



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 April 2017
EMA/815114/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Avastin

International non-proprietary name: bevacizumab

Procedure No. EMEA/H/C/000582/II/0092

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

| | |
|------------|---|
| Bev | bevacizumab |
| CA-125 | cancer antigen 125 |
| CI | confidence interval |
| CR | complete response |
| CSR | Clinical Study Report |
| BOCR | best overall confirmed response |
| eCRF | electronic case report form |
| EOC | epithelial ovarian carcinoma |
| FACT-O TOI | Functional Assessment of Cancer Therapy-Ovarian Trial Outcome Index |
| FIGO | International Federation of Gynecology and Obstetrics |
| FTC | fallopian tube carcinoma |
| GOG | Gynecologic Oncology Group |
| HR | hazard ratio |
| HRQoL | health-related quality of life |
| ITT | intent to treat |
| NPT | non-protocol-specified cancer therapy |
| OC | ovarian cancer |
| OR | objective response |
| ORR | objective response rate |
| OS | overall survival |
| PD | progressive disease |
| PFS | progression-free survival |
| PPC | primary peritoneal carcinoma |
| PR | partial response |
| q2w | every 14 days |
| q3w | every 21 days |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SF-36 | 36-item short-form health survey |

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration Limited submitted to the European Medicines Agency on 26 August 2016 an application for a variation.

The following variation was requested:

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

Extension of Indication to include the use of Avastin in combination with paclitaxel and carboplatin for the treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated with efficacy and safety information from study GOG-0213. The Package Leaflet is updated in accordance. An update RMP is also included (version 27).

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

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 application included 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: Sinan B. Sarac Co-Rapporteur: Bjorg Bolstad

| Timetable | Actual dates |
|--|-------------------|
| Submission date | 26 August 2016 |
| Start of procedure: | 17 September 2016 |
| CHMP Rapporteur Assessment Report | 11 November 2016 |
| CHMP Co-Rapporteur Assessment Report | 14 November 2016 |
| PRAC Rapporteur Assessment Report | 21 November 2016 |
| PRAC members comments | 23 November 2016 |
| PRAC Outcome | 1 December 2016 |
| CHMP members comments | 5 December 2016 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 9 December 2016 |
| Request for supplementary information (RSI) | 15 December 2016 |
| CHMP Rapporteur Assessment Report | 23 March 2017 |
| PRAC Rapporteur Assessment Report | 24 March 2017 |
| PRAC members comments | 29 March 2017 |
| Updated PRAC Rapporteur Assessment Report | 30 March 2017 |
| PRAC Outcome | 6 April 2017 |
| CHMP members comments | 10 April 2017 |
| Updated CHMP Rapporteur Assessment Report | 12 April 2017 |
| Opinion | 21 April 2017 |

2. Scientific discussion

2.1. Introduction

Problem statement

Epithelial ovarian carcinoma and its histological and clinical equivalents, primary peritoneal carcinoma (PPC) and primary peritoneal carcinoma (FTC), continue to be a highly lethal primary gynecologic malignancy and is a leading cause of gynecologic cancer-related mortality among women globally. Worldwide, ovarian cancer affects 225,500 women annually and results in 140,200 cancer-related deaths around the world, with an annual incidence of 65,584 (42,749 deaths) in Europe¹.

As the disease tends to be asymptomatic in the early stages, the majority of women are diagnosed with disseminated advanced-stage disease. Standard of care at initial diagnosis includes cytoreductive surgery (CRS) followed by platinum and taxane systemic chemotherapy. Despite optimal upfront surgery and the administration of front line chemotherapy approximately 70% of patients will relapse in the first 3 years².

¹ GLOBOCAN, Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012

² J. A. Ledermann et al., Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, *Ann Oncol* 2013; 24 (Suppl 6): vi24-vi32

Recurrent disease is classified as either platinum-resistant or platinum-sensitive, depending on whether the disease recurs < 6 or ≥6 months, respectively, following last cycle of previous platinum therapy; this classification is highly prognostic and is important in determining treatment options. An increased duration of this platinum-free interval (PFI) to ≥6 months corresponds to the likelihood of achieving another response with a platinum-based regimen as well as improvements in progression-free survival (PFS) and overall survival (OS). As such, treatment for recurrent ovarian cancer is directed by the patient's previously demonstrated sensitivity to their platinum-based chemotherapy.

For recurrent platinum-sensitive disease, carboplatin in combination with either paclitaxel, gemcitabine, or pegylated liposomal doxorubicin (PLD) are the most commonly used chemotherapy regimens^{2,3}. Bevacizumab is used in combination with carboplatin and gemcitabine for treatment of adult patients with 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 agents⁴.

About the product

Bevacizumab (Avastin) is a recombinant humanized monoclonal antibody that inhibits angiogenesis by neutralizing all isoforms of human vascular endothelial growth factor (VEGF) and by blocking their binding to VEGF receptors. Bevacizumab received Marketing Authorisation (MA) approval in the European Union (EU) on 12 January 2005 for the first-line treatment of patients with mCRC in combination with intravenous 5-FU/folinic acid or intravenous 5-FU/folinic acid/irinotecan. Since the initial MA, bevacizumab has been approved for use in a variety of indications, including locally recurrent or metastatic breast cancer (mBC), advanced, metastatic, or recurrent non-small cell lung cancer (NSCLC), advanced and/or metastatic renal cell cancer (mRCC), newly diagnosed glioblastoma multiforme (GBM) and GBM after relapse or disease progression, persistent, recurrent, or metastatic cervical cancer, front-line treatment of epithelial ovarian (EOC), primary peritoneal cancer (PPC), or fallopian tube (FTC).

Avastin has been authorised on 31 July 2014 for the treatment of platinum-sensitive or platinum-resistant recurrent ovarian cancer in combination with carboplatin and gemcitabine.

The MAH applied for an extension of indication for bevacizumab in combination with carboplatin and paclitaxel in adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer based on the results from Study GOG-0213 (Gynecologic Oncology Group [GOG] Study-0213), a phase III randomized controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab followed by bevacizumab, and secondary cytoreductive surgery in platinum-sensitive, recurrent ovarian, primary peritoneal, and fallopian tube cancer.

The applied indication was as follows:

Bevacizumab, in combination with carboplatin and gemcitabine **or in combination with carboplatin and paclitaxel**, is indicated for treatment of adult patients with 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 recommended indication is as follows:

Bevacizumab, in combination with carboplatin and gemcitabine **or in combination with carboplatin and paclitaxel**, is indicated for treatment of adult patients with 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.

Avastin is administered in combination with either carboplatin and gemcitabine for 6 cycles and up to 10

³ NCCN Clinical Practices Guidelines in oncology, Ovarian Cancer, version 1.2016

⁴ EPAR Avastin

cycles or in combination with carboplatin and paclitaxel for 6 cycles and up to 8 cycles, followed by continued use of Avastin as single agent until disease progression. The recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion (see SmPC section 4.2).

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

Bevacizumab is a recombinant humanised immunoglobulin of isotype IgG1, which will to a high degree be metabolised by normal proteolytic pathways and excreted as non-recognisable and non-functional fragments. As a protein bevacizumab is exempted from the necessity of ERA studies. Nonetheless, a ready biodegradability test (OECD 301F), an algal growth test (OECD 201) and an acute daphnia immobilisation (OECD 202) inhibition study have been conducted. The studies indicate that bevacizumab is readily biodegradable, and without potential for unexpectedly high ecotoxicity.

2.2.2. Discussion on non-clinical aspects

An adequate justification for not providing a full ERA has been provided.

2.2.3. Conclusion on the non-clinical aspects

Considering the above data, bevacizumab is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

Efficacy and safety data to support this application are derived from Phase III Study GOG-0213 in adult women with platinum-sensitive recurrent EOC, PPC, or FTC.

GCP

The Clinical trial was performed in accordance with GCP as claimed by the applicant.

The applicant 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.

- Tabular overview of clinical studies

Table 1: Clinical package supporting the variation application

| Protocol No. | Location of Synopsis Location of Report | Objective(s) of the Study | Study Design and Type of Control | Test Product(s); Dosage regimen; Route of Admin. | Number of Subjects | Healthy Subjects or Diagnosis of Patients | Duration of Treatment | Study Status; Type of Report |
|--|--|--|---|--|--------------------|---|--|------------------------------|
| 5.3.5 Efficacy and Safety Studies | | | | | | | | |
| GOG-0213 (Roche No: ML01187) | | To determine if the addition of Bev to second-line Crb and Pac increases the duration of OS relative to second-line Crb + Pac alone in patients with platinum-sensitive ovarian cancer. Efficacy endpoints: Primary: OS. Secondary: PFS, PRO (HRQoL), hypersensitivity to Crb and Pac Exploratory: ORR. Safety endpoints: Adverse events Lab tests. | Phase III randomized, open-label, multicenter controlled study. | Crb + Pac ^a Crb + Pac + Bev ^b | 336 337 | Patients with platinum-sensitive recurrent EOC, PPC, or FTC who had a CR to front-line platinum-taxane therapy and had a treatment-free interval without clinical evidence of PD of at least 6 months from completion of front-line chemotherapy (both platinum and taxane) | Crb + Pac ^a : 6 - 8 cycles. Crb + Pac + Bev ^b : 6 - 8 cycles then Bev alone until PD or unacceptable toxicity precluded further treatment | Ongoing Full Report |

AUC = area under the curve; Bev = bevacizumab; Crb = carboplatin; EOC = epithelial ovarian cancer; FTC = fallopian tube cancer; HRQoL = health related quality of life; ORR = objective response rate; OS = overall survival; Pac = paclitaxel; PD = progressive disease; PPC = primary peritoneal cancer; PRO = patient reported outcomes.

^a Crb (AUC 5) + Pac (175 mg/m²) every 21 days (q3w) for 6 - 8 cycles.

^b Crb (AUC 5) + Pac (175 mg/m²) + Bev (15 mg/kg) IV q3w for 6 - 8 cycles followed by Bev (15 mg/kg) IV q3w alone until PD or unacceptable toxicity precluded further treatment.

2.4. Clinical efficacy

2.4.1. Dose response study

No formal dose study was submitted in support of this application which was considered acceptable (see discussion on clinical efficacy).

2.4.2. Main study

Study GOG-0213

Methods

Study GOG-0213 is a multicenter, randomized, open-label Phase III study comprised of two parts, Objective 1 and Objective 2. Objective 1 evaluated whether the addition of bevacizumab to the second-line and maintenance phases of treatment improves the duration of OS relative to second-line paclitaxel (Pac) and carboplatin (Crb) alone in patients with recurrent, platinum-sensitive, ovarian cancer (OC). Objective 2 is evaluating whether the addition of surgical secondary cytoreduction to adjuvant chemotherapy improves the duration of OS in patients with recurrent, platinum-sensitive, OC.

The CSR submitted only reports the data collected on or before 5 November 2014 for Objective 1. The study is ongoing to address Objective 2 regarding secondary cytoreduction and is outside the scope of the CSR.

An overview of the study design (objective 1) is presented below.

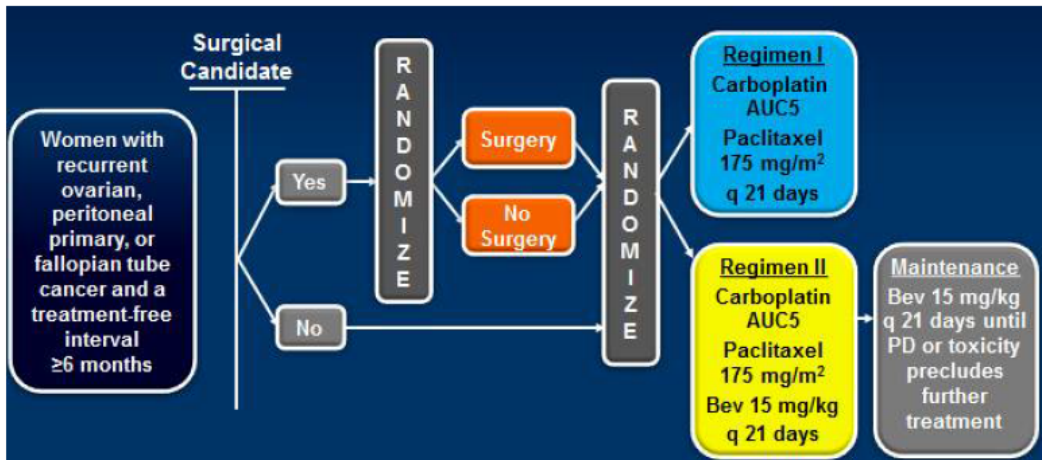


Figure 1: Study GOG-0213 shema for patients enrolled prior to 29 August 2011 (objective 1)

Study participants

Inclusion Criteria

- Patients must have had a histologic diagnosis of EOC, PPC or FTC which was recurrent.
- Patients with the following histologic epithelial cell types were eligible: Serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's Tumor, or adenocarcinoma not otherwise specified (N.O.S.).
- Patients must have had a complete response to front-line platinum-taxane therapy (at least three cycles).
 - A complete response to front-line chemotherapy must have included: negative physical exam, negative pelvic exam and normalization of CA-125, if elevated at baseline. Although not required, any radiographic assessment of disease status (e.g. CT, MRI, PET/CT, etc) obtained following the completion of primary therapy (defined below) was to be considered negative for disease.
 - All patients must have also had a treatment-free interval without clinical evidence of progressive disease of at least 6 months from completion of front-line chemotherapy (both platinum and taxane). Front-line therapy may have included a biologic agent (i.e. bevacizumab).
 - Front-line treatment could include maintenance therapy following complete clinical or pathological response. However, maintenance cytotoxic chemotherapy must have been discontinued for a minimum of 6 months prior to documentation of recurrent disease. Patients receiving maintenance biological therapy or hormonal therapy were eligible provided their recurrence was documented ≥ 6 months from primary cytotoxic chemotherapy completion (including maintenance chemotherapy) and a minimum 4 weeks had elapsed since their last infusion of biological therapy.
- Patients must have had adequate:
 - Bone marrow function: Absolute neutrophil count (ANC) greater than or equal to 1,500/mm³, equivalent to Common Toxicity Criteria for Adverse Events v3.0 (CTCAE) Grade 1.
 - Platelets greater than or equal to 100,000/mm³ (CTCAE Grade 0-1).
 - Renal function: Creatinine (non-IDMS) $\leq 1.5 \times$ institutional upper limit normal (ULN), CTCAE Grade 1.

– Hepatic function:

- Total bilirubin \leq 1.5 ULN (CTCAE Grade 1).
- SGOT/AST and Alkaline Phosphatase \leq 2.5 times the upper limit of normal in the absence of liver metastasis.
- SGOT/AST and Alkaline Phosphatase $<$ 5.0 times ULN in the presence of liver metastasis.
- Patients must have had a urine protein-to-creatinine ratio (UPCR) $<$ 1.0 mg/dL.
- Patients who were not candidates for surgical cytoreduction were eligible for the chemotherapy randomization. Patients were not considered candidates for surgical cytoreduction if complete cytoreduction in the estimation of the investigator was impossible or a medical infirmity precluded exploration and debulking.
- Patients must have met the pre-entry requirements specified in the protocol
- Patients must have signed an approved informed consent and authorization permitting release of personal health information.
- Patients must have had a GOG Performance Status of 0, 1, or 2.
- Patients must have been at least 18 years old.

Exclusion Criteria

- Patients who had received more than one previous regimen of chemotherapy (maintenance was not considered a second regimen).
- Patients receiving concurrent immunotherapy, or radiotherapy.
- Patients who had received prior radiotherapy to any portion of the abdominal cavity or pelvis.
- Patients with a prior histologic diagnosis of borderline, low malignant potential (grade 0) EOC was surgically resected and who subsequently developed an unrelated, new invasive EOC or PPC were eligible provided that they meet the criteria listed in the protocol.
- Patients who required parenteral hydration or nutrition and had evidence of partial bowel obstruction or perforation.
- Patients who had received prior chemotherapy for any abdominal or pelvic tumor (other than EOC, PPC or FTC).
- Patients with synchronous primary endometrial cancer, or a past history of primary endometrial cancer, unless all of the following conditions were met: Stage not greater than I-B; no more than superficial myometrial invasion, without vascular or lymphatic invasion; no poorly differentiated subtypes, including papillary serous, clear cell or other FIGO Grade 3 lesions.
- Patients with uncontrolled infection.
- Patients with concurrent severe medical problems unrelated to the malignancy that would significantly limit full compliance with the study or expose the patient to extreme risk or decreased life expectancy.
- Patients with \geq grade 2 peripheral neuropathy
- Patients with a history of allergic reactions to carboplatin and/or paclitaxel or chemically similar compounds.
- Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies.
- Patients of childbearing potential, not practicing adequate contraception, patients who were pregnant or patients who were nursing were not eligible for this trial.
- Patients with other invasive malignancies, with the exception of nonmelanoma skin cancer, who had (or have) any evidence of the other cancer present within the last 5 years or whose previous cancer treatment contraindicated this protocol therapy.
- Patients with active bleeding or pathologic conditions that carried a high risk of bleeding such as a known bleeding disorder, coagulopathy, or tumor involving major vessels.
- Patients with a history or evidence upon physical examination of CNS disease.

- Patients with clinically significant cardiovascular disease.
- Patients who had a major surgical procedure, open biopsy, dental extractions or other dental surgery/procedure that resulted in an open wound, or significant traumatic injury within 28 days prior to the first date of treatment on this study, or anticipation of need for major surgical procedure during the course of the study; patients with placement of vascular access device or core biopsy within 7 days prior to the first date of treatment on this study.
- Patients who underwent pre-treatment secondary cytoreduction were to undergo therapy with bevacizumab on cycle #2.
- Patients who underwent pre-treatment surgery for purposes other than cytoreduction could also participate provided they met the eligibility criteria in the Protocol.

Treatments

Bevacizumab

The dose of bevacizumab was 15 mg/kg administered by IV infusion on Day 1 of each 21-day cycle.

Carboplatin

The dose of carboplatin (AUC5) was calculated to reach a target area under the curve (AUC) according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula. Carboplatin was administered as a 60-minute infusion. When administered in conjunction with other medications, carboplatin was to be infused after the other agents. Carboplatin, either alone or in combination was to be premedicated with dexamethasone (either IV or PO), anti-histamine H1 (such as diphenhydramine) and anti-histamine H2 (such as cimetidine, ranitidine, or famotidine).

Carboplatin doses were based on the patient's weight at baseline and were to remain the same throughout the study. However, the doses were to be recalculated if the patient had a weight change of greater than or equal to 10% from baseline.

Paclitaxel

The initial dose of paclitaxel was 175 mg/m² given on Day 1 of each 21 day-cycle. Patients whose body weight changed by 10% or more were to undergo recalculation of the dose based on the adjusted body surface area.

Docetaxel

Docetaxel 75 mg/m² IV over 1 hour could be substituted for paclitaxel.

Objectives

Primary objectives

- To determine whether the addition of bevacizumab to the second-line and maintenance phases of treatment increases the duration of OS relative to second-line carboplatin and paclitaxel alone in patients with platinum-sensitive, recurrent epithelial ovarian cancer, primary peritoneal or fallopian tube cancer (Objective 1).

Secondary objectives

- To determine if the addition of bevacizumab to the second-line and maintenance phase of treatment increases the duration of PFS relative to second-line carboplatin and paclitaxel alone in patients with platinum-sensitive, recurrent epithelial ovarian cancer, primary peritoneal or fallopian tube cancer.

- To prospectively determine the incidence of carboplatin and paclitaxel hypersensitivity in these patients undergoing retreatment with both agents as first recurrence therapy.
- To determine if the addition of bevacizumab to the second-line and maintenance phases of treatment increases quality of life (QOL) relative to second-line carboplatin and paclitaxel alone in patients with platinum-sensitive, recurrent epithelial ovarian, primary peritoneal or fallopian tube cancer.

Outcomes/endpoints

- Primary endpoint: OS defined as the time from randomization until death from any cause.
- Secondary endpoint:
 - PFS defined as the time between the date of randomization and the date of first documented disease progression or death, whichever occurred first. Tumor assessments and response evaluations were determined by the investigators using GOG Response Evaluation Criteria in Solid Tumors (RECIST) criteria (a modification of standard RECIST criteria per Therasse, 2000). Measurable disease was defined as at least one lesion that could be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion was to be ≥ 20 mm when measured by conventional techniques, including palpation, plain X-ray, CT, and MRI, or ≥ 10 mm when measured by spiral CT.
 - Safety
 - Quality of life (QoL)

Sample size

The targeted accrual for Objective 1 of the study was 660 patients. It was anticipated that 240 eligible patients per year could be enrolled from GOG treatment centers. Therefore, the expected time to accrue the targeted sample size was 2.75 years. An additional 1.5 year post-accrual follow-up period was anticipated.

Randomisation

Patients meeting eligibility requirements were to be considered first for the surgical randomization aspect of the trial.

Chemotherapy was to be administered following recovery up to 6 weeks after surgery. Patients who were surgical candidates and consented to be randomized to the surgical objective underwent randomization to the surgical objective followed by randomization to the bevacizumab objective: Crb+Pac or Crb+Pac+Bev. Patients who were not surgical candidates or who declined randomization to the surgical objective, were randomized only to the bevacizumab objective: Crb+Pac or Crb+Pac+Bev.

Randomization was stratified by secondary surgical debulking status (randomized to undergo cytoreduction or randomized to not undergo secondary cytoreduction vs. not a candidate or did not consent to secondary surgical cytoreduction) and time from completing first-line platinum chemotherapy to registration onto this study (6 – 12 months vs. > 12 months). The registration form, i.e. randomization schema defined the stratification factor as “treatment-free interval” that does not consistently represent the platinum-free interval due to the inconsistent use of maintenance therapy in the front-line setting.

Blinding (masking)

This was an open-label study.

Statistical methods

Objective 1 of this study was to determine whether bevacizumab reduced the overall death rate when compared to the standard treatment (CT).

The null hypotheses: $H_0: HR = \lambda_{CTB} / \lambda_{CT} = 1$ was assessed, where λ is the death rate for the indicated treatment. The treatment regimens (Crb+Pac alone and Crb+Pac+Bev) were compared with a log-rank procedure which included all of the patients categorized by their randomly assigned treatment. This comparison only included patients enrolled prior to 29 August 2011 and hence selected their systemic treatment. The type I error for this comparison was limited to 2.5% (one-tail) accounting for the planned interim analyses. This is equivalent to a 5% (two-tailed) test as described in the Roche SAP.

The log-rank test was stratified (using stratification factors as recorded on the CRF) by the secondary surgical debulking status (randomized to undergo cytoreduction or randomized to not undergo secondary cytoreduction vs. not a candidate or did not consent to secondary surgical cytoreduction) and the duration of platinum-free interval prior to enrolling onto this study (6 - 12 months vs. > 12 months).

If the bevacizumab-containing regimen reduced the overall death rate of the control regimen by 25%, then this was considered clinically significant. Assuming proportional hazards, this effect size was comparable to increasing the expected proportion surviving for at least 22 months (median from previous studies) by 9.5% (50.0% vs. 59.5%). In order to provide an 81% chance of detecting this effect size, the study was considered sufficiently mature to permit a final analysis of the systemic regimens when there were at least 214 deaths ($214/330 = 0.65$) reported among those patients assigned to the standard regimen (CT). If the alternative hypothesis was true, then the expected total number of deaths at the time of the final analyses would be 394. The critical values for rejecting the null hypothesis were adjusted for one interim analysis at 50% information to control the Type I error, using the O'Brien and Fleming like type I error spending function proposed by Lan and DeMets

An interim analysis of efficacy and futility with a data cutoff of 30 August 2012 was conducted as pre-specified in the protocol when at least 110 deaths were reported among all those patients randomly allocated prior to 29 August 2011 to the Crb+Pac alone regimen (approximately 50% of the full information for Objective 1). A total number of 209 deaths among all patients randomized prior to 29 August 2011 had occurred at this interim analysis (114 in the Crb+Pac alone arm, 95 in the Crb+Pac+Bev arm).

The study was not stopped at the interim analysis (no information was released) and Genentech / Roche was made aware of the results after the final analysis, corresponding to the full information required for the final overall survival (OS) analysis pre-specified in the GOG-0213 protocol. At the time of the GOG data cutoff on 5 November 2014, there were 415 deaths reported among all patients randomly allocated prior to 29 August 2011.

The efficacy analysis population was the intent-to-treat (ITT) population, defined as all patients who were randomized to study treatment.

