None proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	been reported in patients treated with Avastin. This condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Avastin therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated Labelled in section 4.8 of the EU SPC.	
Adverse events following off-label intravitreal use	Routine EU SPC section 4.4: Intravitreal use Avastin is not formulated for intravitreal use. Eye disorders Individual cases and clusters of serious ocular adverse reactions have been reported following unapproved intravitreal use of Avastin compounded from vials approved for intravenous administration in cancer patients. These reactions included infectious endophthalmitis, intraocular inflammation such as sterile endophthalmitis, uveitis and vitritis, retinal detachment, retinal pigment epithelial tear, intraocular pressure increased, intraocular haemorrhage such as vitreous haemorrhage or retinal haemorrhage and conjunctival haemorrhage. Some of these reactions have resulted in various degrees of visual loss, including permanent blindness. Systemic effects following intravitreal use A reduction of circulating VEGF concentration has been demonstrated following intravitreal anti-VEGF therapy. Systemic adverse reactions including non-ocular haemorrhages and arterial thromboembolic reactions have been reported following intravitreal injection of VEGF inhibitors	None proposed
Important potential risks		
Embryo-foetal development disturbance	Routine. Labelled in section 5.3 of the EU SPC.	None proposed
Physeal dysplasia	Routine. Labelled in section 5.3 of the EU SPC.	None proposed
Missing information		
Safety profile of the different treatment combinations in patients with non-squamous NSCLC	Routine. EU SPC text not applicable.	None proposed
Long-term use in pediatric patients	Routine. EU SPC section 4.2: The safety and efficacy of bevacizumab in children and adolescents have not been established. There is no relevant use of bevacizumab in the paediatric population in the granted indications. Currently available data are described in sections 5.1, 5.2 and 5.3 but no recommendation on a posology can be made. Avastin should not be used in children aged 3 years to less than 18 years with recurrent or progressive high-grade glioma because of efficacy concerns (see section 5.1 for results of paediatric trials).	None proposed
Patients with renal	Routine.	None proposed

Safety concern	Routine risk minimization measures	Additional risk minimization measures
impairment	EU SPC section 4.2: safety and efficacy have not been studied in patients with renal impairment. Section 5.2: No trials have been conducted to investigate the pharmacokinetics of bevacizumab in renally impaired patients since the kidneys are not a major organ for bevacizumab metabolism or excretion.	
Patients with hepatic impairment	Routine EU SPC section 4.2: safety and efficacy have not been studied in patients with hepatic impairment. Section 5.2: No trials have been conducted to investigate the pharmacokinetics of bevacizumab in patients with hepatic impairment since the liver is not a major organ for bevacizumab metabolism or excretion.	None proposed
Use in pregnancy and lactation	Pregnancy is a contraindication in section 4.3 of the EU SPC	None proposed.

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

3. Benefit- Risk Balance

Benefits

Beneficial effects

There is a statistically significant and clinically relevant PFS result that is considered highly valuable in a patient population, where life-expectancy is short and few effective treatments are available. The primary analysis is supported by several sensitivity tests, and subgroup analyses showed a consistent effect in favour of CT+Bv in almost all subgroups. Most importantly PFS by IRC supports the PFS by INV, however this is most pronounced in the paclitaxel cohort.

The PFS results are further supported by the key secondary endpoints ORR and duration of objective response where a significant difference in favour of CT+Bv is observed.

Subgroup analyses of both PFS and OS, indicated that the addition of bevacizumab to CT in patients that have received prior anti-angiogenic therapy, may lead to no effect with regard to PFS and a detrimental effect with regard to OS. This could mean that the effect of prior anti-angiogenic therapy may induce resistance to anti-angiogenic therapies in later disease stages. The indication has been revised to address this.

In terms of the secondary efficacy endpoint OS, the results showed no detrimental effect. However, looking at the different cohorts there seems to be some differences between them. The OS results have been included in section 5.1 of the SmPC in order to reflect the fact that the outcome in the three chemotherapy cohorts is not the same.

Uncertainty in the knowledge about the beneficial effects

There are no uncertainties in the knowledge about the beneficial effects.

Risks

Unfavourable effects

There is a high discontinuation rate in the CT+Bv arm due to AEs, which is expected and mainly due to longer exposure to study treatment in the CT+Bv arm. No new safety signals have been observed. The main AEs leading to discontinuation are neutropenia, gastrointestinal disorders, fatigue, neuropathy, pulmonary embolism, PPES, and hypertension.

As expected from previous bevacizumab studies, the majority of patients experienced one or more AE of any grade, but, as grade 1 AEs are not collected in this study, the exact incidence is not known. However, a total of 91.1% in the CT+BV arm and 87.3% in the CT arm and experienced Grade 2–5 adverse events, and for grade 3-5 the reported frequencies were 59.2% and 53.0%, respectively.

The total incidence of Grade 2–5 serious AEs (SAEs) was 31.3% in the CT+BV arm compared with 27.1% in the CT arm. For Grade 3–5 SAEs the incidences were 24.6% and 19.3%, respectively.

Regarding the individual chemotherapy cohorts, the incidence of Grade 2–5 SAEs was 20.0% CT and 28.3% CT+BV for paclitaxel, 30.2% CT and 37.1% CT+BV for PLD, and 30.2% CT and 28.1% CT+BV for topotecan. Only Grade 2-5 AEs in at least 10% of patients in any treatment group between CT cohorts were presented. These data showed some striking differences, which is reflected briefly in the SmPC.

A higher incidence of certain AEs has been observed in patients ≥ 65 years (peripheral sensory neuropathy, proteinuria, mucosal inflammation, infections, and Palmar-Plantar Erythrodysaesthesia Syndrome (PPES)). The large increase (12%) in serious toxicity in elderly population is of concern and this is addressed in the SmPC.

Uncertainty in the knowledge about the unfavourable effects

In the pivotal study, patients with a history of bowel obstruction were excluded, which is accepted. It is however unclear if patients who previously experienced bowel resection as part of their initial debulking surgery have a higher risk for GI perforations and fistulae. However, the details of the prior debulking surgery were not collected in this study. Therefore, if patients who previously experienced bowel resection as part of their initial debulking surgery have a higher risk for GI perforations and fistulae is not known at the time being. The current wording in the SmPC (sections 4.4 and 4.8) addresses this issue.

Benefit-risk balance

Importance of favourable and unfavourable effects

In a patient population with platinum-resistant disease, there are few effective treatment options. Thus, a delay of disease progression in terms of a favourable PFS estimate is of high importance for both patients and clinicians.

A total of 91.1% in the CT+BV arm and 87.3% patients in the CT arm experienced Grade 2–5 adverse events, and for grade 3-5 the reported frequencies were 59.2% and 53.0%, respectively.

Benefit-risk balance

Overall, the efficacy of bevacizumab in combination with CT in the treatment of patients with platinum-resistant ovarian cancer has been demonstrated.

The benefit-risk balance of bevacizumab in combination with CT in the treatment of patients with platinum-resistant ovarian cancer is considered positive. Delaying progression of disease is of high importance to a population with a poor prognosis and few therapeutic options. Overall, the robust and clinically relevant PFS effects with no detrimental effect on OS outweigh the risks of adding bevacizumab to CT.

4. Recommendations

Final Outcome

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

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

Extension of Indication to include Avastin in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet is updated accordingly.

The requested variation proposed amendments to the SmPC and Package Leaflet.

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Avastin is not similar to Yondelis within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include Avastin in combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet is updated accordingly.

Summary

Please refer to the Scientific Discussion Avastin-H-C-582-II-63

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