The primary safety population consisted of all randomized patients who received at least one full or partial dose of any component of the study treatment (bevacizumab or chemotherapy).

The comparison of OS between the two treatment arms was based on a two-sided stratified log-rank test at the overall 0.05 level of significance. Adjusting for the alpha spent during the first interim analysis, the two-sided alpha boundary for the final analysis was recalculated to be 0.0489 (adjusted two sided alpha

level). Median OS for both treatment arms was estimated using Kaplan-Meier methodology and 95% confidence intervals for median OS were computed on the basis of standard errors from Greenwoods formula. Kaplan-Meier curves were constructed for the two treatment arms. For patients who have not died by the time of analysis, data was censored as of the last contact date at which the patient was known to be alive. Data for patients who were lost to follow-up were analyzed as censored observations on the date of last contact. Estimate of the treatment effect was expressed as a hazard ratio (HR, with two-sided 95% confidence interval [CI]) using a stratified Cox proportional hazards model fitted with the treatment (carboplatin plus paclitaxel with bevacizumab compared to carboplatin plus paclitaxel alone) and adjusted for the stratification factors at randomization (the same as used in the stratified log-rank test).

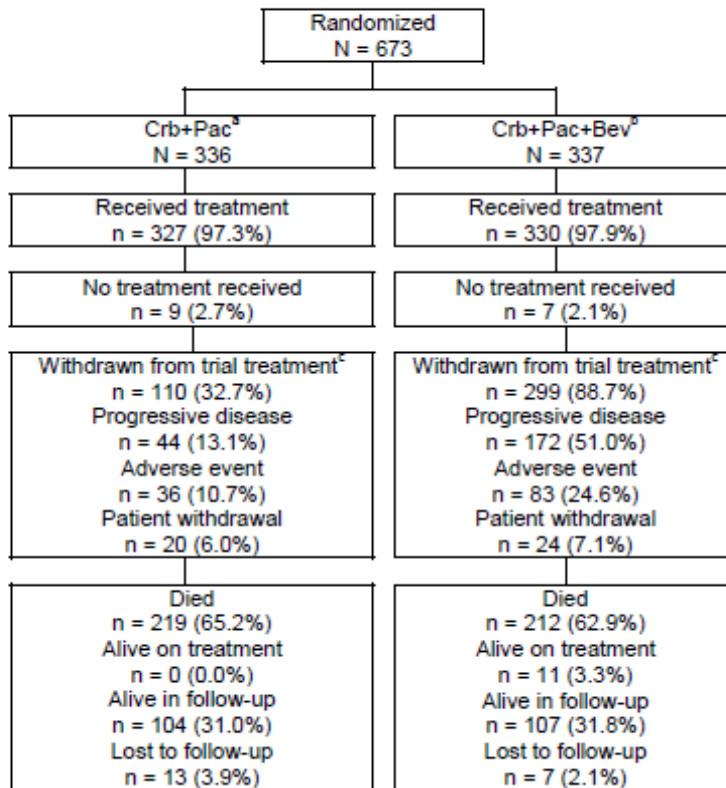
A stratified log-rank test (using the same stratification factors as for the primary efficacy analysis) was used to compare the duration of PFS between treatment arms. The Kaplan-Meier method was used to estimate median PFS for both treatment arms, and the 95% CI for median PFS was computed using Greenwoods formula. Kaplan-Meier curves were constructed to provide a visual depiction of the difference between the treatment arms. Data from patients who have not experienced disease progression or death was censored at the last tumour assessment date. Data for patients who were lost to follow-up were analyzed as censored observations on the date of the last tumour assessment or if no post-randomization tumour assessment was available, at the date of randomization. Data for patients who received non-protocol specified anti-cancer therapy (NPT) prior to their PFS event were censored at the last disease assessment prior to receiving NPT. Data for patients without an event were censored at the date of the last disease assessment prior to receiving NPT. The HR was estimated using the stratified Cox proportional hazards regression model.

Descriptive summary statistics of the baseline HRQoL data were calculated, including descriptions of the distribution of HRQoL scores (mean, standard deviation, median, etc.). A repeated mixed-effect model (including patients as random effects) was used to assess the difference in mean FACT-O-TOI scores over time and between treatment arms. This model had a term for time that was treated as a categorical variable, a term for treatment group, and a term for treatment-by-time interaction. Baseline scores were included as covariates in the model. Statistically significant differences were interpreted with reference to published estimates of clinically meaningful differences

ORR was defined as percentage of patients with a complete or partial overall response determined by two consecutive investigator assessments \geq 4 weeks apart, was compared between the two treatment arms using the Mantel-Haenszel χ^2 test, stratified by the same factors used in the primary efficacy analysis. For both treatment arms, an estimate of the ORR and its 95% CI was determined; an exact 95% CI was constructed using the Clopper-Pearson method. CIs for the difference in ORRs between the two arms were determined using the normal approximation to the binomial distribution.

Results

Participant flow



Source: [sptdisp_10_I002](#), [sptdisc_I002](#)

^a Carboplatin AUC5 + paclitaxel 175 mg/m² every 21 days for 6 - 8 cycles or until disease progression or adverse events precluded further treatment)

^b Carboplatin AUC5 + paclitaxel 175 mg/m² + bevacizumab 15 mg/kg every 21 days for 6- 8 cycles (bevacizumab continued until disease progression or adverse events precluded further treatment).

^c See Section 4.2 for a full list of reasons for treatment withdrawal. Note that patients in the Crb+Pac+Bev arm were at risk for withdrawal from treatment for longer than patients in the Crb+Pac alone arm. Patients in the Crb+Pac alone arm only received 6 - 8 cycles of treatment, whereas patients in the Crb+Pac+Bev arm received treatment with 6 - 8 cycles of Crb+Pac+Bev followed by bevacizumab alone until PD or unacceptable toxicity.

Figure 2: Disposition of patients at clinical cutoff (5 November 2014) (overall ITT population)

Table 2: Summary of patients withdrawn from trial treatment

| | Crb+Pac (N=336) | Crb+Pac+Bev (N=337) |
|---|--------------------|------------------------|
| Number of Patients who Discontinued Trial Treatment | 110 (32.7%) | 299 (88.7%) |
| Adverse Event/Side Effects/Complications | 36 (10.7%) | 83 (24.6%) |
| Death on study | 1 (0.3%) | 6 (1.8%) |
| Disease progression relapse during active treatment | 44 (13.1%) | 172 (51.0%) |
| Patient off-treatment for other complicating disease | 1 (0.3%) | 5 (1.5%) |
| Patient withdrawal/Refusal for reason other than toxicity | 20 (6.0%) | 24 (7.1%) |
| Other | 8 (2.4%) | 9 (2.7%) |

Percentages are based on N

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Recruitment

First Patient Entered: 10 December 2007.

Last Patient Entered: 26 August 2011 (for Objective 1) Data cutoff: 5 November 2014.

67 centers: United States (65 centers), South Korea (1 center), Japan (1 center).

Conduct of the study

Protocol deviations

A total of 33 patients were reported to have major protocol deviations, and these occurred with a similar frequency in the Crb+Pac alone arm (16 patients: 4.8%) and Crb+Pac+Bev arm (17 patients: 5.0%). A total of 11 patients (3.3%) in the Crb+Pac alone arm and 8 patients (2.4%) in the Crb+Pac+Bev arm were deemed to have deviations based on pathology committee review. These included 11 patients due to inadequate pathology, 5 patients due to wrong cell type and 3 patients due to wrong primary.

Table 3: Summary of protocol deviations by trial treatment (overall ITT population)

| | Crb+Pac (N=336) | Crb+Pac+Bev (N=337) |
|---|--------------------|------------------------|
| Violation | | |
| MAJOR VIOLATION | 16 (4.8%) | 17 (5.0%) |
| MINOR VIOLATION | 27 (8.0%) | 14 (4.2%) |
| Results of pathology committee review of patient eligibility for protocol and tumor grade | | |
| WELL DIFFERENTIATED | 17 (5.1%) | 20 (5.9%) |
| MODERATELY DIFFERENTIATED | 44 (13.1%) | 53 (15.7%) |
| POORLY DIFFERENTIATED | 253 (75.3%) | 249 (73.9%) |
| NOT GRADED | 11 (3.3%) | 7 (2.1%) |
| EXCLUSION | 11 (3.3%) | 8 (2.4%) |
| Results of gynecologic committee review of patient eligibility | | |
| ACCEPT | 309 (92.0%) | 304 (90.2%) |
| Reason for exclusion from protocol | | |
| ADDITIONAL THERAPY WITHOUT RECURRENCE | 1 (0.3%) | 0 (0.0%) |
| INADEQUATE PATHOLOGY | 8 (2.4%) | 3 (0.9%) |
| WRONG CELL TYPE | 3 (0.9%) | 2 (0.6%) |
| WRONG PRIMARY | 0 (0.0%) | 3 (0.9%) |

Percentages are based on N

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Changes to study conduct

The original version of the protocol dated 6 December 2007 was amended 5 times for patients enrolled in the first part of the study prior to 29 August 2011 (for Objective 1).

Changes to the Statistical Analysis

The Statistical Analysis Plan (SAP), although written retrospectively by Roche, was based on the pre-specified GOG-0213 SAP as defined in the GOG-0213 protocol. All analyses pertaining to the primary and secondary endpoints were performed on the basis of the outline in the protocol. Additional sensitivity analyses were performed to confirm the robustness of the primary and secondary analyses.

The results presented in the CSR are based on the data that was transferred from GOG to Genentech / Roche on 10 December 2015, cleaned per Genentech / Roche standards and analyzed using methods considered appropriate for detailed scientific review. The major differences between the GOG and Roche analyses of the study included:

- For the stratified efficacy analysis, instead of using treatment-free-interval data based on the randomization system as one of the stratification factors as used by the GOG, Roche used the platinum-free-interval data based on the eCRF. Clinically, PFI is deemed to be the more robust prognostic factor than TFI. Furthermore, it can be more accurately assessed using eCRF inputs since it would take into consideration modifications in front-line treatment such as maintenance therapy with a taxane, bevacizumab, or another agent. The stratified OS analysis based on GOG's approach was also performed and is reported in this CSR as a sensitivity analysis.
- A two-sided test with 5% alpha which is equivalent to a 1-sided test with 2.5% alpha was used.
- ORR was added as an exploratory analysis in Roche's analysis plan although it was not part of the original protocol specified endpoints.
- Adverse event reporting from Roche was through MedDRA coding.

The table below shows the concordance between platinum-free interval reported on the eCRF and the treatment free interval reported on the registration form (randomisation schema) for all randomised patients in the study. 45 patients (6.7%) had a discrepancy in the stratification factors (TFI vs. PFI) at randomisation between the eCRF and registration form.

Table 4: Concordance between PFI and TFI

| All 673 patients | $6 \leq \text{TFI} \leq 12$ months | TFI > 12 months |
|------------------------------------|------------------------------------|-----------------|
| $6 \leq \text{PFI} \leq 12$ months | 169 (25.1%) | 5 (0.7%) |
| PFI > 12 months | 40 (5.9%) | 459 (68.3%) |

There were 5 patients with $6 \leq \text{PFI} \leq 12$ months and TFI > 12 months. For one patient the date of recurrence was 9 days short of 12 months. The date of the recurrence was clarified and confirmed with the GOG after querying the site. For the other 4 patients, the TFI interval appears to have been incorrectly entered on the registration form.

Baseline data

Table 5: Summary of demographic data and baseline characteristics by trial treatment (overall ITT population)

| | Crb+Pac N = 336 | Crb+Pac+Bev N = 337 | All Patients N = 673 |
|--|--------------------|------------------------|-------------------------|
| Age in years | | | |
| Mean | 60.1 | 59.5 | 59.8 |
| SD | 9.93 | 10.18 | 10.05 |
| Median | 60.0 | 59.0 | 60.0 |
| Min-Max | 23 - 85 | 26 - 84 | 23 - 85 |
| n | 336 | 337 | 673 |
| Age Category | | | |
| <65 | 217 (64.6%) | 232 (68.8%) | 449 (66.7%) |
| >=65 | 119 (35.4%) | 105 (31.2%) | 224 (33.3%) |
| n | 336 | 337 | 673 |
| Race | | | |
| American Indian/Alaska Native | 1 (0.3%) | 4 (1.2%) | 5 (0.7%) |
| Asian | 44 (13.1%) | 48 (14.2%) | 92 (13.7%) |
| Black | 15 (4.5%) | 15 (4.5%) | 30 (4.5%) |
| Missing | 3 (0.9%) | - | 3 (0.4%) |
| Native Hawaiian/Other Pacific Islander | - | 1 (0.3%) | 1 (0.1%) |
| Unknown | 3 (0.9%) | 3 (0.9%) | 6 (0.9%) |
| White | 270 (80.4%) | 266 (78.9%) | 536 (79.6%) |
| n | 336 | 337 | 673 |
| Ethnicity | | | |
| Hispanic | 14 (4.2%) | 19 (5.6%) | 33 (4.9%) |
| Non-hispanic | 291 (86.6%) | 293 (86.9%) | 584 (86.8%) |
| Unknown | 31 (9.2%) | 25 (7.4%) | 56 (8.3%) |
| n | 336 | 337 | 673 |
| Height in cm | | | |
| Mean | 161.407 | 161.250 | 161.328 |
| SD | 6.7698 | 7.0811 | 6.9227 |
| Median | 162.000 | 161.290 | 161.800 |
| Min-Max | 144.78 - 185.42 | 144.20 - 180.34 | 144.20 - 185.42 |
| n | 336 | 337 | 673 |
| Weight in kg | | | |
| Mean | 75.591 | 74.545 | 75.067 |
| SD | 19.0304 | 20.6954 | 19.8737 |
| Median | 71.815 | 69.600 | 70.500 |
| Min-Max | 33.64 - 167.00 | 39.40 - 155.13 | 33.64 - 167.00 |
| n | 336 | 337 | 673 |
| GOG Performance Status | | | |
| 0 | 277 (82.4%) | 272 (80.7%) | 549 (81.6%) |
| 1 | 56 (16.7%) | 61 (18.1%) | 117 (17.4%) |
| 2 | 3 (0.9%) | 4 (1.2%) | 7 (1.0%) |
| n | 336 | 337 | 673 |
| Country | | | |
| Japan | 12 (3.6%) | 16 (4.7%) | 28 (4.2%) |
| Korea (South) | 24 (7.1%) | 25 (7.4%) | 49 (7.3%) |
| USA | 300 (89.3%) | 296 (87.8%) | 596 (88.6%) |
| n | 336 | 337 | 673 |

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
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Table 6: Summary of baseline ovarian cancer disease characteristics by trial treatment (overall ITT)

| | Crb+Pac (N=336) | Crb+Pac+Bev (N=337) | All Patients (N=673) |
|--------------------------------|--------------------|------------------------|-------------------------|
| Histology | | | |
| Adenocarcinoma, Unsp. | 5 (1.5%) | 4 (1.2%) | 9 (1.3%) |
| Clear Cell Carcinoma | 14 (4.2%) | 10 (3.0%) | 24 (3.6%) |
| Endometrioid Adenocarcinoma | 23 (6.8%) | 20 (5.9%) | 43 (6.4%) |
| Mucinous Adenocarcinoma | 2 (0.6%) | 2 (0.6%) | 4 (0.6%) |
| Serous Adenocarcinoma | 272 (81.0%) | 274 (81.3%) | 546 (81.1%) |
| Other | 20 (6.0%) | 27 (8.0%) | 47 (7.0%) |
| FIGO stage | | | |
| I | 17 (5.1%) | 22 (6.5%) | 39 (5.8%) |
| II | 36 (10.7%) | 18 (5.3%) | 54 (8.0%) |
| III | 245 (72.9%) | 261 (77.4%) | 506 (75.2%) |
| IV | 38 (11.3%) | 36 (10.7%) | 74 (11.0%) |
| Histologic Grade | | | |
| Well Differentiated | 17 (5.1%) | 20 (5.9%) | 37 (5.5%) |
| Moderately Differentiated | 44 (13.1%) | 53 (15.7%) | 97 (14.4%) |
| Poorly Differentiated | 253 (75.3%) | 249 (73.9%) | 502 (74.6%) |
| Not Available | 22 (6.5%) | 15 (4.5%) | 37 (5.5%) |
| Primary site of disease | | | |
| Ovary | 285 (84.8%) | 280 (83.1%) | 565 (84.0%) |
| Fallopian tube | 17 (5.1%) | 13 (3.9%) | 30 (4.5%) |
| Other | 34 (10.1%) | 44 (13.1%) | 78 (11.6%) |
| Disease Status | | | |
| Recurrence | 329 (97.9%) | 325 (96.4%) | 654 (97.2%) |
| Persistent | 0 (0.0%) | 2 (0.6%) | 2 (0.3%) |
| Progression | 7 (2.1%) | 10 (3.0%) | 17 (2.5%) |
| Measurable Disease | | | |
| Yes | 286 (85.1%) | 274 (81.3%) | 560 (83.2%) |
| No | 50 (14.9%) | 63 (18.7%) | 113 (16.8%) |
| Pre-treatment CA125 | | | |
| WNL | 72 (21.4%) | 83 (24.6%) | 155 (23.0%) |
| Abnormal | 253 (75.3%) | 246 (73.0%) | 499 (74.1%) |
| N/A | 11 (3.3%) | 8 (2.4%) | 19 (2.8%) |

Percentages are based on N.

Histologic Grade "Not Available" includes "Exclusion" and "Not Graded" results

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Table 7: Summary of previous treatment for ovarian cancer by trial treatment (overall ITT population)

| | Crb+Pac (N=336) | Crb+Pac+Bev (N=337) | All Patients (N=673) |
|--------------------------------------|--------------------|------------------------|-------------------------|
| Prior Systemic Chemotherapy | | | |
| YES | 336 (100%) | 337 (100%) | 673 (100%) |
| Prior IP Chemotherapy | | | |
| NO | 271 (80.7%) | 282 (83.7%) | 553 (82.2%) |
| YES | 65 (19.3%) | 55 (16.3%) | 120 (17.8%) |
| Prior Hormonal Therapy | | | |
| NO | 326 (97.0%) | 326 (96.7%) | 652 (96.9%) |
| YES | 10 (3.0%) | 11 (3.3%) | 21 (3.1%) |
| Prior Anti-VEGF/Bevacizumab | | | |
| NO | 302 (89.9%) | 302 (89.6%) | 604 (89.7%) |
| YES | 34 (10.1%) | 35 (10.4%) | 69 (10.3%) |
| Frontline Maintenance Therapy | | | |
| NO | 285 (84.8%) | 299 (88.7%) | 584 (86.6%) |
| YES | 51 (15.2%) | 38 (11.3%) | 89 (13.2%) |
| Frontline Taxane Maintenance Therapy | | | |
| NO | 309 (92.0%) | 317 (94.1%) | 626 (93.0%) |
| YES | 27 (8.0%) | 20 (5.9%) | 47 (7.0%) |
| Frontline Bev Maintenance Therapy | | | |
| NO | 314 (93.5%) | 323 (95.8%) | 637 (94.7%) |
| YES | 22 (6.5%) | 14 (4.2%) | 36 (5.3%) |
| Frontline Other Maintenance Therapy | | | |
| NO | 334 (99.4%) | 333 (98.8%) | 667 (99.1%) |
| YES | 2 (0.6%) | 4 (1.2%) | 6 (0.9%) |

*** Percentages are based on N (number of valid values)

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Table 8: Summary of non-protocol specified anti-cancer therapy received prior to disease progression by trial treatment (overall ITT population)

| | Crb+Fac (N=336) | Crb+Fac+Bev (N=337) |
|---|--------------------|------------------------|
| Number of patients with "X" post-protocol therapy regimens | | |
| 0 | 297 (88.4%) | 320 (95.0%) |
| 1 | 34 (10.1%) | 14 (4.2%) |
| 2 | 5 (1.5%) | 3 (0.9%) |
| # patients receiving any Bevacizumab therapy, post-protocol | 9 (2.7%) | 5 (1.5%) |
| # patients receiving "X" Platinum based chemotherapy | | |
| 0 | 324 (96.4%) | 331 (98.2%) |
| 1 | 12 (3.6%) | 6 (1.8%) |
| Surgery | 3 (0.9%) | 1 (0.3%) |
| Biologics/targeted therapies | 5 (1.5%) | 1 (0.3%) |
| Radiotherapies | 0 (0.0%) | 0 (0.0%) |
| Hormonal/Endocrine therapies | 4 (1.2%) | 2 (0.6%) |

Percentages are based on N
Treatments given in combination are summarised in each category to which they belong
Multiple regimens of a specific treatment for a patient are counted separately in the frequency for the treatment
If Disease Progression or Death did not occur, date of censoring for PFS is used to determine Prior NPT.

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Table 9: Summary of non-protocol specified anti-cancer therapy received after disease progression by trial treatment (overall ITT population)

| | Crb+Fac (N=336) | Crb+Fac+Bev (N=337) |
|---|--------------------|------------------------|
| Number of patients with "X" post-protocol therapy regimens | | |
| 0 | 46 (13.7%) | 62 (18.4%) |
| 1 | 78 (23.2%) | 82 (24.3%) |
| 2 | 68 (20.2%) | 71 (21.1%) |
| >=3 | 144 (42.9%) | 122 (36.2%) |
| # patients receiving any Bevacizumab therapy, post-protocol | 115 (34.2%) | 56 (16.6%) |
| # patients receiving "X" Platinum based chemotherapy | | |
| 0 | 216 (64.3%) | 185 (54.9%) |
| 1 | 79 (23.5%) | 113 (33.5%) |
| >=2 | 41 (12.2%) | 39 (11.6%) |
| Surgery | 13 (3.9%) | 17 (5.0%) |
| Biologics/targeted therapies | 63 (18.8%) | 44 (13.1%) |
| Radiotherapies | 33 (9.8%) | 28 (8.3%) |
| Hormonal/Endocrine therapies | 27 (8.0%) | 28 (8.3%) |

Percentages are based on N
Treatments given in combination are summarised in each category to which they belong
Multiple regimens of a specific treatment for a patient are counted separately in the frequency for the treatment
If Disease Progression did not occur, date of censoring for PFS is used to determine NPT After PD.

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Numbers analysed

The ITT population of patients included all 673 patients who were randomized to treatment: 336 patients in the Crb+Pac alone arm and 337 patients in the Crb+Pac+Bev arm. The ITT population of patients who were previously treated with bevacizumab included 34 patients (10.1%) in the Crb+Pac alone arm and 35 patients (10.4%) in the Crb+Pac+Bev arm.

Outcomes and estimation

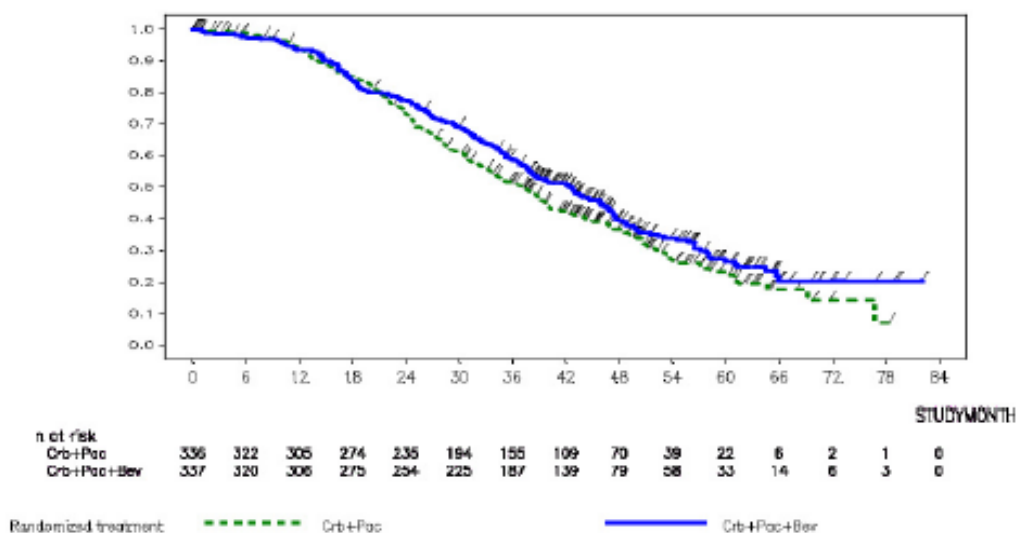
Primary endpoint: OS

Overall ITT population

Table 10: Overall Survival by Trial Treatment (Stratified Analysis: Platinum-Free Interval Category based on eCRF From) (overall ITT population)

| | Crb+Pac (N=336) | Crb+Pac+Bev (N=337) |
|------------------------------------|--------------------|------------------------|
| Patients who died | 219 (65.2%) | 212 (62.9%) |
| Patients alive* | 117 (34.8%) | 125 (37.1%) |
| Time to death (months) | | |
| Median# | 37.3 | 42.6 |
| 95% CI for Median# | [33.3;39.8] | [37.8;46.2] |
| 25% and 75%-ile | 23.6;57.3 | 25.7;61.3 |
| Range## | 0.0 to 78.4 | 0.0 to 82.1 |
| p-Value (Stratified Log-Rank Test) | | 0.0447 |
| Hazard Ratio | | 0.823 |
| 95% CI | | [0.680;0.996] |

Time to Death [months] (TMDIED) - Censoring: Overall Survival (CSDIED)
 Stratification factors used include secondary surgical debulking status Yes/No (Yes=randomized to undergo cytoreduction or randomized to not undergo cytoreduction; No= not a candidate or did not consent to cytoreduction) based on the registration form and Platinum-free interval (6-12 months vs >12 months) based on the eCRF
 * censored
 Hazard ratio based on stratified Cox proportional hazards model including treatment group
 # Kaplan-Meier estimate
 ## including censored observations



A listing by patient of survival status is appended.

Figure 3: Kaplan-Meier Plot of overall survival (Overall ITT population)

Prior Bevacizumab ITT population

Table 11: Overall Survival by Trial Treatment (Unstratified Analysis) (Prior Bevacizumab ITT population)

| | Crb+Pac (N=34) | Crb+Pac+Bev (N=35) |
|-------------------------|-------------------|-----------------------|
| Patients who died | 25 (73.5%) | 26 (74.3%) |
| Patients alive* | 9 (26.5%) | 9 (25.7%) |
| Time to death (months) | | |
| Median# | 32.0 | 36.8 |
| 95% CI for Median# | [27.0;37.3] | [27.0;48.8] |
| 25% and 75%-ile | 25.6;42.2 | 23.5;52.4 |
| Range## | 5.7 to 65.1 | 0.0 to 66.0 |
| p-Value (Log-Rank Test) | | 0.3461 |
| Hazard Ratio | | 0.764 |
| 95% CI | | [0.436;1.340] |

Time to Death [months] (TIMDIED) - Censoring: Overall Survival (CSDIED)
 * censored
 # Kaplan-Meier estimate
 ## including censored observations

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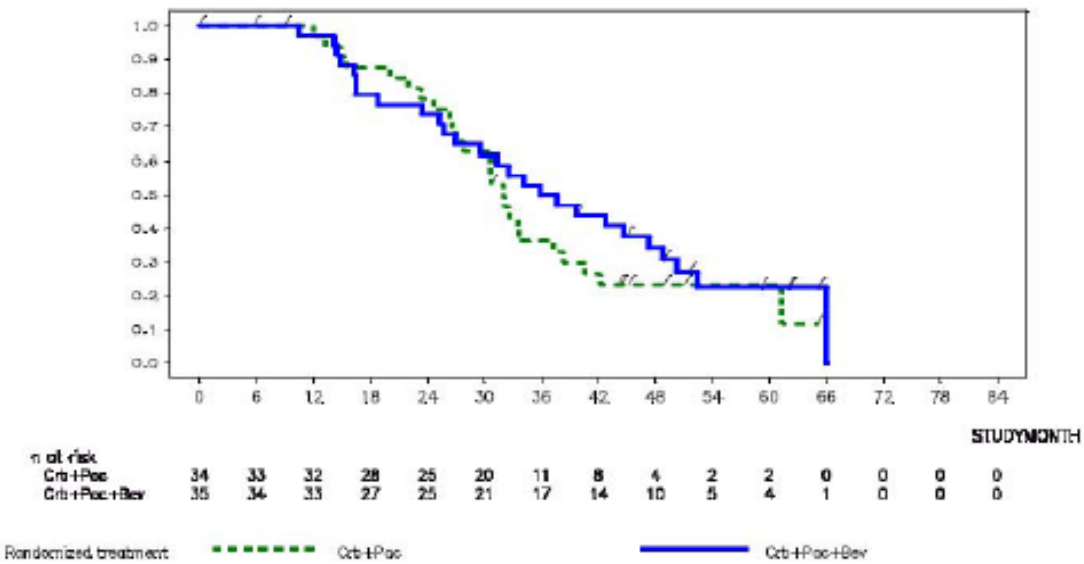


Figure 4: Kaplan-Meier Plot of overall survival (Prior Bevacizumab ITT population)

Subgroup analyses of OS – Overall ITT population

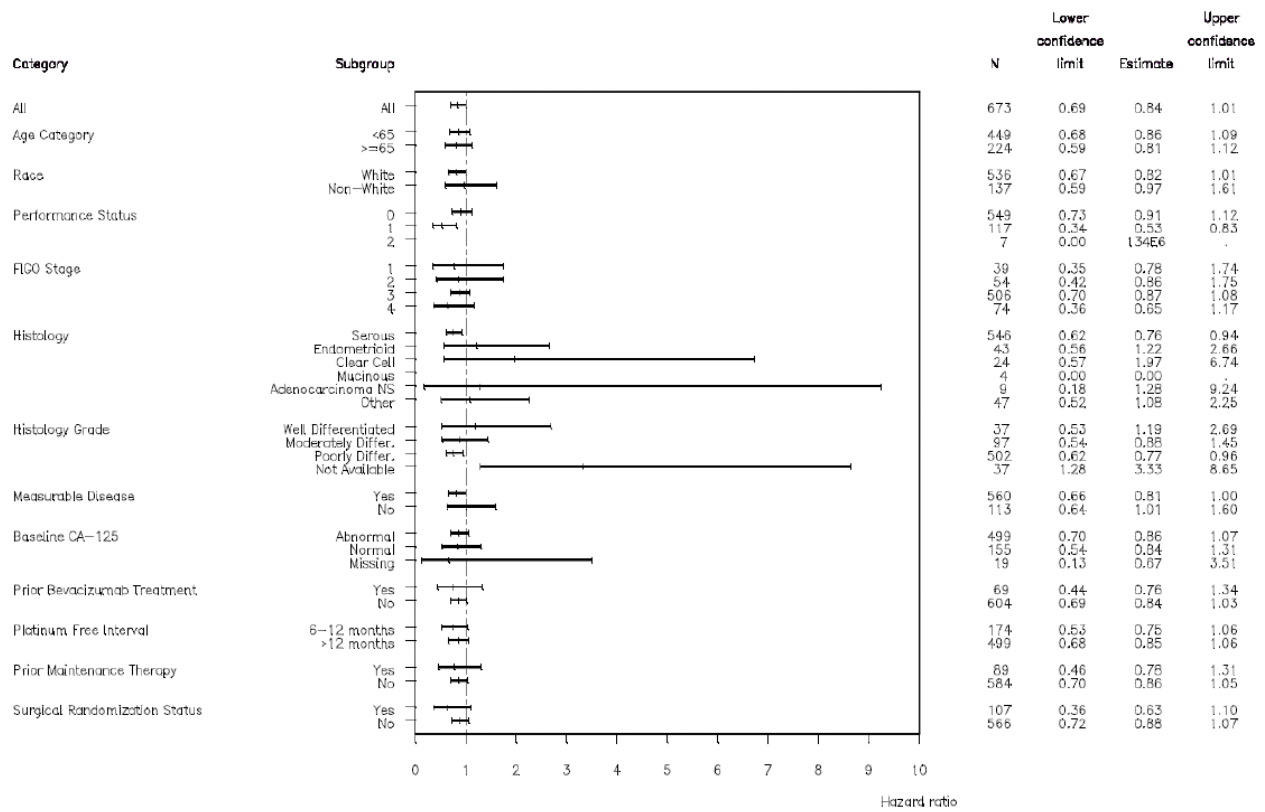


Figure 5: Forest Plot of Overall Survival by Subgroup (Study GOG-0213: Overall ITT Population)

Secondary endpoint – PFS

Overall ITT population

Table 12: Progression- free Survival by Trial Treatment (Stratified Analysis: Platinum-Free Interval Category Based on eCRF Form) (Overall ITT population)

| | Crb+Pac (N=336) | Crb+Pac+Bev (N=337) |
|------------------------------------|--------------------|------------------------|
| Patients with event | 305 (90.8%) | 298 (88.4%) |
| Patients without event* | 31 (9.2%) | 39 (11.6%) |
| Time to event (months) | | |
| Median# | 10.2 | 13.8 |
| 95% CI for Median# | [9.7;10.8] | [12.9;14.8] |
| 25% and 75%-ile | 7.2;14.3 | 9.1;24.1 |
| Range## | 0.0 to 69.2 | 0.0 to 72.6 |
| p-Value (Stratified Log-Rank Test) | <.0001 | |
| Hazard Ratio | 0.613 | |
| 95% CI | [0.521;0.721] | |

Time to CSPFS [months] (TTFPS) - Censoring: First Inv PD (With Bio Prog) or Death (CSPFS)
 Stratification factors used include secondary surgical debulking status Yes/No (Yes=randomized to undergo cytoreduction or randomized to not undergo cytoreduction; No= not a candidate or did not consent to cytoreduction) based on the registration form and Platinum-free interval (6-12 months vs >12 months) based on the eCRF
 * censored
 Hazard ratio based on stratified Cox proportional hazards model including treatment group
 # Kaplan-Meier estimate
 ## including censored observations

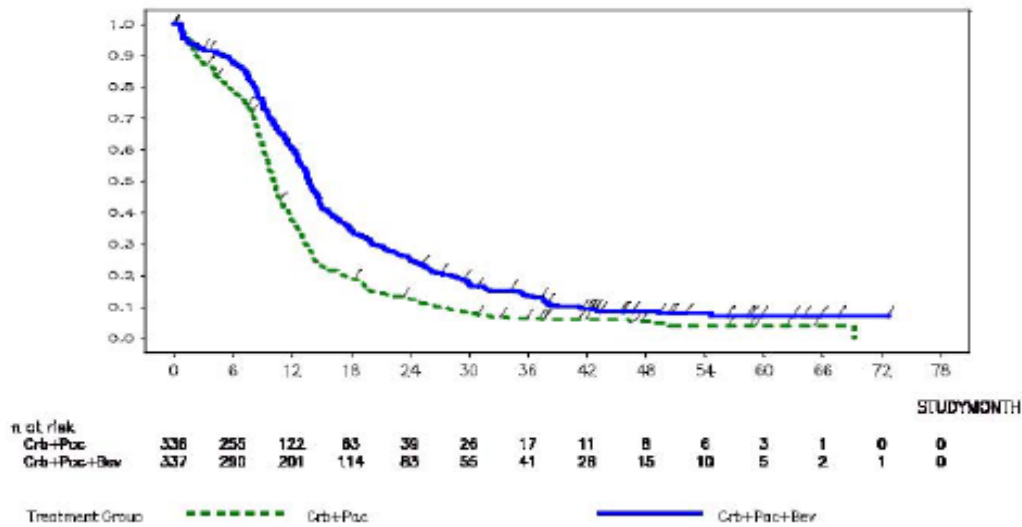


Figure 6: Kaplan-Meier Plot of progression-free survival (Overall ITT population)

Prior bevacizumab ITT population

Table 13: Progression- free Survival by Trial Treatment (Unstratified Analysis) (Prior Bevacizumab ITT population)

| | Crb+Pac (N=34) | Crb+Pac+Bev (N=35) |
|--------------------------|-------------------|-----------------------|
| Patients with event | 31 (91.2%) | 34 (97.1%) |
| Patients without events* | 3 (8.8%) | 1 (2.9%) |
| Time to event (months) | | |
| Median# | 9.8 | 10.7 |
| 95% CI for Median# | [8.9;11.1] | [9.2;13.3] |
| 25% and 75%-ile | 7.8;12.3 | 7.3;14.6 |
| Range## | 0.9 to 65.1 | 0.0 to 37.8 |
| p-Value (Log-Rank Test) | | 0.4877 |
| Hazard Ratio | | 0.841 |
| 95% CI | | [0.516;1.373] |

Time to CSFFS [months] (TTMFSS) - Censoring: First Inv PD (With Bio Prog) or Death (CSFFS)

* censored
Kaplan-Meier estimate
including censored observations

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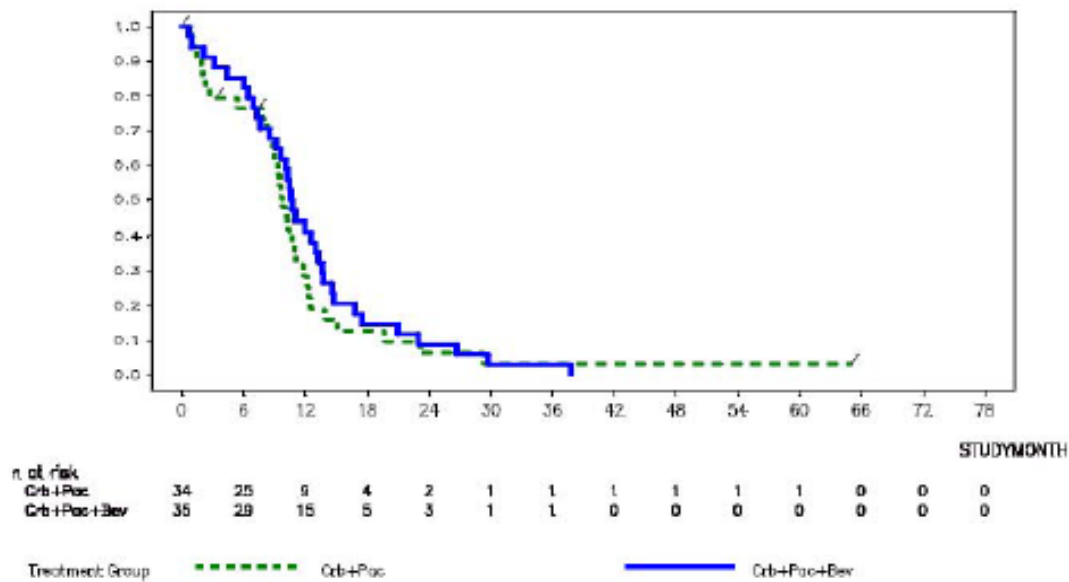


Figure 7: Kaplan-Meier Plot of progression-free survival (Prior Bevacizumab ITT population)

Subgroup analyses of PFS – Overall ITT population

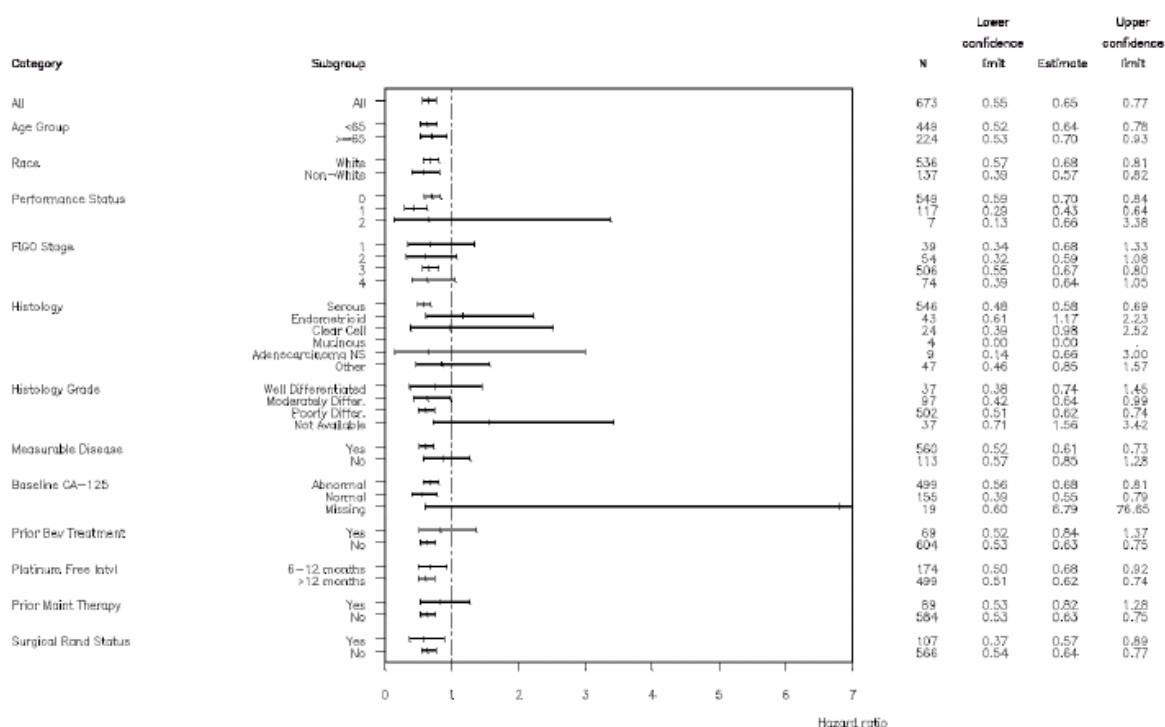


Figure 8: Forest Plot of progression-free survival by subgroup (Overall ITT population)

Secondary endpoint – HRQoL

Table 14: Quality of life assessment compliance by visit and trial treatment (Prior Bevacizumab ITT population)

| | Crb+Pac (N=34) | | Crb+Pac+Bev (N=35) | |
|---|----------------|---------|--------------------|---------|
| Prior to cycle 1 | 33/34 | (97.1%) | 30/35 | (85.7%) |
| Prior to cycle 3 (6 weeks after starting systemic therapy) | 33/34 | (97.1%) | 31/34 | (91.2%) |
| Prior to cycle 6 (12 weeks after starting systemic therapy) | 28/32 | (87.5%) | 29/34 | (85.3%) |
| 6 months after starting systemic therapy | 30/33 | (90.9%) | 30/33 | (90.9%) |
| 12 months after starting systemic therapy | 24/30 | (80.0%) | 29/31 | (93.5%) |

Compliance is based on the status of the QoL assessment at the bottom of the Fast Fact Scantron which included collection of the FACT-O, SF-36, and TSE
 If the QoL assessment is not answered and the questionnaire is completed, the patient is considered compliant
 n represents the number of patients who completed the questionnaire
 Denominator excludes patients who died (selection of '5' on QoL Status); were off study treatment and could not be contacted for follow-up (selection of '4' on QoL Status); or could not complete the questionnaire due to illness (selection of '1' on QoL Status)

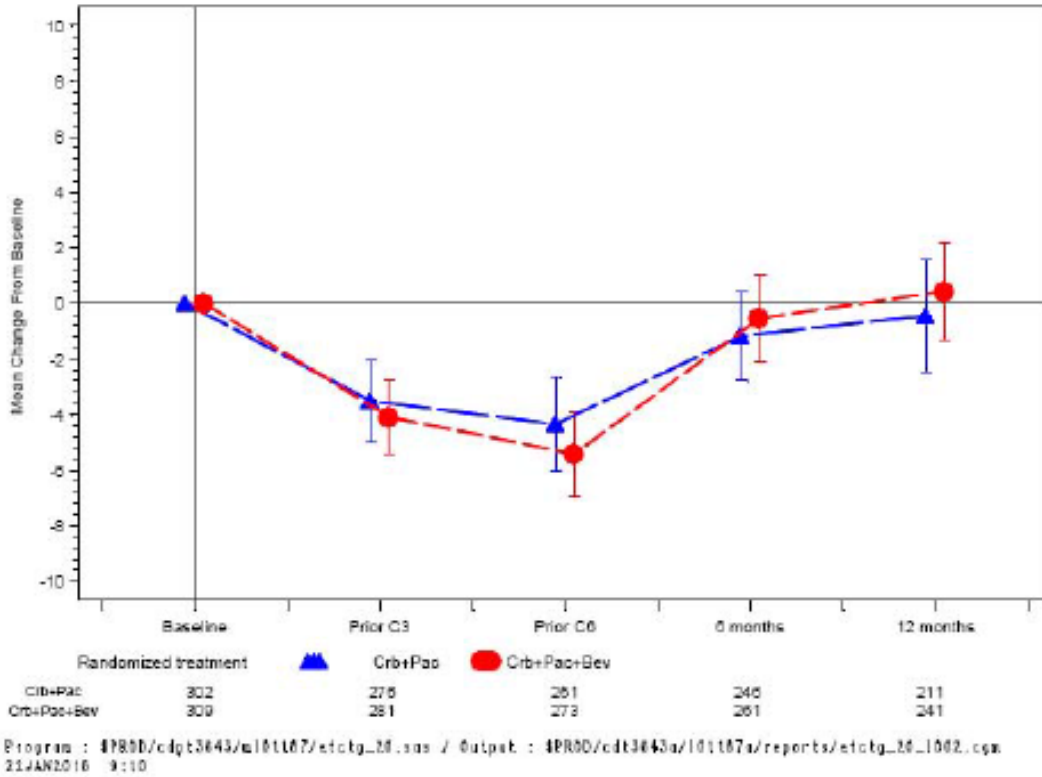


Figure 9: Plot of change from baseline in FACT-O TOI Score by visit and Trial treatment (Overall ITT population)

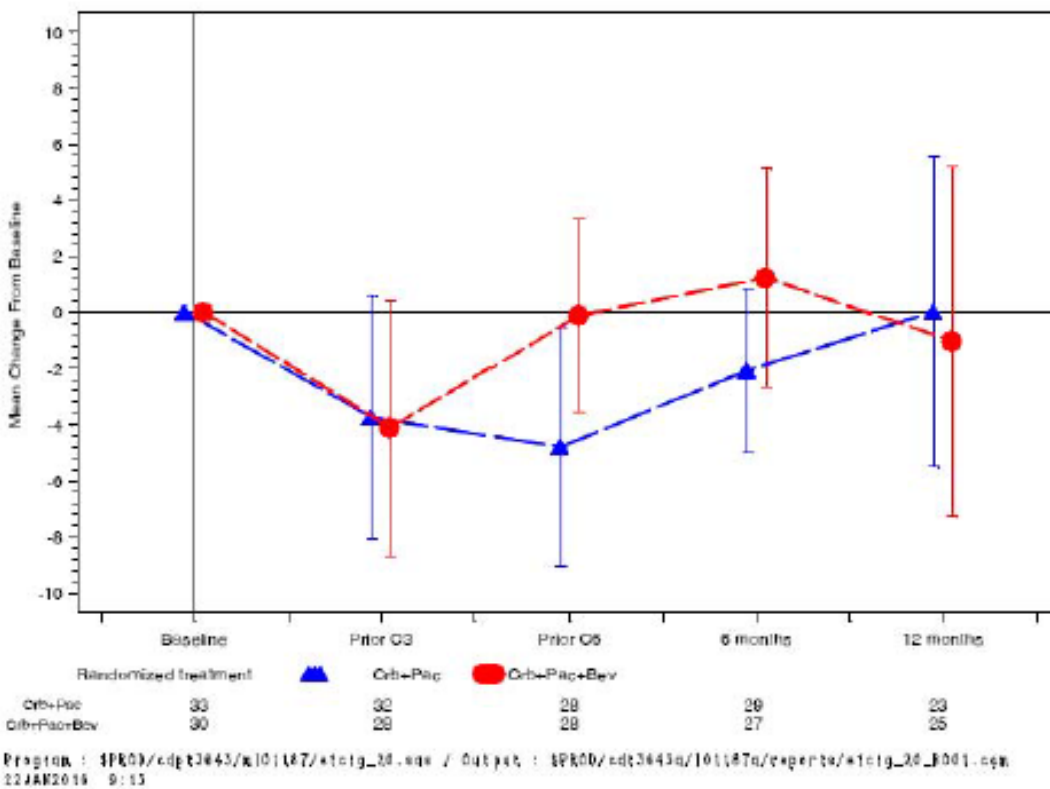


Figure 10: Plot of change from baseline in FACT-O TOI Score by visit and Trial treatment (Prior Bevacizumab ITT population)

Table 15: FACT-O TOI Repeated Measure Mixed-Effect Model by Trial Treatment (Prior Bevacizumab ITT population)

| Visit | Crb+Fac (N=34) | | Crb+Fac+Bev (N=35) | | Estimate Difference | Difference 95% CI | p-value |
|---|-------------------------------|----------------|-------------------------------|----------------|------------------------|----------------------|---------|
| | Least Square Mean Estimate | 95% CI | Least Square Mean Estimate | 95% CI | | | |
| Prior to cycle 3 (6 weeks after starting systemic therapy) | 77.38 | (73.81, 80.95) | 75.02 | (71.23, 78.82) | -2.35 | (-7.59, 2.89) | 0.3766 |
| Prior to cycle 6 (12 weeks after starting systemic therapy) | 75.72 | (71.95, 79.48) | 78.83 | (75.03, 82.63) | 3.12 | (-2.26, 8.49) | 0.2540 |
| 6 months after starting systemic therapy | 79.34 | (75.62, 83.06) | 79.86 | (75.99, 83.72) | 0.51 | (-4.89, 5.91) | 0.8513 |
| 12 months after starting systemic therapy | 80.29 | (76.21, 84.37) | 77.14 | (73.16, 81.12) | -3.15 | (-8.88, 2.58) | 0.2794 |
| Overall | 78.18 | (75.52, 80.85) | 77.71 | (74.95, 80.48) | -0.47 | (-4.35, 3.41) | 0.8101 |

A higher score indicates better quality of life
Mixed effect model for repeated measures, including patients as random effect, assuming unstructured
variance/covariance structure, with a term for time as a categorical variable, a term for treatment group,
a term for treatment-by-time interaction, and baseline score included as covariate in the model

Exploratory endpoint – ORR

ORR was not a pre-specified endpoint in the GOG protocol but was analysed by Roche/Genentech as an exploratory efficacy endpoint.

Table 16: Objective Response Rate for Patients with measurable Disease at Baseline by Trial Treatment (investigator Assessment) (Overall ITT population).

| | Crb+Fac (N=286) | Crb+Fac+Bev (N=274) |
|--|--------------------|------------------------|
| Responders [§] | 159 (55.6%) | 213 (77.7%) |
| Non-Responders | 127 (44.4%) | 61 (22.3%) |
| 95% CI for Response Rates [*] | [49.6; 61.4] | [72.3; 82.5] |
| Difference in Response Rates | | 22.14 |
| 95% CI for Difference in Response Rates [‡] | | [14.6; 29.7] |
| p-Value (2-sided Fishers Exact Test) | | <.0001 |
| p-Value (CMH Chi-square Test) | | <.0001 |
| Complete Response (CR) | 31 (10.8%) | 86 (31.4%) |
| 95% CI for CR Rates [*] | [7.5; 15.0] | [25.9; 37.2] |
| Partial Response (PR) | 128 (44.8%) | 127 (46.4%) |
| 95% CI for PR Rates [*] | [38.9; 50.7] | [40.3; 52.4] |
| Stable Disease (SD) | 78 (27.3%) | 37 (13.5%) |
| 95% CI for SD Rates [*] | [22.2; 32.8] | [9.7; 18.1] |
| Progressive Disease (PD) | 25 (8.7%) | 8 (2.9%) |
| 95% CI for PD Rates [*] | [5.7; 12.6] | [1.3; 5.7] |
| Missing (No Response Assessment) | 24 (8.4%) | 16 (5.8%) |

Best Overall Response (derived) (BORESF)
^{*} 95% CI for one sample binomial using Clopper-Pearson method
[‡] 95% CI for difference of two rates using normal approximation
Response rates are based on patients with measurable disease at baseline
[§] Patients with best overall response of confirmed CR or PR
Stratification factors used include secondary surgical debulking status Yes/No (Yes=Randomized to
undergo cytoreduction or randomized to not undergo cytoreduction; No= not a candidate or did not
consent to cytoreduction) based on the registration form and Platinum-free interval (6-12 months vs
>12 months) based on the eCRF
Note: PD includes Progressive and Increasing Disease. CMH=Cochran-Mantel-Haenszel.

Ancillary analyses

Sensitivity analyses for OS

a) Time to censoring

The Kaplan-Meier curves of time to censoring remained close over the course of the study.

b) Multiple cox regression model for overall survival

A summary of a multiple Cox regression model adjusted for treatment and baseline prognostic factors that might be associated with OS is shown below. No covariate selection process was applied; all covariates were included in the model, regardless of statistical significance. An estimated HR in one subgroup level is defined by the covariate (e.g., White for covariate race) relative to those in the other subgroup level (e.g., non-White) resulting from the model containing all covariates. The adjusted hazard ratio for treatment group was 0.80 (95% CI [0.66, 0.98], p-value = 0.0312).

Table 17: Multiple Cox Regression for Overall Survival by Trial Treatment (Overall ITT Population)

| Effect/ Covariate included in the Model | Hazard Ratio | 95% CI for Hazard Ratio | p-Value |
|---|-----------------|----------------------------|---------|
| Bevacizumab | 0.80 | [0.66;0.98] | 0.0312 |
| Age (<65 vs >=65) | 0.91 | [0.74;1.13] | 0.3840 |
| Race (white vs non-white) | 1.51 | [1.13;2.01] | 0.0055 |
| Performance status 1 vs 0 | 1.36 | [1.05;1.76] | 0.0191 |
| Performance status 2 vs 0 | 4.39 | [1.91;10.11] | 0.0005 |
| FIGO stage 1 vs 4 | 1.24 | [0.70;2.20] | 0.4537 |
| FIGO stage 2 vs 4 | 1.37 | [0.84;2.23] | 0.2024 |
| FIGO stage 3 vs 4 | 1.04 | [0.76;1.44] | 0.7901 |
| Well vs poorly differentiated | 1.15 | [0.74;1.79] | 0.5255 |
| Moderately vs poorly differentiated | 1.15 | [0.87;1.53] | 0.3373 |
| Serous vs other | 0.78 | [0.55;1.12] | 0.1783 |
| Endometrioid vs other | 0.79 | [0.46;1.36] | 0.3967 |
| Clear Cell Carcinoma vs other | 0.44 | [0.10;1.88] | 0.2667 |
| Measurable disease (yes vs no) | 1.01 | [0.78;1.32] | 0.9259 |
| Abnormal C-125 at baseline (yes vs no) | 1.76 | [1.35;2.29] | <.0001 |
| Prior Bevacizumab (yes vs no) | 1.22 | [0.87;1.71] | 0.2408 |
| Plat free intvl (6-12 mo vs >12 mo) | 1.63 | [1.30;2.03] | <.0001 |
| Maintenance Therapy (yes vs no) | 1.17 | [0.85;1.61] | 0.3441 |
| Surgery (randomised vs non-rand) | 0.68 | [0.49;0.93] | 0.0154 |

Time to Death [months] (TTMDIED) - Censoring: Overall Survival (CSDIED)
 "Other" histologies include: "Adenocarcinoma, Unsp.", "Mucinous Adenocarcinoma" and "Other", in addition to (2/3): "Serous", "Endometrioid" and "Clear cell".

c) Overall Survival Stratified Using Stratification Factors as Recorded During Randomisation (Based on Registration Form, TFI)

In the stratified analysis using the stratification factors based on the registration form (during randomisation), the HR for OS was 0.838 (95% CI [0.693; 1.014]) and the log-rank test p-value was 0.0683.

Table 18 Overall Survival Using Stratification Factors as Recorded During Randomization by Trial Treatment (Overall ITT Population)

| | Crb+Pac (N=336) | Crb+Pac+Bev (N=337) |
|------------------------------------|--------------------|------------------------|
| Patients who died | 219 (65.2 %) | 212 (62.9 %) |
| Patients alive* | 117 (34.8 %) | 125 (37.1 %) |
| Time to death (months) | | |
| Median# | 37.3 | 42.6 |
| 95% CI for Median# | [33.3;39.8] | [37.8;46.2] |
| 25% and 75%-ile | 23.6;57.3 | 25.7;61.3 |
| Range## | 0.0 to 78.4 | 0.0 to 82.1 |
| p-Value (Stratified Log-Rank Test) | | 0.0683 |
| Hazard Ratio | | 0.838 |
| 95% CI | | [0.693;1.014] |

Time to Death [months] (TMDIED) - Censoring: Overall Survival (CSDIED)
 Stratification factors used include secondary surgical debulking status Yes/No (Yes=randomized to undergo cytoreduction or randomised to not undergo cytoreduction; No= not a candidate or did not consent to cytoreduction) and treatment-free interval (6-12 months vs >12 months), both from the registration form

* censored

Hazard ratio based on stratified Cox proportional hazards model including treatment group

Kaplan-Meier estimate

including censored observations

This was the originally planned analysis in the clinical study protocol by GOG, which did not reach statistical significance (p=0.0683).

d) Overall survival unstratified analysis

In the unstratified analysis, the HR for OS was 0.840 (95% CI [0.695; 1.015]) and the log-rank test p-value was 0.0698.

Table 19 Overall Survival by Trial Treatment (Unstratified Analysis) (Overall ITT Population)

| | Crb+Pac (N=336) | Crb+Pac+Bev (N=337) |
|-------------------------|--------------------|------------------------|
| Patients who died | 219 (65.2 %) | 212 (62.9 %) |
| Patients alive* | 117 (34.8 %) | 125 (37.1 %) |
| Time to death (months) | | |
| Median# | 37.3 | 42.6 |
| 95% CI for Median# | [33.3;39.8] | [37.8;46.2] |
| 25% and 75%-ile | 23.6;57.3 | 25.7;61.3 |
| Range## | 0.0 to 78.4 | 0.0 to 82.1 |
| p-Value (Log-Rank Test) | | 0.0698 |
| Hazard Ratio | | 0.840 |
| 95% CI | | [0.695;1.015] |

Time to Death [months] (TMDIED) - Censoring: Overall Survival (CSDIED)

* censored

Kaplan-Meier estimate

including censored observations

The stratified OS analysis by trial treatment (p=0.0683) and unstratified analysis did not reach statistical significance (p=0.0698). Both the HR and median survival times were similar to the OS analysis based on the on eCRF.

Sensitivity analyses for PFS

Table 20: Progression-free Survival Censored for Non-Protocol Therapy Prior to Progressive Disease by Trial Treatment (Overall ITT Population)

| | Crb+Pac (N=336) | Crb+Pac+Bev (N=337) |
|------------------------------------|--------------------|------------------------|
| Patients with event | 262 (78.0%) | 282 (83.7%) |
| Patients without event* | 74 (22.0%) | 55 (16.3%) |
| Time to event (months) | | |
| Median# | 10.2 | 13.8 |
| 95% CI for Median# | [9.6;10.8] | [12.9;14.8] |
| 25% and 75%-ile | 7.5;14.2 | 9.1;24.1 |
| Range## | 0.0 to 65.1 | 0.0 to 72.6 |
| p-Value (Stratified Log-Rank Test) | | <.0001 |
| Hazard Ratio | | 0.600 |
| 95% CI | | [0.505;0.712] |

Time to CSSPFS [months] (TMSPFS) - Censoring: First Inv PFS before NPT (Sensi I) (CSSPFS)
 Stratification factors used include secondary surgical debulking status Yes/No (Yes=randomized to undergo cytoreduction or randomized to not undergo cytoreduction; No = not a candidate or did not consent to cytoreduction) based on the registration form and Platinum-free interval (6-12 months vs >12 months) based on the eCRF
 Hazard ratio based on stratified Cox proportional hazards model including treatment group
 * censored
 # Kaplan-Meier estimate
 ## including censored observations

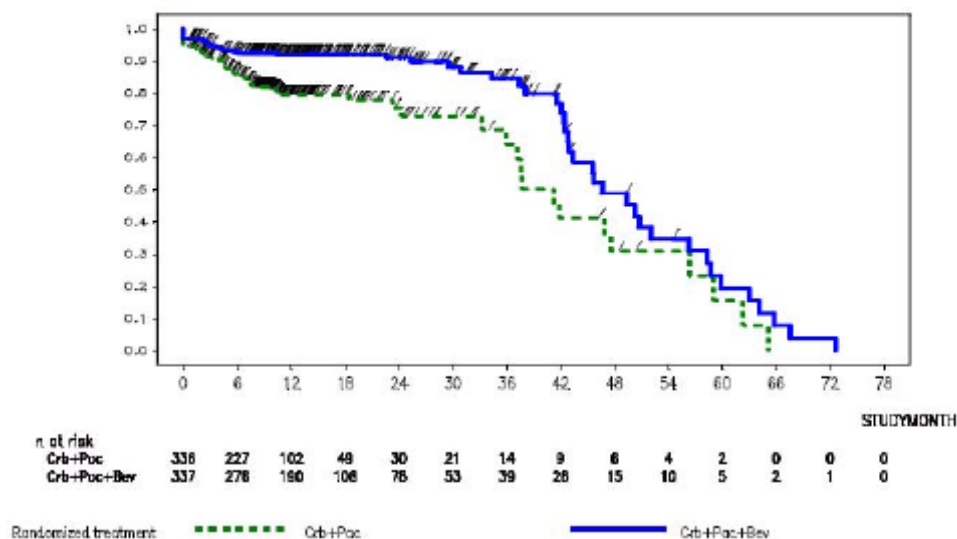


Figure 11: Kaplan-Meier Plot of progression-free survival censored for Non-Protocol Therapy Prior to progressive disease(Overall ITT population)

Table 21 Progression-free Survival not considering biologic progression as an event by trial treatment (Overall ITT Population)

| | Crb+Fac (N=336) | Crb+Fac+Bev (N=337) |
|------------------------------------|--------------------|------------------------|
| Patients with event | 304 (90.5%) | 298 (88.4%) |
| Patients without event* | 32 (9.5%) | 39 (11.6%) |
| Time to event (months) | | |
| Median# | 10.5 | 13.8 |
| 95% CI for Median# | [10.0;11.1] | [13.1;14.8] |
| 25% and 75%-ile | 7.9;14.7 | 9.5;24.7 |
| Range## | 0.0 to 69.2 | 0.0 to 72.6 |
| p-Value (Stratified Log-Rank Test) | | <.0001 |
| Hazard Ratio | | 0.621 |
| 95% CI | | [0.528;0.730] |

Time to CSSSPFS [months] (TMS3PFS) - Censoring: First Inv PD (No Bio Prog) or Death (CSSSPFS)
 Stratification factors used include secondary surgical debulking status Yes/No (Yes=Randomized to undergo cytoreduction or randomized to not undergo cytoreduction; No= not a candidate or did not consent to cytoreduction) based on the registration form and Platinum-free interval (6-12 months vs >12 months) based on the eCRF
 Hazard ratio based on stratified Cox proportional hazards model including treatment group
 * censored
 # Kaplan-Meier estimate
 ## including censored observations

Program : \$PROD/cdpt3643/ml01187/ettpfss_20.sas / Output :
 \$PROD/cdt3643a/i01187a/reports/ettpfss_20_I002.lst
 29DEC2015 11:57

Table 22: Progression-free Survival censored at last adequate disease assessment date when there were two or more missed visits by trial treatment (Overall ITT Population)

| | Crb+Fac (N=336) | Crb+Fac+Bev (N=337) |
|------------------------------------|--------------------|------------------------|
| Patients with event | 286 (85.1%) | 282 (83.7%) |
| Patients without event* | 50 (14.9%) | 55 (16.3%) |
| Time to event (months) | | |
| Median# | 10.1 | 13.8 |
| 95% CI for Median# | [9.6;10.6] | [12.9;14.7] |
| 25% and 75%-ile | 7.2;14.0 | 9.0;23.9 |
| Range## | 0.0 to 69.2 | 0.0 to 72.6 |
| p-Value (Stratified Log-Rank Test) | | <.0001 |
| Hazard Ratio | | 0.595 |
| 95% CI | | [0.503;0.703] |

Time to CSSSPFS [months] (TMS3PFS) - Censoring: First Inv PD (With Bio Prog - Not 2 or more missing assess.) or Death (CSSSPFS)
 Stratification factors used include secondary surgical debulking status Yes/No (Yes=Randomized to undergo cytoreduction or randomized to not undergo cytoreduction; No= not a candidate or did not consent to cytoreduction) based on the registration form and Platinum-free interval (6-12 months vs >12 months) based on the eCRF
 Hazard ratio based on stratified Cox proportional hazards model including treatment group
 * censored
 # Kaplan-Meier estimate
 ## including censored observations

Program : \$PROD/cdpt3643/ml01187/ettpfss_30.sas / Output :
 \$PROD/cdt3643a/i01187a/reports/ettpfss_30_I002.lst
 29DEC2015 11:58

Table 23 Progression-free Survival by Trial Treatment (Stratified Analysis Using Stratification factors based on the registration form) (Overall ITT Population)

| | Crb+Fac (N=336) | Crb+Fac+Bev (N=337) |
|------------------------------------|--------------------|------------------------|
| Patients with event | 305 (90.8%) | 298 (88.4%) |
| Patients without event* | 31 (9.2%) | 39 (11.6%) |
| Time to event (months) | | |
| Median# | 10.2 | 13.8 |
| 95% CI for Median# | [9.7;10.8] | [12.9;14.8] |
| 25% and 75%-ile | 7.2;14.3 | 9.1;24.1 |
| Range## | 0.0 to 69.2 | 0.0 to 72.6 |
| p-Value (Stratified Log-Rank Test) | | <.0001 |
| Hazard Ratio | | 0.631 |
| 95% CI | | [0.537;0.743] |

Time to CSPFS [months] (TMEFS) - Censoring: First Inv PD (With Bio Prog) or Death (CSPFS)
 Stratification factors used include secondary surgical debulking status Yes/No (Yes=randomized to undergo cytoreduction or randomized to not undergo cytoreduction; No= not a candidate or did not consent to cytoreduction) and treatment-free interval (6-12 months vs >12 months), both from the registration form
 * censored
 Hazard ratio based on stratified Cox proportional hazards model including treatment group
 # Kaplan-Meier estimate
 ## including censored observations

Table 24 Progression-free Survival by Trial Treatment (Unstratified) (Overall ITT Population)

| | Crb+Fac (N=336) | Crb+Fac+Bev (N=337) |
|--------------------------------------|--------------------|------------------------|
| Patients with event | 305 (90.8%) | 298 (88.4%) |
| Patients without events* | 31 (9.2%) | 39 (11.6%) |
| Time to event (months) | | |
| Median# | 10.2 | 13.8 |
| 95% CI for Median# | [9.7;10.8] | [12.9;14.8] |
| 25% and 75%-ile | 7.2;14.3 | 9.1;24.1 |
| Range## | 0.0 to 69.2 | 0.0 to 72.6 |
| p-Value (Unstratified Log-Rank Test) | | <.0001 |
| Hazard Ratio | | 0.651 |
| 95% CI | | [0.554;0.765] |

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

Summary of main study

The following tables summarise 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 25: Summary of Efficacy for trial GOG-0213 (ML01187)

| | | |
|---|-----------------------------------|---|
| Title: GOG-0213 (Roche No. ML01187) - A phase III randomized controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab (NSC #704865, IND #113912) followed by bevacizumab and secondary cytoreductive surgery in platinum-sensitive, recurrent ovarian, peritoneal primary and fallopian tube cancer. | | |
| Study identifier | GOG-0213 (ML 01187) | |
| Design | Phase III, randomised, open-label | |
| | Duration of main phase: | First Patient Entered: 10 December 2007 Last Patient Entered: 26 August 2011 (for Objective 1) |
| Hypothesis | Superiority | |

| | | | |
|---------------------------|------------------------------|-----|--|
| Treatments groups | Crb+pac | | Carboplatin AUC 5 + paclitaxel* 175 mg/m2 IV every 21 days for 6 - 8 cycles. * Docetaxel 75mg/m2 IV could be substituted for paclitaxel. |
| | Crb+pac+bev | | Carboplatin AUC 5 + paclitaxel* 175 mg/m2 + bevacizumab 15 mg/kg IV every 21 days for 6 - 8 cycles followed by bevacizumab alone 15mg.kg every 21 days until disease progression or toxicity precluded further treatment. * Docetaxel 75mg/m2 IV could be substituted for paclitaxe |
| Endpoints definitions and | Primary endpoint | OS | Overall Survival |
| | Secondary endpoint | PFS | Progression-free survival |
| Database lock | Data cutoff: 5 November 2014 | | |

| Results and Analysis | | | |
|---|--|---|-------------------------------|
| Analysis description | Primary Analysis | | |
| Analysis population and time point description | Intent to treat | | |
| Descriptive statistics and variability estimate | Treatment group | Crb+pac | Crb+pac+bev |
| | Number of subject | 336 | 337 |
| | OS (median in months) | 37.3 | 42.6 |
| | 95%CI | 33.3, 39.8 | 37.8, 46.2 |
| | PFS (median in months) 95%CI | 10.2 9.7, 10.8 | 13.8 12.9, 14.8 |
| Effect estimate per comparison | Primary endpoint | Comparison groups | Crb+pac vs. Crb+pac+bev |
| | | HR | 0.823 |
| | | 95%CI | 0.680, 0.996 |
| | | P-value | 0.0447 |
| | Secondary endpoint | Comparison groups | Crb+pac vs. Crb+pac+bev |
| | | HR | 0.613 |
| | | 95%CI | 0.521, 0.721 |
| | | P-value | < 0.0001 |
| | Primary endpoint OS ("GOG analysis") | Comparison groups | Crb + Pac + Bev vs. Crb + Pac |
| | | Hazard ratio (HR) | 0.838 |
| | | 95% CI for HR | (0.693, 1.014) |
| | | P-value | 0.0683 |
| | Analysis description | Subgroup of patients with <u>prior exposure to bevacizumab</u> | |
| Analysis population and time point description | Prior Bevacizumab Intent to treat | | |
| Descriptive statistics and variability estimate | Treatment group | Crb+pac | Crb+pac+bev |
| | Number of subject | 34 | 35 |
| | OS (median in months) (unstratified) | 32.0 | 36.8 |
| | 95%CI | 27.0,37.3 | 27.0,48.8 |
| | PFS (median in months) 95%CI (unstratified) | 9.8 8.9,11.1 | 10.7 9.2,13.3 |

| | | | |
|--------------------------------|--------------------|-------------------|-------------------------|
| Effect estimate per comparison | Primary endpoint | Comparison groups | Crb+pac vs. Crb+pac+bev |
| | | HR | 0.764 |
| | | 95%CI | 0.436, 1.340 |
| | Secondary endpoint | P-value | 0.3461 |
| | | Comparison groups | Crb+pac vs. Crb+pac+bev |
| | | HR | 0.841 |
| | | 95%CI | 0.516, 1.373 |
| P-value | 0.4877 | | |

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

No formal dose-response studies were submitted in support of this indication. The chosen dose is similar to other indications. The recommended dose of bevacizumab, 15 mg/kg bw given once every 21 days (q3w) as an intravenous infusion, is acceptable. The clinical studies performed in 7.5 and 10 mg/kg bw, are not convincing enough to change the 15 mg/kg bw dose, which is the currently approved dose in the front-line and recurrent platinum-sensitive ovarian cancer settings.

The Applicant initially submitted the results of one single pivotal trial to support the proposed indication. The treatment of platinum-sensitive epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer (hereafter referred to as "ovarian cancer") is based on platinum-doublet therapy. The commonly used agents are carboplatin and paclitaxel. Thus, the chemotherapy backbone is acceptable. Data from patients who underwent surgery were pooled with those who did not have surgery in the two treatment groups. Since these patients were randomised into the two treatment arms, it should be fairly balanced, and thus any possible impact of surgery status would be similar in the two groups.

The Applicant applied acceptable inclusion/exclusion criteria that clearly define patients with histological diagnosed recurrent EOC, PPC or FTC after complete response to front-line platinum-taxane therapy, and treatment-free interval of at least 6 months. Patients with prior exposure to bevacizumab were also enrolled in the study and this subgroup will provide valuable information with regard to continued bevacizumab treatment in the proposed patient population. Patients were excluded if they had conditions that may have been exacerbated upon treatment with bevacizumab.

Patients were randomised to crb+pac or crb+pac+bev. The used doses/schedules of bevacizumab, carboplatin, paclitaxel and docetaxel are in alignment with current clinical practice.

The primary objective of the study was to determine whether the addition of bevacizumab to the crb+pac chemo-backbone increase median OS. The Applicant has defined one primary endpoint, OS, and several secondary endpoints, incl. PFS. The primary endpoint, OS, is fully acceptable and secondary endpoints will provide further valuable evidence/data with regard to the use of bevacizumab in this patient population. Tumour assessments and response evaluations were determined by the investigators. The GOG RECIST criteria have been used in this study which may differ from other studies with bevacizumab. Disease progression could be defined by CA-125 criteria alone. It is reflected in the SmPC 5.1, that GOG RECIST criteria have been used. Furthermore, the Applicant has post-hoc added ORR as an exploratory endpoint. This endpoint was not part of original protocol from GOG, and consequently the value of these data is very limited.

Patients were randomized based on secondary surgical debulking and treatment-free period, which both are important prognostic factors. The MAH has applied slightly different criteria how to interpret/define treatment-free interval compared to the GOG. However, analysis of OS by the GOG criteria were included as sensitivity analysis. Forty five (45) patients (6.7%) had a discrepancy in the stratification factors (TFI vs. PFI) at randomisation between the eCRF and registration form. The 40 patients with $6 \leq \text{TFI} \leq 12$ months and $\text{PFI} > 12$ months could, according to the MAH, possibly be explained by the inconsistent use of maintenance therapy in the front-line setting obscuring the actual date of last platinum treatment.

The study is open-label thus there is a theoretical chance that secondary endpoints such as PFS, HRQoL and safety may have been biased due to the study design.

In terms of statistical methods, the MAH has correctly adjusted for multiplicity due to the interim analysis. The sample size calculation seems reasonable. The decision to stratify by platinum-free interval and not by the originally planned treatment-free interval was made retrospectively after the study results were published and well known to personnel involved in the reporting of the study. In the primary analysis of OS the stratification factors defined in the original randomisation schema would have been preferred ($p=0.0683$, a non-significant difference).

A higher percentage of patients had withdrawn from trial treatment in the Crb+ Pac + Bev arm (88.7%) than in the Crb + Pac alone arm (32.7%). However, this difference is largely attributed to the longer observation period in the Crb + Pac + Bev arm due to the continued treatment with Bev alone in that arm. The number of patients that did not receive treatment, patients that withdrew from treatment due to "patient withdrawal" and patients lost to follow-up were quite similar between arms.

There were comparable numbers of major protocol deviations in the two arms, and these were mostly related to pathology committee review. The MAH has provided an overview of the protocol deviations, which were minor and are deemed not to have had any major influence on the trial results.

The baseline demographic characteristics were well-balanced with no major differences. Mean age is approximately 60 years, ranging from 23 to 85. The majority of patients are below 65 years, white, ECOG 0 or 1. Very few patients were ECOG 3. These characteristics are reflected in section 5.1 of the SmPC.

The majority of patients were diagnosed with serous adenocarcinoma, FIGO stage III, poorly differentiated histology, with ovary as the primary site and with CA-125 being abnormal. The baseline disease characteristics were well-balanced; however, there were slightly more patients with FIGO stage III in the bev+chemo arm. If any, this slight imbalance is in favour of the control arm, however, this is considered unlikely.

In total 69 patients had received prior anti-VEGF/bevacizumab. The Applicant clarified that all of the 69 patients had received bevacizumab as part of frontline therapy. Furthermore, only 36 patients (ca. 5-6 %) had received frontline bevacizumab maintenance therapy, thus, only a limited number of patient are treated with prior bev/anti-VEGF or maintenance bevacizumab.

The applicant discussed results from three supportive studies in the platinum-sensitive recurrent OC setting as response to CHMP request to further justify the indication in patients previously treated with bevacizumab (data not shown). Among the 29 patients in the single arm phase 2 trial of irinotecan in combination with bevacizumab in recurrent OC (Musa et al. 2016), 12 patients (41.3%) had received prior bevacizumab and the clinical benefit rate was similar to that in the ITT population of the study [67% (95% CI: 35%, 90%) vs. 72.4% (95% CI: 52.8%, 87.3%)]. The AURELIA study included 26 patients (7%) who were previously treated with anti-angiogenic therapy and then were treated with bevacizumab. Sample size was deemed to be inadequate to draw any conclusions. Results from a single institutional pilot study examining the efficacy and safety of adding oral cyclophosphamide to sequential bevacizumab therapy in recurrent OC (Matulonis et al. 2012) were also provided. Thirteen (13) patients (of the total 20

enrolled) who progressed with single bevacizumab were continued on bevacizumab with added oral cyclophosphamide, resulting in 4 patients with confirmed clinical benefit. The authors concluded that adding oral cyclophosphamide to bevacizumab after tumour progression on single-agent bevacizumab appears to be safe and tolerable. Overall, the three supportive studies mentioned are very small, single arm studies and therefore it is not possible to draw any conclusions from these.

Efficacy data and additional analyses

The pivotal study met its primary endpoint. The HR is 0.823 (0.680, 0.996), p-value = 0.0447. Median OS improved 5.3 months from 37.3 to 42.6 months, adding almost an additional half year of survival is considered of clinical relevance. In the stratified analysis using the stratification factors based on the registration form during randomisation the HR for OS was 0.838 (95% CI [0.693; 1.014]) and the log-rank test p-value was 0.0683. This was the planned analysis in the clinical study protocol by GOG, and did not reach statistical significance. However, both the HR and median survival times were similar to the OS analysis based on the on the eCRF. These data have been reflected in the SmPC (see section 5.1).

The results of the subgroup analyses for OS in the ITT population were generally consistent with the results of the protocol-specified primary analysis of OS with the majority of subgroups having the point estimate of the HR below 1 and were consistent with the overall treatment effect. Note, however, that the study was not powered to detect differences in the individual subgroups, and that many of the subgroups included small numbers of patients as seen by the wide 95% CIs.

With regard the subgroup of patients with prior exposure to bevacizumab/ant-VEGF, it is important to emphasize that only 69 patients are included in this subgroup. There is no clear benefit of treating patients with prior exposure to bevacizumab in first-line, with bevacizumab at first platinum-sensitive relapse. Even though additional supportive studies have been presented, there is no strong scientific rationale to support removing the limitation from the current label.

Additionally, the proposed removal of the limitation to previous bevacizumab use will not only apply to paclitaxel and carboplatin, but also to carboplatin and gemcitabine. However, no data were presented in the dossier to substantiate a removal of the limitation for previous bevacizumab use for the already approved carboplatin and gemcitabine combination. Therefore, the provided data are not supportive of the indication of bevacizumab and chemotherapy using the carboplatin and gemcitabine combination in patients who received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.

The PFS result support the primary endpoint, median PFS improved from 10.2 to 13.8 months, and these findings are also overall in line the PFS results in study AVF4095g, where the PFS by INV was 8.4 vs. 12.4 in the crb+gem and crb+gem+bev arm respectively. It is acknowledged that the chemotherapy backbone is different between studies AVF4095g and GOG-0213, but it is nonetheless encouraging to observe that the PFS results in the bevacizumab arms are similar. PFS was primary endpoint in study AVF4095g that led to the extension of the indication to use bevacizumab in combination with carboplatin and gemcitabine in patients with platinum-sensitive disease.

The performance of bevacizumab in different subgroups in terms of PFS is overall in line with the ITT result. However, some of the subgroups are very small leading to great uncertainty. No firm conclusions can be drawn from these subgroups.

There is no indication of any detrimental effect on QoL by adding bevacizumab to crb-pac, but having in mind that the study is open-label, the value of these data are questioned. The Applicant also defined and performed post-hoc analysis of ORR, and as such it has limited value. However, the results seem to support the OS and PFS results.

Hence, the presented data from Study GOG-0213 show non-significant changes in OS and PFS for this small subgroup of patients with prior exposure to bevacizumab. In addition, the three supportive studies mentioned are very small, single arm studies and therefore it is not possible to draw any conclusions from these. A summary of data on bevacizumab in the treatment of metastatic colorectal cancer, breast cancer, and glioblastoma multiforme was provided, however, these data are not considered possible to extrapolate into the platinum-sensitive recurrent OC setting.

No explanation was provided regarding a possible resistance mechanism to bevacizumab in non-naïve patients and its potential impact on the efficacy of re-treatment with bevacizumab in the relevant setting.

2.4.4. Conclusions on the clinical efficacy

In conclusion, the pivotal study met its primary endpoint and clinically relevant results are observed with regard to OS and PFS in the ITT population. Additional data from three supportive studies were also presented. However, no sufficient clinical data or strong scientific rationale were provided for the continuous treatment of patients with prior exposure to bevacizumab.

2.5. Clinical safety

Introduction

Consistent with the objectives of the study, the primary comparison of safety was based on the safety population over the entire study (i.e., Crb+Pac+Bev followed by bevacizumab alone compared with Crb+Pac alone without any further treatment). This provides a conservative assessment of the safety profile of bevacizumab as well as of the bevacizumab based regimen investigated in this trial. No analysis by treatment phase was undertaken given the known safety profile of bevacizumab treatment. An overview of safety in patients previously treated with bevacizumab is also provided.

Patient exposure

The safety population in the study comprised those patients who received at least one full or partial dose of any component of trial treatment, with patients assigned according to the treatment they actually received. Of the 336 patients randomized to Crb+Pac alone, 327 received the randomized treatment (i.e., Crb+Pac). Of the 337 patients randomized to Crb+Pac+Bev, 325 patients received at least one dose of Bev and 5 patients only received Crb+Pac. As a result, these 5 patients were included in the Crb+Pac alone arm for the safety analysis. Thus, the safety analysis population included 332 patients (98.8%) in the Crb+Pac alone arm and 325 patients (96.4%) in the Crb+Pac+Bev arm. The safety population who were previously treated with bevacizumab included 35 patients (10.4%) in the Crb+Pac alone arm and 33 patients (9.8%) in the Crb+Pac+Bev arm.

The overall median duration of exposure in the overall safety population was 18.6 (range 0.1 – 65.1) weeks in the Crb+Pac alone arm and 48.9 (range 0.1 – 333.9) weeks in the Crb+Pac+Bev arm.

The median duration of exposure of bevacizumab was 48.9 (range 0.1 – 333.9) weeks in the Crb+Pac+Bev arm, and the median duration of carboplatin (Crb+Pac: 18.1 weeks; Crb+Pac+Bev: 18.7

weeks) and paclitaxel/docetaxel (Crb+Pac: 18.3 weeks; Crb+Pac+Bev: 19.3 weeks) was comparable between the Crb+Pac alone arm and the Crb+Pac+Bev arm.

Table 26 Summary of Duration of Exposure to Trial Treatment: Study GOG-0213

Protocol(s): (I01187A)
 Analysis: SAFETY POPULATION

| Duration (weeks) | Crb+Pac (N=332) | Crb+Pac+Bev (N=325) |
|----------------------|--------------------|------------------------|
| Overall | | |
| Mean | 18.5 | 61.3 |
| SD | 8.02 | 53.10 |
| Median | 18.6 | 48.9 |
| Min - Max | 0.1 - 65.1 | 0.1 - 333.9 |
| n | 332 | 325 |
| Bevacizumab | | |
| Mean | | 59.5 |
| SD | | 54.34 |
| Median | | 48.9 |
| Min - Max | - | 0.1 - 333.9 |
| n | 0 | 325 |
| Carboplatin | | |
| Mean | 17.9 | 18.5 |
| SD | 7.93 | 6.73 |
| Median | 18.1 | 18.7 |
| Min - Max | 0.1 - 65.1 | 0.1 - 61.1 |
| n | 332 | 325 |
| Paclitaxel/Docetaxel | | |
| Mean | 18.3 | 19.0 |
| SD | 7.62 | 7.47 |
| Median | 18.3 | 19.3 |
| Min - Max | 0.1 - 50.1 | 0.1 - 100.1 |
| n | 332 | 325 |

n represents number of patients contributing to summary statistics.
 Overall duration is based on the start date of the very first component and the last date of protocol therapy from the treatment completion form
 Individual component durations are based on the individual component cycle start dates from the cycle dose drug form

Program : \$PROD/cdpt3643/ml01187/smtdur_10.sas / Output : \$PROD/cdt3643a/i01187a/reports/smtdur_10_S001.lst
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Table 27 Summary of Cycles of Trial Treatment Received: Study GOG-0213

Protocol(s): (I01187A)
 Analysis: SAFETY POPULATION

| | Crb+Pac (N=332) | Crb+Pac+Bev (N=325) |
|--|--------------------|------------------------|
| Number of patients starting x cycles of Bevacizumab | | |
| 1-3 | 0 (0%) | 325 (100%) |
| 4-6 | 0 (0%) | 285 (87.7%) |
| 7-8 | 0 (0%) | 249 (76.6%) |
| 9-11 | 0 (0%) | 236 (72.6%) |
| 12-15 | 0 (0%) | 207 (63.7%) |
| >15 | 0 (0%) | 169 (52.0%) |
| Min-Max | | 1-111 |
| Mean | | 19.36 |
| Median | | 16 |
| Number of patients starting x cycles of Carboplatin | | |
| 1-3 | 332 (100%) | 325 (100%) |
| 4-6 | 277 (83.4%) | 295 (90.8%) |
| 7-8 | 141 (42.5%) | 148 (45.5%) |
| 9-11 | 15 (4.5%) | 3 (0.9%) |
| 12-15 | 3 (0.9%) | 2 (0.6%) |
| >15 | 1 (0.3%) | 0 (0%) |
| Min-Max | 1-20 | 1-13 |
| Mean | 6.26 | 6.44 |
| Median | 6 | 6 |
| Number of patients starting x cycles of Paclitaxel (or Docetaxel) | | |
| 1-3 | 332 (100%) | 325 (100%) |
| 4-6 | 286 (86.1%) | 303 (93.2%) |
| 7-8 | 144 (43.4%) | 155 (47.7%) |
| 9-11 | 19 (5.7%) | 7 (2.2%) |
| 12-15 | 5 (1.5%) | 1 (0.3%) |
| >15 | 1 (0.3%) | 0 (0%) |
| Min-Max | 1-16 | 1-13 |
| Mean | 6.41 | 6.61 |
| Median | 6 | 6 |
| Number of patients starting x cycles of All components of study medication | | |
| 1-3 | 332 (100%) | 325 (100%) |
| 4-6 | 277 (83.4%) | 279 (85.8%) |
| 7-8 | 139 (41.9%) | 128 (39.4%) |
| 9-11 | 14 (4.2%) | 1 (0.3%) |
| 12-15 | 3 (0.9%) | 1 (0.3%) |
| Min-Max | 1-14 | 1-12 |
| Mean | 6.21 | 6.00 |
| Median | 6 | 6 |

Percentages are based on N.

Program : \$PROD/cdpt3643/ml01187/smtcyc_10.sas
 Output : \$PROD/cdt3643a/i01187a/reports/smtcyc_10_S001.lst
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Table 28 Summary of Total Dose of Trial Treatment (overall Safety population)

| | - | Crb+Pac (N=332) | Crb+Pac+Bev (N=325) |
|-------------------------|---|--------------------|------------------------|
| Bevacizumab (mg) | | | |
| Mean | | | 21526.6 |
| SD | | | 20400.74 |
| 25th percentile | | | 7980.0 |
| Median | | | 16337.0 |
| 75th percentile | | | 29374.0 |
| Min | | | 721.0 |
| Max | | | 165200.0 |
| n | | 0 | 325 |
| Carboplatin (mg) | | | |
| Mean | | 2958.3 | 3055.4 |
| SD | | 1211.92 | 1029.79 |
| 25th percentile | | 2343.0 | 2412.0 |
| Median | | 3031.0 | 3230.0 |
| 75th percentile | | 3670.5 | 3736.0 |
| Min | | 373.0 | 309.0 |
| Max | | 10700.0 | 5800.0 |
| n | | 332 | 325 |
| Paclitaxel (mg) | | | |
| Mean | | 1883.9 | 1952.8 |
| SD | | 663.08 | 564.39 |
| 25th percentile | | 1581.0 | 1662.0 |
| Median | | 1917.0 | 1999.0 |
| 75th percentile | | 2307.8 | 2360.0 |
| Min | | 267.0 | 277.0 |
| Max | | 4600.0 | 3280.0 |
| n | | 324 | 314 |
| Docetaxel (mg) | | | |
| Mean | | 509.3 | 551.2 |
| SD | | 343.29 | 290.41 |
| 25th percentile | | 232.0 | 279.0 |
| Median | | 450.0 | 600.9 |
| 75th percentile | | 700.0 | 755.5 |
| Min | | 118.0 | 118.5 |
| Max | | 1200.0 | 1140.0 |
| n | | 21 | 20 |

n represents number of patients contributing to summary statistics.

Program : \$PROD/cdpt3643a/m101187/smtdos_10.sas
 Output : \$PROD/cdpt3643a/i01187a/reports/smtdos_10_S001.lst
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Duration of safety follow-up

The median duration of safety follow-up for the overall safety population was 22.9 (range 4.4 – 69.4) weeks in the Crb+Pac, and 53.1 (range 4.4 – 338.1) weeks in the Crb+Pac+Bev arm. The median duration of safety follow-up for the prior bevacizumab safety population was 23.3 (range 7.4 – 44.9) weeks in the Crb+Pac alone arm, and 44.7 (range 10.4 – 142.3) weeks in the Crb+Pac+Bev arm.

Adverse events

Table 29 Overview of Key Safety by Tril Treatment (overall Safety Population)

| Adverse Event | Crb+Fac (N=332) | | Crb+Fac+Bev (N=325) | |
|---|--------------------|---------|------------------------|---------|
| | n | (%) | n | (%) |
| All Adverse Events #: | | | | |
| Pts w. AE | 327 | (98.5%) | 324 | (99.7%) |
| Pts w. Serious AE | 37 | (11.1%) | 92 | (28.3%) |
| Pts w. Grade 3/4/5 AE | 112 | (33.7%) | 197 | (60.6%) |
| Pts w. Grade 5 AE (Outcome Death) | 3 | (0.9%) | 5 | (1.5%) |
| Pts who Disc. Any Treatment due to AE | 37 | (11.1%) | 82 | (25.2%) |
| Deaths: | | | | |
| All Deaths | 219 | (66.0%) | 207 | (63.7%) |
| Deaths not due to Progression | 6 | (1.8%) | 9 | (2.8%) |
| AE of Special Interest for Bevacizumab ##: | | | | |
| Pts w. AE of Special Interest | 75 | (22.6%) | 237 | (72.9%) |
| Pts w. AE of Special Interest Grade 3/4/5 | 25 | (7.5%) | 98 | (30.2%) |
| Pts w. Serious AE of Special Interest | 19 | (5.7%) | 49 | (15.1%) |
| Pts w. Bleeding (CNS) | 2 | (0.6%) | 0 | (0.0%) |
| Pts w. Bleeding (Non-CNS) | 36 | (10.8%) | 137 | (42.2%) |
| Pts w. CHF | 0 | (0.0%) | 1 | (0.3%) |
| Pts w. Fistula/Abscess (non gastrointestinal) | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Gastrointestinal perforations | 1 | (0.3%) | 6 | (1.8%) |
| Pts w. Hypertension | 10 | (3.0%) | 135 | (41.5%) |
| Pts w. Neutropenia & associated complications | 26 | (7.8%) | 40 | (12.3%) |
| Pts w. Posterior rev encephalopathy syndrome | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Proteinuria | 3 | (0.9%) | 56 | (17.2%) |
| Pts w. Secondary Primary Malignancies | 1 | (0.3%) | 0 | (0.0%) |
| Pts w. Thromboembolic event - arterial | 6 | (1.8%) | 22 | (6.8%) |
| Pts w. Thromboembolic event - venous | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Wound healing complication | 2 | (0.6%) | 10 | (3.1%) |

Adverse Events: Occurring Within First Study Treatment Date and Last Study Treatment Date plus 30 days

AE of Special Interest as defined in SAP: Occurring Within First Study Treatment Date and Last Study Treatment Date plus 183 days

Percentages are based on N

Table 30 Summary of Adverse Events with an Incidence rate of at least 10% in any Study arm by trial treatment (overall Safety Population)

| Body System/ Adverse Event | Crb+Fac | Crb+Fac+Bev |
|---|--------------------|--------------------|
| | N = 332 No. (%) | N = 325 No. (%) |
| GASTROINTESTINAL DISORDERS | | |
| NAUSEA | 197 (59) | 203 (62) |
| CONSTIPATION | 182 (55) | 189 (52) |
| DIARRHOEA | 106 (32) | 126 (39) |
| ABDOMINAL PAIN | 94 (28) | 108 (33) |
| VOMITING | 83 (25) | 108 (33) |
| STOMATITIS | 52 (16) | 106 (33) |
| DYSPEPSIA | 32 (10) | 47 (14) |
| NERVOUS SYSTEM DISORDERS | | |
| PERIPHERAL SENSORY NEUROPATHY | 245 (74) | 234 (72) |
| HEADACHE | 65 (20) | 125 (38) |
| DYSGEUSIA | 37 (11) | 42 (13) |
| DIZZINESS | 27 (8) | 44 (14) |
| DYSARTHRIA | 6 (2) | 46 (14) |
| METABOLISM AND NUTRITION DISORDERS | | |
| DECREASED APPETITE | 84 (25) | 114 (35) |
| HYPERGLYCAEMIA | 79 (24) | 100 (31) |
| HYPOMAGNESAEMIA | 56 (17) | 89 (27) |
| HYPONATRAEMIA | 35 (11) | 44 (14) |
| HYPONATRAEMIA | 19 (6) | 54 (17) |
| HYPOALBUMINAEMIA | 20 (6) | 36 (11) |
| HYPOCALCAEMIA | 16 (5) | 40 (12) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | |
| ALOPECIA | 262 (79) | 265 (82) |
| EXFOLIATIVE RASH | 52 (16) | 76 (23) |
| PRURITUS | 26 (8) | 38 (12) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | |
| ARTHRALGIA | 101 (30) | 145 (45) |
| MYALGIA | 60 (18) | 94 (29) |
| PAIN IN EXTREMITY | 46 (14) | 82 (25) |
| BACK PAIN | 34 (10) | 56 (17) |
| MUSCULAR WEAKNESS | 27 (8) | 43 (13) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | |
| FATIGUE | 264 (80) | 266 (82) |
| OEDEMA PERIPHERAL | 40 (12) | 35 (11) |
| PYREXIA | 32 (10) | 43 (13) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | |
| DYSPNOEA | 84 (25) | 99 (30) |
| COUGH | 56 (17) | 96 (30) |
| EPISTAXIS | 7 (2) | 108 (33) |
| RHINITIS ALLERGIC | 13 (4) | 56 (17) |
| NASAL MUCOSAL DISORDER | 9 (3) | 47 (14) |
| PSYCHIATRIC DISORDERS | | |
| INSOMNIA | 47 (14) | 58 (18) |
| DEPRESSION | 47 (14) | 43 (13) |
| ANXIETY | 42 (13) | 46 (14) |
| INVESTIGATIONS | | |
| ASPARTATE AMINOTRANSFERASE IMPROVEMENT | 31 (9) | 50 (15) |
| ALANINE AMINOTRANSFERASE IMPROVEMENT | 27 (8) | 37 (11) |
| WEIGHT DECREASED | 13 (4) | 48 (15) |
| BLOOD CREATININE IMPROVEMENT | 18 (5) | 42 (13) |
| VASCULAR DISORDERS | | |
| HYPERTENSION | 10 (3) | 135 (42) |
| HOT FLUSH | 29 (9) | 37 (11) |
| IMMUNE SYSTEM DISORDERS | | |
| HYPERSENSITIVITY | 79 (24) | 85 (26) |
| EYE DISORDERS | | |
| VISION BLURRED | 37 (11) | 47 (14) |
| RENAL AND URINARY DISORDERS | | |
| PROTEINURIA | 3 (<1) | 56 (17) |

Investigator text for Adverse Events encoded using MedDRA version 18.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
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Grade \geq 3 AEs

Table 31 Summary of Grade \geq 3 Adverse Events occurring in \geq 5% of Patients in any treatment arm by trial treatment (overall Safety Population)

| Body System/ Adverse Event | Crb+Pac | Crb+Pac+Bev |
|--|--------------------|--------------------|
| | N = 332 No. (%) | N = 325 No. (%) |
| IMMUNE SYSTEM DISORDERS HYPERSENSITIVITY | 26 (8) | 30 (9) |
| VASCULAR DISORDERS HYPERTENSION | 2 (<1) | 36 (11) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS FATIGUE | 9 (3) | 25 (8) |
| METABOLISM AND NUTRITION DISORDERS HYPERGLYCAEMIA | 17 (5) | 14 (4) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS FEBRILE NEUTROPENIA | 9 (3) | 20 (6) |
| RENAL AND URINARY DISORDERS PROTEINURIA | - | 26 (8) |
| GASTROINTESTINAL DISORDERS ABDOMINAL PAIN | 3 (<1) | 19 (6) |

Investigator text for Adverse Events encoded using MedDRA version 18.1.
For processing, missing TT end date and time are replaced by TT start date and time.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
AE13 17FEB2016:10:12:21

Table 32 Summary of Grade \geq 3 Adverse Events with an incidence difference of \geq 2% between treatment arms (overall Safety Population)

| Body System/ Adverse Event | Crb+Pac | Crb+Pac+Bev |
|---|------------------|------------------|
| | N=332 No. (%) | N=325 No. (%) |
| VASCULAR DISORDERS HYPERTENSION | 2 (0.6) | 36 (11.1) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS FATIGUE | 9 (2.7) | 25 (7.7) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS FEBRILE NEUTROPENIA | 9 (2.7) | 20 (6.2) |
| RENAL AND URINARY DISORDERS PROTEINURIA | - | 26 (8.0) |
| GASTROINTESTINAL DISORDERS ABDOMINAL PAIN | 3 (0.9) | 19 (5.8) |
| METABOLISM AND NUTRITION DISORDERS HYPONATRAEMIA | 3 (0.9) | 12 (3.7) |
| NERVOUS SYSTEM DISORDERS HEADACHE | 3 (0.9) | 10 (3.1) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS PAIN IN EXTREMITY | - | 11 (3.4) |

Program : \$PROD/cdpt3643/ml01187/aedf2_10.sas
Output : \$PROD/cdt3643a/i01187a/report5/aedf2_10_8002.lst
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Adverse Events of Special Interest (AESI)

In the overall safety population, one or more AESIs of any grade were reported in a higher proportion of patients in the Crb+Pac+Bev arm (73%) compared to the Crb+Pac alone arm (23%). This difference was mainly due to an increase of specific AESIs in the Crb+Pac+Bev arm compared to the Crb+Pac alone arm. These were bleeding events (42% patients vs. 11% patients, respectively), hypertension (42% patients vs. 3% patients, respectively), proteinuria (17% patients vs. <1% patients, respectively) and neutropenia and associated complications (Crb+Pac; 8%; Crb+Pac+Bev: 12%).

Table 33 Summary of Adverse Events of special interest by trial treatment (overall Safety Population)

| Special Interest/ Adverse Event | Crb+Pac | Crb+Pac+Bev |
|---|--------------------|--------------------|
| | N = 332 No. (%) | N = 325 No. (%) |
| ALL SPECIAL INTEREST | | |
| Total Pts with at Least one AE | 75 (23) | 237 (73) |
| Total Number of AEs | 93 | 472 |
| BLEEDING | | |
| Total Pts With at Least one AE | 38 (11) | 137 (42) |
| EPISTAXIS | 7 (2) | 108 (33) |
| CONTUSION | 11 (3) | 14 (4) |
| RECTAL HAEMORRHAGE | 5 (2) | 19 (6) |
| MOUTH HAEMORRHAGE | 2 (<1) | 17 (5) |
| VAGINAL HAEMORRHAGE | 9 (3) | 9 (3) |
| ANAL HAEMORRHAGE | - | 6 (2) |
| HAEMORRHAGIC DISORDER | 1 (<1) | 3 (<1) |
| GASTRIC HAEMORRHAGE | 2 (<1) | 1 (<1) |
| HAEMORRHAGE URINARY TRACT | - | 3 (<1) |
| LARGE INTESTINAL HAEMORRHAGE | - | 3 (<1) |
| URINARY BLADDER HAEMORRHAGE | 1 (<1) | 2 (<1) |
| CEREBROVASCULAR ACCIDENT | 2 (<1) | - |
| HAEMATOMA | 1 (<1) | 1 (<1) |
| RESPIRATORY TRACT HAEMORRHAGE | - | 2 (<1) |
| ANORECTAL VARICES HAEMORRHAGE | 1 (<1) | - |
| DISSEMINATED INTRAVASCULAR COAGULATION | - | 1 (<1) |
| GASTROINTESTINAL ANASTOMOTIC LEAK | 1 (<1) | - |

| | | |
|--|---------|-----------|
| BLEEDING (Cont.) | | |
| LOWER GASTROINTESTINAL HAEMORRHAGE | - | 1 (<1) |
| PETECHIAE | - | 1 (<1) |
| PULMONARY HAEMORRHAGE | 1 (<1) | - |
| STOMA SITE HAEMORRHAGE | - | 1 (<1) |
| UPPER GASTROINTESTINAL HAEMORRHAGE | - | 1 (<1) |
| URETERIC HAEMORRHAGE | - | 1 (<1) |
| Total Number of AEs | 44 | 194 |
| HYPERTENSION | | |
| Total Pts With at Least one AE | 10 (3) | 135 (42) |
| HYPERTENSION | 10 (3) | 135 (42) |
| Total Number of AEs | 10 | 135 |
| ROCHE STANDARD AEGT - NEUTROPENIA AND ASSOCIATED COMPLICATIONS | | |
| Total Pts With at Least one AE | 26 (8) | 40 (12) |
| NEUTROPENIA | 18 (6) | 25 (8) |
| FEBRILE NEUTROPENIA | 8 (3) | 15 (6) |
| Total Number of AEs | 26 | 45 |
| PROTEINURIA | | |
| Total Pts With at Least one AE | 3 (<1) | 56 (17) |
| PROTEINURIA | 3 (<1) | 56 (17) |
| Total Number of AEs | 3 | 56 |
| ARTERIAL THROMBOEMBOLIC EVENTS | | |
| Total Pts With at Least one AE | 6 (2) | 22 (7) |
| THROMBOSIS | 2 (<1) | 8 (2) |
| EMBOLISM | 2 (<1) | 4 (1) |
| CEREBRAL ISCHAEMIA | - | 4 (1) |
| THROMBOSIS IN DEVICE | 1 (<1) | 2 (<1) |
| ACUTE MYOCARDIAL INFARCTION | - | 2 (<1) |
| CEREBROVASCULAR ACCIDENT | 2 (<1) | - |
| HEMIPARESIS | - | 2 (<1) |
| DISSEMINATED INTRAVASCULAR COAGULATION | - | 1 (<1) |
| THROMBOTIC MICROANGIOPATHY | - | 1 (<1) |
| Total Number of AEs | 7 | 24 |
| WOUND HEALING COMPLICATION | | |
| Total Pts With at Least one AE | 2 (<1) | 10 (3) |
| WOUND COMPLICATION | 1 (<1) | 8 (2) |
| WOUND INFECTION | 1 (<1) | 3 (<1) |
| Total Number of AEs | 2 | 11 |
| GASTROINTESTINAL PERFORATIONS | | |
| Total Pts With at Least one AE | 1 (<1) | 6 (2) |
| FISTULA OF SMALL INTESTINE | - | 3 (<1) |
| SMALL INTESTINAL PERFORATION | - | 1 (<1) |
| COLONIC FISTULA | - | 1 (<1) |
| GASTROINTESTINAL ANASTOMOTIC LEAK | 1 (<1) | - |
| INTESTINAL PERFORATION | - | 1 (<1) |
| LARGE INTESTINE PERFORATION | - | 1 (<1) |
| Total Number of AEs | 1 | 7 |
| CHF | | |
| Total Pts With at Least one AE | - | 1 (<1) |
| LEFT VENTRICULAR DYSFUNCTION | - | 1 (<1) |
| Total Number of AEs | - | 1 |
| SECONDARY PRIMARY MALIGNANCIES | | |
| Total Pts With at Least one AE | 1 (<1) | - |
| METASTASIS | 1 (<1) | - |
| Total Number of AEs | 1 | - |

Investigator text for Adverse Events encoded using MedDRA version 18.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 28JAN2016:16:00:37

Table 34 Summary of Grade ≥3 Adverse Events of Special interests (overall Safety Population)

| Special Interest/ Adverse Event | Crb+Pac | Crb+Pac+Bev |
|---|--------------------|--------------------|
| | N = 332 No. (%) | N = 325 No. (%) |
| ALL SPECIAL INTEREST | | |
| Total Pts with at Least one AE | 25 (8) | 98 (30) |
| Total Number of AEs | 27 | 120 |
| HYPERTENSION | | |
| Total Pts With at Least one AE | 2 (<1) | 36 (11) |
| HYPERTENSION | 2 (<1) | 36 (11) |
| Total Number of AEs | 2 | 36 |
| ROCHE STANDARD AEGT - NEUTROPENIA AND ASSOCIATED COMPLICATIONS | | |
| Total Pts With at Least one AE | 14 (4) | 23 (7) |
| FEBRILE NEUTROPENIA | 9 (3) | 20 (6) |
| NEUTROPENIA | 5 (2) | 4 (1) |
| Total Number of AEs | 14 | 24 |
| PROTEINURIA | | |
| Total Pts With at Least one AE | - | 26 (8) |
| PROTEINURIA | - | 26 (8) |
| Total Number of AEs | - | 26 |
| ARTERIAL THROMBOEMBOLIC EVENTS | | |
| Total Pts With at Least one AE | 6 (2) | 17 (5) |
| THROMBOSIS | 2 (<1) | 6 (2) |
| EMBOLISM | 2 (<1) | 4 (1) |
| CEREBRAL ISCHAEMIA | - | 3 (<1) |
| ACUTE MYOCARDIAL INFARCTION | - | 2 (<1) |
| CEREBROVASCULAR ACCIDENT | 2 (<1) | - |
| THROMBOSIS IN DEVICE | 1 (<1) | 1 (<1) |
| HEMIPARESIS | - | 1 (<1) |
| Total Number of AEs | 7 | 17 |
| BLEEDING | | |
| Total Pts With at Least one AE | 5 (2) | 5 (2) |
| EPISTAXIS | - | 3 (<1) |
| GASTRIC HAEMORRHAGE | 2 (<1) | 1 (<1) |
| CEREBROVASCULAR ACCIDENT | 2 (<1) | - |
| LARGE INTESTINAL HAEMORRHAGE | - | 1 (<1) |
| RECTAL HAEMORRHAGE | - | 1 (<1) |
| VAGINAL HAEMORRHAGE | 1 (<1) | - |
| Total Number of AEs | 5 | 6 |
| WOUND HEALING COMPLICATION | | |
| Total Pts With at Least one AE | - | 6 (2) |
| WOUND COMPLICATION | - | 4 (1) |
| WOUND INFECTION | - | 2 (<1) |
| Total Number of AEs | - | 6 |
| GASTROINTESTINAL PERFORATIONS | | |
| Total Pts With at Least one AE | - | 4 (1) |
| COLONIC FISTULA | - | 1 (<1) |
| INTESTINAL PERFORATION | - | 1 (<1) |
| LARGE INTESTINE PERFORATION | - | 1 (<1) |
| SMALL INTESTINAL PERFORATION | - | 1 (<1) |
| Total Number of AEs | - | 4 |

Serious adverse event/deaths/other significant events

Serious adverse event

Table 35 Summary of Grade ≥ 3 Serious Adverse events by trial treatment (overall Safety Population)

| Body System/ Adverse Event | Crb+Pac N = 332 No. (%) | Crb+Pac+Bev N = 325 No. (%) |
|-----------------------------------|-------------------------------|-----------------------------------|
| ALL BODY SYSTEMS | | |
| Total Pts with at Least one AE | 35 (11) | 90 (28) |
| Total Number of AEs | 77 | 199 |
| GASTROINTESTINAL DISORDERS | | |
| Total Pts With at Least one AE | 12 (4) | 23 (7) |
| SMALL INTESTINAL OBSTRUCTION | 5 (2) | 8 (2) |
| NAUSEA | 4 (1) | 7 (2) |
| ABDOMINAL PAIN | 2 (<1) | 8 (2) |
| DIARRHOEA | 2 (<1) | 5 (2) |
| VOMITING | 3 (<1) | 4 (1) |
| CONSTIPATION | 1 (<1) | 2 (<1) |
| COLITIS | - | 2 (<1) |
| GASTRIC HAEMORRHAGE | 1 (<1) | 1 (<1) |
| ABDOMINAL DISTENSION | - | 1 (<1) |
| COLONIC FISTULA | - | 1 (<1) |
| GASTRIC ULCER | - | 1 (<1) |
| ILEUS | 1 (<1) | - |

| | | |
|--------------------------------------|---------|---------|
| GASTROINTESTINAL DISORDERS (cont.) | | |
| LARGE INTESTINAL HAEMORRHAGE | - | 1 (<1) |
| LARGE INTESTINAL OBSTRUCTION | - | 1 (<1) |
| LARGE INTESTINE PERFORATION | - | 1 (<1) |
| ESOPHAGITIS | - | 1 (<1) |
| RECTAL HAEMORRHAGE | - | 1 (<1) |
| SMALL INTESTINAL PERFORATION | - | 1 (<1) |
| Total Number of AEs | 19 | 46 |
| METABOLISM AND NUTRITION DISORDERS | | |
| Total Pts With at Least one AE | 10 (3) | 19 (6) |
| DEHYDRATION | 5 (2) | 5 (2) |
| HYPONATRAEMIA | - | 6 (2) |
| HYPERGLYCAEMIA | 3 (<1) | 2 (<1) |
| HYPOKALAEMIA | 2 (<1) | 3 (<1) |
| HYPOPHOSPHATAEMIA | 1 (<1) | 1 (<1) |
| DECREASED APPETITE | - | 1 (<1) |
| HYPERCALCAEMIA | - | 1 (<1) |
| HYPERCHOLESTEROLAEMIA | - | 1 (<1) |
| HYPERMAGNESEAEMIA | - | 1 (<1) |
| HYPERTRIGLYCERIDAEMIA | 1 (<1) | - |
| HYPOALBUMINAEMIA | - | 1 (<1) |
| Total Number of AEs | 12 | 22 (<1) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | |
| Total Pts With at Least one AE | 10 (3) | 18 (6) |
| FEBRILE NEUTROPENIA | 7 (2) | 15 (5) |
| NEUTROPENIA | 3 (<1) | 4 (1) |
| LYMPHOPENIA | 1 (<1) | - |
| Total Number of AEs | 11 | 19 |
| INFECTIONS AND INFESTATIONS | | |
| Total Pts With at Least one AE | 8 (2) | 19 (6) |
| URINARY TRACT INFECTION | 2 (<1) | 6 (2) |
| INFECTION | - | 5 (2) |
| SEPSIS | 1 (<1) | 2 (<1) |
| DEVICE RELATED INFECTION | 1 (<1) | 1 (<1) |
| INFECTIOUS COLITIS | 1 (<1) | 1 (<1) |
| PNEUMONIA | - | 2 (<1) |
| SOFT TISSUE INFECTION | - | 2 (<1) |
| WOUND INFECTION | - | 2 (<1) |
| CELLULITIS | 1 (<1) | - |
| CYSTITIS | - | 1 (<1) |
| ENCEPHALITIS | - | 1 (<1) |
| EYE INFECTION | - | 1 (<1) |
| KIDNEY INFECTION | 1 (<1) | - |
| OPPORTUNISTIC INFECTION | 1 (<1) | - |
| PELVIC INFECTION | - | 1 (<1) |
| SINUSITIS | - | 1 (<1) |
| UPPER RESPIRATORY TRACT INFECTION | 1 (<1) | - |
| Total Number of AEs | 9 | 26 |
| NERVOUS SYSTEM DISORDERS | | |
| Total Pts With at Least one AE | 4 (1) | 14 (4) |
| SYNCOPE | 2 (<1) | 4 (1) |
| CEREBRAL ISCHAEMIA | - | 3 (<1) |
| CEREBROVASCULAR ACCIDENT | 2 (<1) | - |
| DIZZINESS | - | 2 (<1) |
| HEADACHE | - | 2 (<1) |
| PERIPHERAL MOTOR NEUROPATHY | 1 (<1) | 1 (<1) |
| PERIPHERAL SENSORY NEUROPATHY | - | 2 (<1) |
| SOMNOLENCE | - | 2 (<1) |
| ENCEPHALOPATHY | - | 1 (<1) |
| HEMIPARESIS | - | 1 (<1) |
| NERVOUS SYSTEM DISORDER | - | 1 (<1) |
| SEIZURE | - | 1 (<1) |
| Total Number of AEs | 5 | 20 |

| | | |
|---|--------|---------|
| VASCULAR DISORDERS | | |
| Total Pts With at Least one AE | 6 (2) | 12 (4) |
| EMBOLISM | 2 (<1) | 4 (1) |
| HYPERTENSION | 1 (<1) | 5 (2) |
| THROMBOSIS | 2 (<1) | 2 (<1) |
| ANGIOPATHY | - | 1 (<1) |
| HYPOTENSION | 1 (<1) | - |
| Total Number of AEs | 6 | 12 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | |
| Total Pts With at Least one AE | 4 (1) | 10 (3) |
| FATIGUE | 1 (<1) | 4 (1) |
| CHEST PAIN | - | 2 (<1) |
| DISEASE PROGRESSION | - | 2 (<1) |
| PAIN | 2 (<1) | - |
| THROMBOSIS IN DEVICE | 1 (<1) | 1 (<1) |
| DEATH | - | 1 (<1) |
| SUDDEN DEATH | - | 1 (<1) |
| Total Number of AEs | 4 | 11 |
| IMMUNE SYSTEM DISORDERS | | |
| Total Pts With at Least one AE | 1 (<1) | 8 (2) |
| HYPERSENSITIVITY | - | 7 (2) |
| ANAPHYLACTIC REACTION | 1 (<1) | 1 (<1) |
| Total Number of AEs | 1 | 8 |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | |
| Total Pts With at Least one AE | 2 (<1) | 6 (2) |
| DYSPNOEA | 1 (<1) | 3 (<1) |
| COUGH | 1 (<1) | 2 (<1) |
| EPISTAXIS | - | 2 (<1) |
| ASPIRATION | - | 1 (<1) |
| Total Number of AEs | 2 | 8 |
| INVESTIGATIONS | | |
| Total Pts With at Least one AE | 3 (<1) | 3 (<1) |
| ALANINE AMINOTRANSFERASE IMPROVEMENTD | 1 (<1) | 2 (<1) |
| ASPARTATE AMINOTRANSFERASE IMPROVEMENTD | 1 (<1) | 1 (<1) |
| BLOOD CREATININE IMPROVEMENTD | 1 (<1) | 1 (<1) |
| BLOOD ALKALINE PHOSPHATASE IMPROVEMENTD | - | 1 (<1) |
| ELECTROCARDIOGRAM QT PROLONGED | 1 (<1) | - |
| TROPONIN I IMPROVEMENTD | - | 1 (<1) |
| Total Number of AEs | 4 | 6 |
| PSYCHIATRIC DISORDERS | | |
| Total Pts With at Least one AE | - | 4 (1) |
| CONFUSIONAL STATE | - | 2 (<1) |
| DEPRESSION | - | 2 (<1) |
| ANXIETY | - | 1 (<1) |
| Total Number of AEs | - | 5 |
| CARDIAC DISORDERS | | |
| Total Pts With at Least one AE | - | 4 (1) |
| ACUTE MYOCARDIAL INFARCTION | - | 2 (<1) |
| ATRIAL FIBRILLATION | - | 2 (<1) |
| Total Number of AEs | - | 4 |
| EYE DISORDERS | | |
| Total Pts With at Least one AE | 1 (<1) | 2 (<1) |
| VISION BLURRED | 1 (<1) | 2 (<1) |
| Total Number of AEs | 1 | 2 |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | |
| Total Pts With at Least one AE | - | 3 (<1) |
| WOUND COMPLICATION | - | 3 (<1) |
| Total Number of AEs | - | 3 |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | |
| Total Pts With at Least one AE | - | 3 (<1) |
| MUSCULAR WEAKNESS | - | 1 (<1) |
| MYALGIA | - | 1 (<1) |
| SOFT TISSUE NECROSIS | - | 1 (<1) |
| Total Number of AEs | - | 3 |
| RENAL AND URINARY DISORDERS | | |
| Total Pts With at Least one AE | 1 (<1) | 2 (<1) |
| PROTEINURIA | - | 1 (<1) |
| RENAL FAILURE | - | 1 (<1) |
| URETERIC OBSTRUCTION | 1 (<1) | - |
| Total Number of AEs | 1 | 2 |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | | |
| Total Pts With at Least one AE | 2 (<1) | - |
| METASTASIS | 1 (<1) | - |
| MYELODYSPLASTIC SYNDROME | 1 (<1) | - |
| Total Number of AEs | 2 | - |
| ENDOCRINE DISORDERS | | |
| Total Pts With at Least one AE | - | 1 (<1) |
| ENDOCRINE DISORDER | - | 1 (<1) |
| Total Number of AEs | - | 1 |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | |
| Total Pts With at Least one AE | - | 1 (<1) |
| SKIN ULCER | - | 1 (<1) |
| Total Number of AEs | - | 1 |

Investigator text for Adverse Events encoded using MedDRA version 18.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 14JAN2016:17:25:33

Deaths/other significant events

A total of 219 (66.0%) deaths were reported in patients receiving Crb+Pac and 207 (63.7%) deaths were reported in patients receiving Crb+Pac+Bev. The most frequently reported cause of death in both treatment arms was "due to this disease" (i.e., ovarian cancer), which accounted for 62.0% of deaths in the Crb+Pac arm and 58.8% of deaths in the Crb+Pac+Bev arm. In addition, 5 patients (1.5%) in each treatment arm died "due to this disease (i.e., ovarian cancer)/due to other cause", and 2 patients (0.6%) in each treatment arm died "due to this disease/due to protocol treatment". One patient (0.3%) in each treatment arm died "due to protocol treatment".

Table 36 Summary of deaths by primary cause of death by trial treatment (overall Safety Population)

```
died_10_3002 FINAL Summary of Deaths and Primary Cause of Death
Protocol(s): (I01187A)
Analysis: SAFETY POPULATION - BEV VS NON BEV
```

| | Crb+Pac (N=332) | Crb+Pac+Bev (N=325) |
|---|--------------------|------------------------|
| Number of patients with death record | 219 (66.0%) | 207 (63.7%) |
| Due to other cause | 4 (1.2%) | 3 (0.9%) |
| Due to protocol treatment | 1 (0.3%) | 1 (0.3%) |
| Due to this disease | 206 (62.0%) | 191 (58.8%) |
| Due to this disease/Due to other cause | 5 (1.5%) | 5 (1.5%) |
| Due to this disease/Due to protocol treatment | 2 (0.6%) | 2 (0.6%) |
| Unknown | 1 (0.3%) | 5 (1.5%) |

Percentages are based on N

```
Program : $PROD/cdct3643/m101187/died_10_sas / Output :
$PROD/cdct3643a/101187a/reports/died_10_3002.lst
29DEC2015 11:33
```

A review of all patients with causes of death recorded as "Due to other cause", "Due to this disease/Due to other cause" and "Unknown" was provided. The analysis revealed that some deaths reported under these categories were due to concomitant diseases. There were 7 patients who died due to unknown cause, and most events occurred during the follow-up period of the trial and in the absence of exposure to any study drug. Although the causes were unknown, they occurred for the most part during the follow up period without exposure to any study drug.

Table 37 Summary of Grade 5 Adverse Events by trial treatment (overall Safety Population)

| Body System/ Adverse Event | Crb+Pac N = 332 No. (%) | Crb+Pac+Bev N = 325 No. (%) |
|---|-------------------------------|-----------------------------------|
| ALL BODY SYSTEMS | | |
| Total Pts with at Least one AE | 3 (<1) | 5 (2) |
| Total Number of AEs | 4 | 5 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | |
| Total Pts With at Least one AE | - | 4 (1) |
| DISEASE PROGRESSION | - | 2 (<1) |
| DEATH | - | 1 (<1) |
| SUDDEN DEATH | - | 1 (<1) |
| Total Number of AEs | - | 4 |

| | | |
|---|--------|--------|
| INFECTIONS AND INFESTATIONS | | |
| Total Pts With at Least one AE | 1 (<1) | 1 (<1) |
| INFECTION | - | 1 (<1) |
| SEPSIS | 1 (<1) | - |
| Total Number of AEs | 1 | 1 |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | | |
| Total Pts With at Least one AE | 2 (<1) | - |
| METASTASIS | 1 (<1) | - |
| MYELODYSPLASTIC SYNDROME | 1 (<1) | - |
| Total Number of AEs | 2 | - |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | |
| Total Pts With at Least one AE | 1 (<1) | - |
| NEUTROPENIA | 1 (<1) | - |
| Total Number of AEs | 1 | - |

Investigator text for Adverse Events encoded using MedDRA version 18.1.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
AE11 14JAN2016:17:30:53

Laboratory findings

Normal ranges were not available in this study. Therefore, Grade 0 and 1 could not be derived and were left as missing in the table below. As a result, this table can only be used to interpret CTCAE v3 Grades 2, 3 and 4. Percentages are based on total number of patients with laboratory values that fall within CTCAEv3 Grade 2, 3 or 4, and not on the overall safety population.

Clinically meaningful laboratory test value abnormalities as assessed by the investigator were reported as AEs. During the study, the proportion of patients who had a worst value of Grade 2 for haemoglobin (Crb+Pac: 98%; Crb+Pac+Bev 92%), WBC (Crb+Pac: 91%; Crb+Pac+Bev 95%) and granulocytes (Crb+Pac: 96%; Crb+Pac+Bev 95%) was similar in both treatment arms. Too few patients had their platelets measured for a meaningful interpretation of the data to be made.

All incidences of Grade 3 haemoglobin and WBC, and Grade 3 and 4 granulocytes in both arms during treatment occurred in patients who had missing baseline values. Thus, it was not possible to determine whether these grades were newly occurring or were already present at baseline. No chemistry laboratory values were available in this trial.

Table 38 Summary of laboratory parameters: worst grade during study by trial treatment (overall Safety Population)

| Parameter | Crb+Pac N = 332 | Crb+Pac+Bev N = 325 |
|--|--------------------|------------------------|
| Haemoglobin g/L (HYPO) | | |
| n | 90 | 59 |
| Grade 0 | - | - |
| Grade 1 | - | - |
| Grade 2 | 88 (98%) | 54 (92%) |
| Grade 3 | 2 (2%) | 5 (8%) |
| Grade 4 | - | - |
| White blood cell (WBC) 10 ⁺⁺⁹ /L (HYPO) | | |
| n | 43 | 40 |
| Grade 0 | - | - |
| Grade 1 | - | - |
| Grade 2 | 39 (91%) | 38 (95%) |
| Grade 3 | 4 (9%) | 2 (5%) |
| Grade 4 | - | - |
| Platelets 10 ⁺⁺⁹ /L (HYPO) | | |
| n | 3 | 9 |
| Grade 0 | - | - |
| Grade 1 | - | - |
| Grade 2 | 1 | 1 |
| Grade 3 | 1 | 1 |
| Grade 4 | 1 | 1 |

| Granulocytes 10**9/L (MYFO) | | |
|-----------------------------|-----------|-----------|
| n | 28 | 60 |
| Grade 0 | - | - |
| Grade 1 | - | - |
| Grade 2 | 27 (96%) | 57 (95%) |
| Grade 3 | - | 3 (5%) |
| Grade 4 | 1 (4%) | - |

n represents number of patients with at least one valid value within the given time window.
Missing and non-numeric values are excluded from the analysis!
Percentages are based on n. Percentages not calculated if n < 10.
Due to the lack of investigator ranges, Grade 0/1 are not calculable.
LB23 08MAR2016:15:45:19

Safety in special populations

Age

Table 39 Overview of Key Safety by Age and trial treatment (overall Safety Population)

| Adverse Event | <65 | | >=65 | |
|---|--------------------|------------------------|--------------------|------------------------|
| | Crb+Pac (N=215) | Crb+Pac+Bev (N=225) | Crb+Pac (N=117) | Crb+Pac+Bev (N=100) |
| All Adverse Events #: | | | | |
| Pts w. AE | 211 (98.1%) | 224 (99.6%) | 116 (99.1%) | 100 (100.0%) |
| Pts w. Serious AE | 18 (8.4%) | 66 (29.3%) | 19 (16.2%) | 26 (26.0%) |
| Pts w. Grade 3/4/5 AE | 76 (35.3%) | 134 (59.6%) | 36 (30.8%) | 63 (63.0%) |
| Pts w. Grade 5 AE (Outcome Death) | 1 (0.5%) | 2 (0.9%) | 2 (1.7%) | 3 (3.0%) |
| Pts who Disc. Any Treatment due to AE | 24 (11.2%) | 62 (27.6%) | 13 (11.1%) | 20 (20.0%) |
| Deaths: | | | | |
| All Deaths | 136 (63.3%) | 143 (63.6%) | 83 (70.9%) | 64 (64.0%) |
| Deaths not due to Progression | 3 (1.4%) | 4 (1.8%) | 3 (2.6%) | 5 (5.0%) |
| AE of Special Interest for Bevacizumab ##: | | | | |
| Pts w. AE of Special Interest | 47 (21.9%) | 170 (75.6%) | 28 (23.9%) | 67 (67.0%) |
| Pts w. AE of Special Interest Grade 3/4/5 | 11 (5.1%) | 63 (28.0%) | 14 (12.0%) | 35 (35.0%) |
| Pts w. Serious AE of Special Interest | 8 (3.7%) | 34 (15.1%) | 11 (9.4%) | 15 (15.0%) |
| Pts w. Bleeding (CNS) | 0 (0.0%) | 0 (0.0%) | 2 (1.7%) | 0 (0.0%) |
| Pts w. Bleeding (Non-CNS) | 26 (12.1%) | 109 (48.4%) | 10 (8.5%) | 28 (28.0%) |
| Pts w. CHF | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (1.0%) |
| Pts w. Fistula/Abscess (non gastrointestinal) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Pts w. Gastrointestinal perforations | 1 (0.5%) | 5 (2.2%) | 0 (0.0%) | 1 (1.0%) |
| Pts w. Hypertension | 8 (3.7%) | 92 (40.9%) | 2 (1.7%) | 43 (43.0%) |
| Pts w. Neutropenia & associated complications | 12 (5.6%) | 32 (14.2%) | 14 (12.0%) | 8 (8.0%) |
| Pts w. Posterior rev encephalopathy syndrome | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Pts w. Proteinuria | 1 (0.5%) | 41 (18.2%) | 2 (1.7%) | 15 (15.0%) |
| Pts w. Secondary Primary Malignancies | 1 (0.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Pts w. Thromboembolic event - arterial | 3 (1.4%) | 15 (6.7%) | 3 (2.6%) | 7 (7.0%) |
| Pts w. Thromboembolic event - venous | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Pts w. Wound healing complication | 1 (0.5%) | 8 (3.6%) | 1 (0.9%) | 2 (2.0%) |

Adverse Events: Occurring Within First Study Treatment Date and Last Study Treatment Date plus 30 days
AEI as defined in SAP: Occurring Within First Study Treatment Date and Last Study Treatment Date plus 183 days
Percentages are based on N

Race

Table 40 Overview of Key Safety by Race and trial treatment (overall Safety Population)

| Adverse Event | White Crb+Pac (N=266) | | White Crb+Pac+Bev (N=259) | | non-White Crb+Pac (N=66) | | non-White Crb+Pac+Bev (N=66) | |
|---|-----------------------------|---------|---------------------------------|---------|--------------------------------|---------|------------------------------------|----------|
| | n | (%) | n | (%) | n | (%) | n | (%) |
| All Adverse Events #: | | | | | | | | |
| Pts w. AE | 262 | (98.5%) | 258 | (99.6%) | 65 | (98.5%) | 66 | (100.0%) |
| Pts w. Serious AE | 32 | (12.0%) | 61 | (23.3%) | 5 | (7.6%) | 11 | (16.7%) |
| Pts w. Grade 3/4/5 AE | 94 | (35.3%) | 163 | (62.9%) | 18 | (27.3%) | 34 | (51.5%) |
| Pts w. Grade 5 AE (Outcome Death) | 3 | (1.1%) | 5 | (1.9%) | 0 | (0.0%) | 0 | (0.0%) |
| Pts who Disc. Any Treatment due to AE | 27 | (10.2%) | 61 | (23.6%) | 10 | (15.2%) | 21 | (31.8%) |
| Deaths: | | | | | | | | |
| All Deaths | 190 | (71.4%) | 175 | (67.6%) | 29 | (43.9%) | 32 | (48.5%) |
| Deaths not due to Progression | 4 | (1.5%) | 7 | (2.7%) | 2 | (3.0%) | 2 | (3.0%) |
| AE of Special Interest for Bevacizumab ##: | | | | | | | | |
| Pts w. AE of Special Interest | 63 | (23.7%) | 193 | (74.5%) | 12 | (18.2%) | 44 | (66.7%) |
| Pts w. AE of Special Interest Grade 3/4/5 | 22 | (8.3%) | 80 | (30.9%) | 3 | (4.5%) | 18 | (27.3%) |
| Pts w. Serious AE of Special Interest | 17 | (6.4%) | 43 | (16.6%) | 2 | (3.0%) | 6 | (9.1%) |
| Pts w. Bleeding (CNS) | 1 | (0.4%) | 0 | (0.0%) | 1 | (1.5%) | 0 | (0.0%) |
| Pts w. Bleeding (Non-CNS) | 30 | (11.3%) | 114 | (44.0%) | 6 | (9.1%) | 23 | (34.8%) |
| Pts w. CHF | 0 | (0.0%) | 1 | (0.4%) | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Fistula/Abscess (non gastrointestinal) | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Gastrointestinal perforations | 1 | (0.4%) | 6 | (2.3%) | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Hypertension | 9 | (3.4%) | 111 | (42.9%) | 1 | (1.5%) | 24 | (36.4%) |
| Pts w. Neutropenia & associated complications | 23 | (8.6%) | 31 | (12.0%) | 3 | (4.5%) | 9 | (13.6%) |
| Pts w. Posterior rev encephalopathy syndrome | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Proteinuria | 2 | (0.8%) | 41 | (15.8%) | 1 | (1.5%) | 15 | (22.7%) |
| Pts w. Secondary Primary Malignancies | 1 | (0.4%) | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Thromboembolic event - arterial | 5 | (1.9%) | 22 | (8.5%) | 1 | (1.5%) | 0 | (0.0%) |
| Pts w. Thromboembolic event - venous | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Wound healing complication | 1 | (0.4%) | 10 | (3.9%) | 1 | (1.5%) | 0 | (0.0%) |

Adverse Events: Occurring Within First Study Treatment Date and Last Study Treatment Date plus 30 days
 ## AEFI as defined in SAP: Occurring Within First Study Treatment Date and Last Study Treatment Date plus 183 days
 Percentages are based on N

Patients previously treated with bevacizumab

An overview of the safety profile of bevacizumab in combination with Crb+Pac (n=33) compared with Crb+Pac (n=35) in patients previously treated with bevacizumab is presented below.

Table 41 : Overview of the safety profile of bevacizumab in combination with Crb+Pac (n=33) compared with Crb+Pac (n=35) in patients previously treated with bevacizumab

| Adverse Event | Crb+Pac (N=35) | | Crb+Pac+Bev (N=33) | |
|---|-------------------|----------|-----------------------|----------|
| | n | (%) | n | (%) |
| Adverse Event | | | | |
| All Adverse Events #: | | | | |
| Pts w. AE | 34 | (97.1%) | 33 | (100.0%) |
| Pts w. Serious AE | 3 | (8.6%) | 9 | (27.3%) |
| Pts w. Grade 3/4/5 AE | 13 | (37.1%) | 17 | (51.5%) |
| Pts w. Grade 5 AE (Outcome Death) | 1 | (2.9%) | 0 | (0.0%) |
| Pts who Disc. Any Treatment due to AE | 1 | (2.9%) | 6 | (18.2%) |
| Deaths: | | | | |
| All Deaths | 26 | (74.3%) | 25 | (75.8%) |
| Deaths not due to Progression | 1 | (2.9%) | 0 | (0.0%) |
| AE of Special Interest for Bevacizumab ##: | | | | |
| Pts w. AE of Special Interest | 4 | (11.4%) | 21 | (63.6%) |
| Pts w. AE of Special Interest Grade 3/4/5 | 2 | (5.7%) | 7 | (21.2%) |
| Pts w. Serious AE of Special Interest | 1 | (2.9%) | 3 | (9.1%) |
| Pts w. Bleeding (CNS) | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Bleeding (Non-CNS) | 2 | (5.7%) | 15 | (45.5%) |
| Pts w. CHF | 0 | (0.0%) | 1 | (3.0%) |
| Pts w. Fistula/Abscess (non gastrointestinal) | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Gastrointestinal perforations | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Hypertension | 0 | (0.0%) | 9 | (27.3%) |
| Pts w. Neutropenia & associated complications | 2 | (5.7%) | 4 | (12.1%) |
| Pts w. Posterior rev encephalopathy syndrome | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Proteinuria | 0 | (0.0%) | 5 | (15.2%) |
| Pts w. Secondary Primary Malignancies | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Thromboembolic event - arterial | 1 | (2.9%) | 1 | (3.0%) |
| Pts w. Thromboembolic event - venous | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Wound healing complication | 0 | (0.0%) | 2 | (6.1%) |

Adverse Events: Occurring Within First Study Treatment Date and Last Study Treatment Date plus 30 days

AESI as defined in SAP: Occurring Within First Study Treatment Date and Last Study Treatment Date plus 183 days

Percentages are based on N
 Program : \$PROD/cdpt3643/ml01187/sae_11.sas / Output :
 \$PROD/cdt3643a/i01187a/reports/sae_11_B002.lst
 11JAN2016 9:59

Discontinuation due to adverse events

Table 42 Summary of adverse events leading to discontinuation of study treatment by trial treatment (overall Safety Population)

| Body System/ Adverse Event | Crb+Pac N = 332 No. (%) | CrB+Pac+Bev N = 325 No. (%) |
|---|-------------------------------|-----------------------------------|
| ALL BODY SYSTEMS | | |
| Total Pts with at Least one AE | 37 (11) | 82 (25) |
| Total Number of AEs | 39 | 90 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | |
| Total Pts With at Least one AE | 14 (4) | 18 (6) |
| ADVERSE DRUG REACTION | 9 (3) | 3 (<1) |
| UNEVALUABLE EVENT | 3 (<1) | 9 (3) |
| ADVERSE EVENT | 1 (<1) | 1 (<1) |
| FATIGUE | - | 2 (<1) |
| ADVERSE REACTION | - | 1 (<1) |
| GENERAL PHYSICAL HEALTH DETERIORATION | 1 (<1) | - |
| HERNIA | - | 1 (<1) |
| THROMBOSIS IN DEVICE | - | 1 (<1) |
| Total Number of AEs | 14 | 18 |
| INVESTIGATIONS | | |
| Total Pts With at Least one AE | 6 (2) | 19 (6) |
| URINE PROTEIN/CREATININE RATIO IMPROVEMENTD | - | 9 (3) |
| UNEVALUABLE INVESTIGATION | 1 (<1) | 5 (2) |
| NEUTROPHIL COUNT DECREASED | 2 (<1) | 2 (<1) |
| PLATELET COUNT DECREASED | 2 (<1) | 1 (<1) |
| BLOOD COUNT ABNORMAL | 1 (<1) | - |
| BLOOD CREATININE IMPROVEMENTD | - | 1 (<1) |
| BLOOD PRESSURE IMPROVEMENTD | - | 1 (<1) |
| Total Number of AEs | 6 | 19 |
| IMMUNE SYSTEM DISORDERS | | |
| Total Pts With at Least one AE | 12 (4) | 5 (2) |
| DRUG HYPERSENSITIVITY | 8 (2) | 2 (<1) |
| HYPERSENSITIVITY | 3 (<1) | 3 (<1) |
| ANAPHYLACTIC REACTION | 1 (<1) | - |
| Total Number of AEs | 12 | 5 |
| NERVOUS SYSTEM DISORDERS | | |
| Total Pts With at Least one AE | 3 (<1) | 7 (2) |
| NEUROPATHY PERIPHERAL | 1 (<1) | 2 (<1) |
| CEREBRAL ISCHAEMIA | 1 (<1) | 1 (<1) |
| CEREBROVASCULAR ACCIDENT | 1 (<1) | - |
| DEMENTIA | - | 1 (<1) |
| HAEMORRHAGE INTRACRANIAL | - | 1 (<1) |
| HEADACHE | - | 1 (<1) |
| SEIZURE | - | 1 (<1) |
| TRANSIENT ISCHAEMIC ATTACK | - | 1 (<1) |
| Total Number of AEs | 3 | 8 |

| | | |
|---|--------|--------|
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | |
| Total Pts With at Least one AE | 2 (<1) | 7 (2) |
| NEUTROPENIA | 2 (<1) | 3 (<1) |
| THROMBOCYTOPENIA | - | 4 (1) |
| HAEMATOTOXICITY | - | 1 (<1) |
| Total Number of AEs | 2 | 8 |
| GASTROINTESTINAL DISORDERS | | |
| Total Pts With at Least one AE | 2 (<1) | 7 (2) |
| SMALL INTESTINAL OBSTRUCTION | - | 2 (<1) |
| COLITIS | - | 1 (<1) |
| GASTROINTESTINAL FISTULA | - | 1 (<1) |
| GINGIVAL BLEEDING | - | 1 (<1) |
| LARGE INTESTINAL OBSTRUCTION | 1 (<1) | - |
| NAUSEA | 1 (<1) | - |
| SMALL INTESTINAL PERFORATION | - | 1 (<1) |
| UPPER GASTROINTESTINAL HAEMORRHAGE | - | 1 (<1) |
| Total Number of AEs | 2 | 7 |
| RENAL AND URINARY DISORDERS | | |
| Total Pts With at Least one AE | - | 8 (2) |
| PROTEINURIA | - | 8 (2) |
| Total Number of AEs | - | 8 |
| CARDIAC DISORDERS | | |
| Total Pts With at Least one AE | - | 3 (<1) |
| ACUTE CORONARY SYNDROME | - | 1 (<1) |
| ACUTE MYOCARDIAL INFARCTION | - | 1 (<1) |
| MYOCARDIAL INFARCTION | - | 1 (<1) |
| Total Number of AEs | - | 3 |
| VASCULAR DISORDERS | | |
| Total Pts With at Least one AE | - | 3 (<1) |
| HYPERTENSION | - | 3 (<1) |
| Total Number of AEs | - | 3 |
| INFECTIONS AND INFESTATIONS | | |
| Total Pts With at Least one AE | - | 2 (<1) |
| HERPES ZOSTER | - | 1 (<1) |
| PELVIC ABSCESS | - | 1 (<1) |
| Total Number of AEs | - | 2 |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | |
| Total Pts With at Least one AE | - | 2 (<1) |
| ARTHRALGIA | - | 2 (<1) |
| Total Number of AEs | - | 2 |
| PSYCHIATRIC DISORDERS | | |
| Total Pts With at Least one AE | - | 2 (<1) |
| DEPRESSION SUICIDAL | - | 1 (<1) |
| MENTAL STATUS CHANGES | - | 1 (<1) |
| Total Number of AEs | - | 2 |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | |
| Total Pts With at Least one AE | - | 2 (<1) |
| PULMONARY EMBOLISM | - | 2 (<1) |
| Total Number of AEs | - | 2 |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | |
| Total Pts With at Least one AE | - | 1 (<1) |
| TOXICITY TO VARIOUS AGENTS | - | 1 (<1) |
| Total Number of AEs | - | 1 |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | |
| Total Pts With at Least one AE | - | 1 (<1) |
| SKIN ULCER | - | 1 (<1) |
| Total Number of AEs | - | 1 |

Adverse events that led to dose modification

In study GOG-0213, dose modifications (increase or decrease in dose) for bevacizumab due to AEs were not allowed, and bevacizumab could be either held or discontinued according to the hematologic and non-hematologic toxicity. For Crb and Pac, the dose could be modified (held, reduced or discontinued) based on hematologic and non-hematologic toxicity. AEs leading to a reduction in the dose of Crb and Pac were not collected consistently in study GOG-0213.

Safety in prior bevacizumab population

The safety profile in patients who were retreated with bevacizumab in this trial was consistent with safety observed in the overall safety population. The key safety data reported in the population of 69 patients previously treated with bevacizumab indicated the following:

- The proportion of patients with at least one AE (all grades) was similar in the two treatment arms (Crb+Pac: 97.1%; Crb+Pac+Bev: 100.0%).

- The proportion of patients with a SAE was higher in the Crb+Pac+Bev arm (27.3%) than in the Crb+Pac alone arm (8.6%). The majority of SAEs occurred in single patients only in either treatment arm.
- The proportion of patients with Grade ≥ 3 AEs was higher in the Crb+Pac+Bev arm (51.5%) than in the Crb+Pac alone arm (37.1%). The most frequently reported Grade ≥ 3 AEs were abdominal pain (Crb+Pac: 0%; Crb+Pac+Bev: 12%), nausea (Crb+Pac: 3%; Crb+Pac+Bev: 9%), small intestine obstruction (Crb+Pac: 3%; Crb+Pac+Bev: 6%), febrile neutropenia (Crb+Pac: 0%; Crb+Pac+Bev: 9%), hypertension (Crb+Pac: 0%; Crb+Pac+Bev: 6%), proteinuria (Crb+Pac: 0%; Crb+Pac+Bev: 6%) and dyspnoea (Crb+Pac: 0%; Crb+Pac+Bev: 6%).
- Grade 5 AEs were reported with a low and equivalent frequency in both treatment arms (Crb+Pac: 1 patient [2.9%]; Crb+Pac+Bev: 0 patients [0%]).
- More patients in the Crb+Pac+Bev arm (18.2%) than in the Crb+Pac alone arm (2.9%) were withdrawn from any study drug due to an AE. The majority of AEs (by preferred term) leading to study treatment discontinuation occurred in $< 1\%$ of patients in either treatment arm.
- AESIs were reported more frequently in patients in the Crb+Pac+Bev arm (63.6% patients) than in the Crb+Pac alone arm (11.4% patients). More patients in the Crb+Pac+Bev arm (21.2%) than in the Crb+Pac alone arm (5.7%) had a Grade ≥ 3 AESI or a serious AESI (Crb+Pac+Bev: 9.1%; Crb+Pac: 2.9%).
- The most common AESIs were non-CNS bleeding (Crb+Pac; 5.7%; Crb+Pac+Bev: 45.5%), hypertension (Crb+Pac; 0%; Crb+Pac+Bev: 27.3%), proteinuria (Crb+Pac; 0%; Crb+Pac+Bev: 15.2%) and neutropenia and associated complications (Crb+Pac; 5.7%; Crb+Pac+Bev: 12.1%).

Table 43 Overview of Key Safety by trial treatment (Prior Bevacizumab Safety Population)

| Adverse Event | Crb+Pac (N=35) | | Crb+Pac+Bev (N=33) | |
|---|-------------------|---------|-----------------------|----------|
| | n | (%) | n | (%) |
| All Adverse Events #: | | | | |
| Pts w. AE | 34 | (97.1%) | 33 | (100.0%) |
| Pts w. Serious AE | 3 | (8.6%) | 9 | (27.3%) |
| Pts w. Grade 3/4/5 AE | 13 | (37.1%) | 17 | (51.5%) |
| Pts w. Grade 5 AE (Outcome Death) | 1 | (2.9%) | 0 | (0.0%) |
| Pts who Disc. Any Treatment due to AE | 1 | (2.9%) | 6 | (18.2%) |
| Deaths: | | | | |
| All Deaths | 26 | (74.3%) | 25 | (75.8%) |
| Deaths not due to Progression | 1 | (2.9%) | 0 | (0.0%) |
| AE of Special Interest for Bevacizumab ##: | | | | |
| Pts w. AE of Special Interest | 4 | (11.4%) | 21 | (63.6%) |
| Pts w. AE of Special Interest Grade 3/4/5 | 2 | (5.7%) | 7 | (21.2%) |
| Pts w. Serious AE of Special Interest | 1 | (2.9%) | 3 | (9.1%) |
| Pts w. Bleeding (CNS) | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Bleeding (Non-CNS) | 2 | (5.7%) | 15 | (45.5%) |
| Pts w. CHF | 0 | (0.0%) | 1 | (3.0%) |
| Pts w. Fistula/Abscess (non gastrointestinal) | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Gastrointestinal perforations | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Hypertension | 0 | (0.0%) | 9 | (27.3%) |
| Pts w. Neutropenia & associated complications | 2 | (5.7%) | 4 | (12.1%) |
| Pts w. Posterior rev encephalopathy syndrome | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Proteinuria | 0 | (0.0%) | 5 | (15.2%) |
| Pts w. Secondary Primary Malignancies | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Thromboembolic event - arterial | 1 | (2.9%) | 1 | (3.0%) |
| Pts w. Thromboembolic event - venous | 0 | (0.0%) | 0 | (0.0%) |
| Pts w. Wound healing complication | 0 | (0.0%) | 2 | (6.1%) |

Adverse Events: Occurring Within First Study Treatment Date and Last Study Treatment Date plus 30 days
AEFI as defined in SAP: Occurring Within First Study Treatment Date and Last Study Treatment Date plus 183 days
Percentages are based on N

Supplemental safety results

An overview of the existing extent of exposure and safety data from clinical trials BO17707/ICON7 and GOG-0218 is provided below.

Table 44 Supplemental safety results - Bevacizumab in combination with Carboplatin+Paclitaxel in Untreated Platinum-Sensitive Ovarian Cancer

| | Platinum Sensitive Ovarian Cancer | | | | First-Line Ovarian Cancer | | | | | | | | | |
|--------------------------------------|-----------------------------------|-----|-------------|------|--|-----|---------|------|------------------------------------|------|---------|------|---------|------|
| | GOG-0213(Cutoff date: 5 Nov 2014) | | | | BO17707/ICON7 Cutoff date: 30 Nov 2010) ¹ | | | | GOG-0218(Cutoff date: 26 Aug 2011) | | | | | |
| | Crb+Pac | | Crb+Pac+Bev | | CP | | CPB7.5+ | | CPP | | CPB15 | | CPB15+ | |
| | (n=332) | | (n=325) | | (n=763) | | (n=746) | | (n=602) | | (n=607) | | (n=608) | |
| All Adverse Events | | | | | | | | | | | | | | |
| Pts w AE | 327 | 98% | 324 | 100% | 756 | 99% | 746 | 100% | 601 | 100% | 607 | 100% | 607 | 100% |
| Pts w Serious AE | 37 | 11% | 92 | 28% | 181 | 24% | 281 | 38% | N/A | | N/A | | N/A | |
| Pts w Grade 3 to 5 AE | 112 | 34% | 197 | 61% | 416 | 55% | 485 | 65% | 561 | 93% | 577 | 95% | 576 | 95% |
| Pts w Grade 5 AE | 3 | 1% | 5 | 2% | 6 | 1% | 4 | 1% | 4 | 1% | 10 | 2% | 15 | 2% |
| Pts who Disc Any Treatment due to AE | 37 | 11% | 82 | 25% | 68 | 9% | 163 | 22% | 62 | 10% | 81 | 13% | 108 | 18% |
| Deaths | | | | | | | | | | | | | | |
| All Deaths ² | 219 | 66% | 207 | 64% | 202 | 26% | 173 | 23% | 286 | 48% | 299 | 49% | 260 | 43% |
| Deaths not due to PD | 6 | 2% | 9 | 3% | 17 | 2% | 24 | 3% | 20 | 3% | 18 | 3% | 25 | 4% |

| AE of Special Interest for Bevacizumab | | | | | | | | | | | | | | |
|--|----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pts w AESI | 76 | 23% | 237 | 73% | 364 | 48% | 552 | 74% | 587 | 98% | 592 | 98% | 591 | 97% |
| Pts w Grade 3 to 5 AESI | 25 | 8% | 98 | 30% | 156 | 20% | 241 | 32% | 536 | 89% | 542 | 89% | 548 | 90% |
| Pts w Serious AESI | 19 | 6% | 49 | 15% | 49 | 6% | 125 | 17% | N/A | N/A | N/A | N/A | N/A | N/A |
| Pts w CNS Bleeding | 2 | 1% | 0 | 0% | 0 | 0% | 3 | 0% | 0 | 0% | 0 | 0% | 3 | 0% |
| Pts w Non-CNS Bleeding | 36 | 11% | 137 | 42% | 84 | 11% | 297 | 40% | 96 | 16% | 217 | 36% | 225 | 37% |
| Pts w CHF | 0 | 0% | 1 | 0% | 3 | 0% | 3 | 0% | 0 | 0% | 0 | 0% | 3 | 0% |
| Pts w Fistula Abscess | 0 | 0% | 0 | 0% | 9 | 1% | 13 | 2% | 7 | 1% | 5 | 1% | 12 | 2% |
| Pts w Gastrointestinal Perforations | 1 | 0% | 6 | 2% | 3 | 0% | 10 | 1% | 2 | 0% | 11 | 2% | 12 | 2% |
| Pts w Hypertension | 10 | 3% | 135 | 42% | 49 | 6% | 191 | 26% | 85 | 14% | 143 | 24% | 196 | 32% |
| Pts w Neutropenia | 26 | 8% | 40 | 12% | 220 | 29% | 212 | 28% | 577 | 96% | 578 | 95% | 581 | 96% |

| AE of Special Interest for Bevacizumab | | | | | | | | | | | | | | |
|--|-----|----|-----|-----|-----|----|-----|-----|-----|----|-----|----|-----|----|
| Pts w PRES | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 0 | 0% | 1 | 0% | 0 | 0% |
| Pts w Proteinuria | 3 | 1% | 56 | 17% | 18 | 2% | 33 | 4% | 39 | 6% | 32 | 5% | 54 | 9% |
| Pts w Secondary Primary Malignancies | 1 | 0% | 0 | 0% | N/A | | N/A | | | 0% | | 0% | | 0% |
| Pts w Thromboembolic Event Arterial | 6 | 2% | 22 | 7% | 12 | 2% | 26 | 3% | 14 | 2% | 19 | 3% | 21 | 3% |
| Pts w Thromboembolic Event Venous | 0 | 0% | 0 | 0% | 34 | 4% | 51 | 7% | 24 | 4% | 21 | 3% | 25 | 4% |
| Pts w Wound Healing Complication | 2 | 1% | 10 | 3% | 12 | 2% | 35 | 5% | 27 | 4% | 29 | 5% | 22 | 4% |
| Pts w Thromboembolic Event | N/A | | N/A | | 46 | 6% | 76 | 10% | N/A | | N/A | | N/A | |
| Pts w Mucocutaneous Bleeding | N/A | | N/A | | 42 | 6% | 256 | 34% | N/A | | N/A | | N/A | |
| Pts w Tumor Associated Haemorrhage | N/A | | N/A | | 0 | 0% | 0 | 0% | N/A | | N/A | | N/A | |
| Pts w Febrile Neutropenia | N/A | | N/A | | 15 | 2% | 21 | 3% | N/A | | N/A | | N/A | |

AE = adverse event; AESI = adverse event of special interest; CHF = congestive heart failure; CNS = central nervous system; CP = Crb+Pac up to 6 cycles; CPB7.5+ = Crb+Pac up to 6 cycles + bevacizumab (7.5 mg/kg q3w) up to 18 cycles; CPB15 = Crb+Pac and up to 5 cycles of 15 mg/kg of bevacizumab;

CPB15+ = Crb+Pac and up to 21 cycles of 15 mg/kg of bevacizumab; CPP = Crb+Pac and up to 21 cycles of placebo; Crb = carboplatin; N/A = not available; Pac = paclitaxel; PRES = Posterior reversible encephalopathy syndrome; Pts = patients; w = with.

¹ A total of seven patients were reported with 8 AEs between the 30 November 2010 and the data cutoff for the final CSR (31 March 2013), including one patient in the CP arm and six patients in the CPB7.5+ arm.

Note: Duration of drug exposure is significantly different between the three studies and may account for the observed differences in the incidences of AEs. However, the observed differences remain consistent with the known safety profile of Avastin®.

Note: MedDRA v14.0 was used for Studies BO17707/ICON7 and GOG-0218. MedDRA v18.1 was used for Study GOG-0213.

Post marketing experience

Globally, bevacizumab is approved for the treatment of metastatic colorectal cancer (mCRC), locally recurrent or metastatic breast cancer (mBC), advanced, metastatic, or recurrent non-small cell lung cancer (NSCLC), advanced and/or metastatic renal cell cancer (mRCC), newly diagnosed glioblastoma multiforme (GBM) and GBM after relapse or disease progression, front-line treatment of EOC, FTC, or PPC, treatment of platinum-sensitive and platinum-resistant recurrent EOC, FTC, or PPC, and cervical cancer.

Since initial market approval in the United States on 26 February 2004 (i.e., international birth date [IBD]) and until the end of the February 2016, bevacizumab has been approved for use in over 100 countries worldwide. The estimated cumulative clinical trial exposure to bevacizumab from the development international birth date (DIBD, 3 March 1997) to February 2016 is 32,237 patients. Since the IBD, an estimated total of 2,394,526 patients have received bevacizumab in the postmarketing setting.

The number of AE and SAEs experienced by patients by SOC since the IBD in all indications and in ovarian cancer was presented. The higher proportion of AEs and SAEs in patients with ovarian cancer compared to the proportion of AEs and SAEs in the overall population (i.e., all indications) within the Gastrointestinal SOC and Reproductive system and breast disorders SOC is confounded by the ovarian patient population. Overall, the safety profile of bevacizumab in ovarian cancer was consistent with the known safety profile.

No relevant new additional safety signals have been identified based on postmarketing data from patients treated with bevacizumab in combination with chemotherapy. The Sponsor will continue to actively monitor safety as part of the ongoing pharmacovigilance program.

2.5.1. Discussion on clinical safety

The results were generally consistent with the known safety profile of bevacizumab across multiple indications. Bevacizumab, in combination with carboplatin and paclitaxel is also indicated for the front-line treatment of adult patients with advanced ovarian cancer.

The median duration of exposure of carboplatin and paclitaxel/docetaxel is comparable between the two treatment arms. The median number of bevacizumab cycles is 16. The total dose of carboplatin and paclitaxel/docetaxel is also comparable between the two arms. Overall, this enables a reasonable assessment of safety in this patient population. The duration of safety follow-up is also considered acceptable.

The overall number of AEs was comparable between the two arms, however, there were more SAEs, Grade 3/4 AEs and discontinuations due to AEs in the crb+pac+bev arm. There were considerably more cases of non-CNS bleedings, hypertension, proteinuria and thromboembolic events. However, the events are expected and observed in clinical trials with bevacizumab. They are clinically manageable and are reflected in the SmPC, where precautionary measures are also provided.

Hypomagnesaemia is often associated with chemotherapy and may in theory be augmented by diarrhoea or by increased excretion from the kidney, however, diarrhoea occurred only slightly more frequently in the crb+pac+bev arm. Proteinuria, as a sign of affected kidney function, was much more frequently observed in the crb+pac+bev arm. There were significantly more patients in the chemo + bev arm who developed hypomagnesaemia (16.9% vs 27.4%) and the applicant conducted a detailed review of all patients who experienced a hypomagnesaemia event. Although hypomagnesaemia was possibly associated with proteinuria, no firm conclusions could be drawn. The nature, severity, and incidence of hypomagnesaemia in bevacizumab-exposed patients was consistent with the known safety profile of bevacizumab and no clinically significant consequences from hypomagnesaemia were observed in the trial. Hypomagnesaemia has been included in section 4.8 of the SmPC. No other change in risk minimization activities was proposed and this is considered acceptable.

In terms of AESIs, bleeding, hypertension, neutropenia, proteinuria, thromboembolic events, wound healing complications and GI perforations occurred more frequently in the bevacizumab arm. These events are AESI and are as such expected to occur more frequently in the bevacizumab arm. This is expected based on previous experience with bevacizumab in different indications over the past decade. These events are clinically manageable and adequately reflected in the SmPC, where precautionary measures are also provided. Most of the bleeding events were epistaxis. There were no cerebrovascular bleeding events in the bevacizumab arm.

The number of patients in the Crb+Pac+Bev arm with a GI fistula did not exceed what has earlier been reported for this patient group and is reflected in the SmPC (2%). In the present trial four patients (1.2%) in the Crb+Pac+Bev arm experienced a Grade ≥ 3 GI perforation event (colonic fistula, intestinal perforation, small intestine perforation, and large intestine perforation). All-grade GI perforations were reported in 6 patients (2%) in the crb+pac+bev arm, of which 4 patients (1%) experienced a Grade ≥ 3 GI perforation event comprising colonic fistula, intestinal perforation, small intestine perforation, and large intestine perforation. Given the frequency of GI perforation events observed in GOG-0213 and the assessment of the cases, it is agreed that the current SmPC covers the risk of GI perforation sufficiently and that no changes in the SmPC based on GOG-0213 are warranted.

Grade ≥ 3 AESIs were reported in the overall safety population more frequently in patients in the Crb+Pac+Bev arm (30% patients) than in the Crb+Pac alone arm (8% patients). This difference was mainly due to an increase in the incidence in the Crb+Pac+Bev arm compared to the Crb+Pac alone arm of hypertension (11% patients vs. <1% patients, respectively) and proteinuria (8% patients vs. 0% patients, respectively).

Overall, SAEs was more frequently observed in the bevacizumab arm, mostly related to GI, neutropenia and infections. The applicant provided an overview of Grade 4 SAE which showed that eight patients (2.4%) experienced a total of 11 Grade 4 SAEs in the Crb+Pac arm and 28 patients (8.6%) experienced a total of 31 Grade 4 SAEs in the Crb+Pac+Bev arm. These Grade 4 SAEs were equally distributed between the System Organ Classes (SOCs) in both arms. Unfortunately, the duration of Grade 4 SAEs could not be determined for most of the events as the investigators did not collect these data.

In terms of laboratory findings, there were no major differences, however, with regard to platelets, too few patients had their platelets measured, and thus no conclusions can be drawn.

The incidence of AEs leading to withdrawal of study treatment was higher in the Crb+Pac+Bev compared to the chemotherapy only arm (25.2% versus 11.1%, respectively); this was mainly due to proteinuria.

Eighty-seven of 325 patients (27%) discontinued bevacizumab during the initial chemotherapy combination treatment phase with a median of 4 cycles of treatment. Additionally, 227 patients (70%) stopped bevacizumab during the maintenance phase with a median of 20 cycles.

There were no relevant imbalances in deaths related to treatment between the two study arms.

Overall, based on the difference of at least 10% in all-grade AEs or 2% difference in Grade ≥ 3 AEs between the bevacizumab arm and the control arm, the following additional ADRs were identified and included in the SmPC (see section 4.8): all grade cough, all grade hypomagnesemia, all grade hyponatremia and Grade 3- 5 hyponatremia. Furthermore the frequency of myalgia and epistaxis has been modified from common to very common based on the data from the pivotal study. The frequency of Grade 3-5 wound healing complications was also updated to 1.8% based on the data from study GOG-213. In addition, two corrections based on previous data from studies OCEANS and AURELIA were made to section 4.8 regarding the frequency Grade 3 proteinuria (10.9%) and reporting rate of Gastrointestinal perforations in patients with ovarian cancer (2%) and were considered acceptable.

With regards to safety in special population, the MAH was asked to comment on the more non-CNS bleedings and neutropenia in patients < 65 years of age in the bevacizumab arm, comprising 2/3 of the population. A review confirmed a high incidence of both epistaxis and neutropenia including febrile neutropenia in patients < 65 years. As epistaxis is a known identified risk associated with exposure to bevacizumab and is included in the "undesirable effects" section of the SmPC, no additional changes are proposed. Neutropenia is already considered an important identified risk associated with exposure to bevacizumab and risk assessment and mitigation activities for neutropenia are included in the bevacizumab Risk Management Plan (RMP). Therefore, no additional changes are proposed.

The majority of patients were below 65, white, ECOG 0 or 1. Very few patients were ECOG 3. These characteristics are reflected in section 5.1 of the SmPC.

The incidence of AEs, SAEs, Grade 5 AEs, AEs leading to discontinuation of treatment, and AESIs was consistent with prior observations in patients aged > 65 years-old being treated with bevacizumab. However, the relatively small sample sizes preclude any very strong conclusions.

Generally, the safety profile of the Crb+Pac+Bev combination was similar in patients who were previously treated with bevacizumab in first line (N=68) compared with patients who were bevacizumab-naïve. Again, the number of SAE/AESIs and treatment discontinuations was higher in the Crb+Pac+Bev arm compared with the Crb+Pac arm. The number of deaths was balanced.

Compared with safety data from the previously assessed Studies BO17707/ICON7 and GOG-0218 that studied the combination bevacizumab + carboplatin + paclitaxel in patients with platinum-sensitive ovarian cancer in the first line setting the absolute incidence of hypertension and proteinuria in the bevacizumab-exposed patients in Study GOG-0213 was higher (42% vs. 26% vs. 32% for hypertension; 17% vs. 4% vs. 9% for proteinuria). Still, there were differences in the design, dose, and population of these studies hampering any direct comparisons. Further, these higher incidences of hypertension and proteinuria were consistent with the known safety profile of bevacizumab.

Generally, the safety profile of the bevacizumab + carboplatin + paclitaxel combination was similar in patients who were previously treated with bevacizumab in first line compared with patients who were bevacizumab naïve. However, the number of patients in this subgroup is limited (Crb+Pac+Bev n=33, Crb+Pac n=35).

2.5.2. Conclusions on clinical safety

The safety of bevacizumab is well-known and as expected. The overall number of AEs is comparable between the two arms, however, there are more SAEs, Grade 3/4 AEs and discontinuations due to AEs in the crb+pac+bev arm. AESI for bevacizumab are not unexpected in the active arm. The following additional ADRs were identified based on the submitted data and included in the SmPC (see section 4.8): all grade cough, all grade hypomagnesemia, all grade hyponatremia and Grade 3- 5 hyponatremia.

In conclusion, there are no new major safety concerns. Although more toxicity was observed with the addition of bevacizumab, it is considered to be clinically manageable and adequately addressed by current risk minimisation activities.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

- The PRAC considered that the risk management plan version 27.0 could be acceptable if the MAH implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 27.1 with the following content:

Safety concerns

Table 45 Summary of safety concerns

| | |
|-----------------------------------|--|
| Important identified risks | Bleeding / haemorrhage Pulmonary haemorrhage Proteinuria Arterial thromboembolic events (ATE) Hypertension Congestive heart failure Wound healing complications Gastrointestinal perforations Posterior reversible encephalopathy syndrome (PRES) 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 Necrotizing fasciitis Adverse events following off-label intravitreal use Embryo-fetal development disturbance Osteonecrosis in children |
| Important potential risks | Not Applicable |
| Missing information | Safety profile of the different treatment combinations in patients with non-squamous NSCLC Long-term effects of bevacizumab when used in the paediatric population Safety and efficacy in patients with renal impairment Safety and efficacy in patients with hepatic impairment Use in lactating women |

Pharmacovigilance plan

Table 46: Ongoing and planned studies in the PhV development plan

| Study /activity Type, title and category (1-3) | Objectives | Safety concerns addressed | Status | Date for submission of interim or final reports |
|---|---|---|---------------|--|
| BO20924 (BERNIE) 3 | Assess safety and efficacy in paediatric patients | Physeal dysplasia Long-term effects of bevacizumab when used in the paediatric population. | On-going | Q1 2017 |
| Obtain long term follow up information from studies in the paediatric population after patients complete their 5.5 years of follow up in study BO20924 3 | Assess safety in paediatric patients | Long-term effects of bevacizumab when used in the paediatric population. | Planned | Protocol submission Q4 2017 |

No changes to the pharmacovigilance plan were introduced as part of this procedure. The already agreed pharmacovigilance plan was considered sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Table 47: Summary table of Risk Minimisation Measures

| Safety concern | Routine risk minimization measures | Additional risk minimization measures |
|-----------------------|---|--|
| | | |

| Safety concern | Routine risk minimization measures | Additional risk minimization measures |
|--|--|---------------------------------------|
| Important identified risks | | |
| Bleeding/ Haemorrhage | Labelled in sections 4.4 and 4.8 of the SmPC | None proposed |
| Pulmonary haemorrhage | Labelled in sections 4.4 and 4.8 of the SmPC | None proposed |
| Proteinuria | Labelled in sections 4.4 and 4.8 of the SmPC | None proposed |
| Arterial thromboembolic events | Labelled in sections 4.4 and 4.8 of the SmPC | None proposed |
| Hypertension | Labelled in sections 4.4 and 4.8 of the SmPC | None proposed |
| Congestive heart failure | Labelled in sections 4.4 and 4.8 of the SmPC | None proposed |
| Wound healing complications | Labelled in sections 4.4 and 4.8 of the SmPC | None proposed |
| Gastrointestinal perforations | Labelled in sections 4.4 <i>Gastrointestinal (GI) perforations and Fistulae</i> and 4.8 of the SmPC | None proposed |
| Posterior Reversible Encephalopathy Syndrome(PRES) | Labelled in sections 4.4 and 4.8 of the SmPC | None proposed |
| Neutropenia | Labelled in sections 4.4, 4.5 and 4.8 of the SmPC | None proposed |
| Venous thromboembolic events | Labelled in sections 4.4 and 4.8 of the SmPC | None proposed |
| Fistula (other than gastrointestinal) | Labelled in sections 4.4 <i>Non-GI Fistulae</i> and 4.8 of the SmPC | None proposed |
| Thrombotic microangiopathy | Labelled in section 4.8 of the EU SmPC. | None proposed |
| Pulmonary hypertension | Labelled in section 4.8 of the EU SmPC. | None proposed |
| Ovarian failure | Labelled in sections 4.4, 4.6 and 4.8 of the EU SPC. | None proposed |
| Hypersensitivity reactions and Infusion Reactions | Labelled in sections 4.4 and 4.8 of the SmPC | None proposed |
| Gall Bladder perforations | Labelled in sections 4.4 <i>Gastrointestinal (GI) perforations and Fistulae</i> and 4.8 of the SmPC | None proposed |
| Peripheral sensory neuropathy | Labelled in section 4.8 of the SmPC. | None proposed |
| Cardiac disorders (excl. CHF and ATE) | Supraventricular tachycardia is labelled in section 4.8 of the EU SPC. | None proposed |
| Osteonecrosis of the Jaw | Labelled in sections 4.4 and 4.8 of the SmPC | None proposed |
| Necrotizing fasciitis | Labelled in sections 4.4 <i>Wound healing complications</i> and 4.8 of the SmPC | None proposed |
| Adverse events following off-label intravitreal use of bevacizumab | Labelled in section 4.4 of the SmPC <i>Intravitreal use</i> <i>Eye disorders</i> <i>Systemic effects following intravitreal use</i> | None proposed |
| Embryo-fetal development | Labelled in section 4.6 of the SmPC | None proposed |

| Safety concern | Routine risk minimization measures | Additional risk minimization measures |
|--|--|--|
| disturbance | <i>Women of childbearing potential</i> <i>Pregnancy</i> Labelled in section 4.8 of the SmPC Mentioned in section 5.3 of the SmPC. | |
| Osteneclerosis in Children | Labelled in section 4.8 of the SmPC <i>Pediatric Population</i> | None Proposed |
| Important potential risks | | |
| Not Applicable | | |
| Missing information | | |
| Safety profile of the different treatment combinations in patients with non-squamous NSCLC | SmPC text not applicable. | None proposed |
| Long-term use in paediatric patients | Labelled in section 4.2 of the SmPC | None proposed |
| Patients with renal impairment | Labelled in sections 4.2 and 5.2 of the SmPC | None proposed |
| Patients with hepatic impairment | Labelled in sections 4.2 and 5.2 of the SmPC | None proposed |
| Use in Lactating Women | Labelled in section 4.6 <i>Breast-feeding</i> of the SmPC. Pregnancy is listed as a contraindication in section 4.3 of the SmPC | None proposed |

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.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable as the changes introduced in the PL as part of this variation application do not have a relevant impact on the readability of the PL.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Epithelial ovarian carcinoma and its histological and clinical equivalents, primary peritoneal carcinoma (PPC) and primary peritoneal carcinoma (FTC), continue to be a highly lethal primary gynecologic malignancy and is a leading cause of gynecologic cancer-related mortality among women globally. Worldwide, ovarian cancer affects 225,500 women annually and results in 140,200 cancer-related deaths around the world, with an annual incidence of 65,584 (42,749 deaths) in Europe¹. As the disease tends to be asymptomatic in the early stages, the majority of women are diagnosed with disseminated advanced-stage disease.

3.1.2. Available therapies and unmet medical need

Standard of care at initial diagnosis includes cytoreductive surgery (CRS) followed by platinum and taxane systemic chemotherapy. Despite optimal upfront surgery and the administration of front line chemotherapy approximately 70% of patients will relapse in the first 3 years².

Recurrent disease is classified as either platinum-resistant or platinum-sensitive, depending on whether the disease recurs < 6 or ≥ 6 months, respectively, following last cycle of previous platinum therapy; this classification is highly prognostic and is important in determining treatment options. For recurrent platinum-sensitive disease, carboplatin in combination with either paclitaxel, gemcitabine, or pegylated liposomal doxorubicin (PLD) are the most commonly used chemotherapy regimens².

Avastin is used, in combination with carboplatin and gemcitabine for treatment of adult patients with 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.

3.1.3. Main clinical studies

Efficacy and safety data supporting this application are derived from a multicenter, randomized, open-label pivotal Phase III Study GOG-0213 in adult women with platinum-sensitive recurrent EOC, PPC, or FTC evaluating whether the addition of bevacizumab to the second-line and maintenance phases of treatment improves the duration of OS relative to second-line paclitaxel (Pac) and carboplatin (Crb) alone in patients with recurrent, platinum-sensitive, ovarian cancer (Objective 1).

3.2. Favourable effects

The study met its primary endpoint. The HR was 0.823 (0.680, 0.996), p-value = 0.0447. Median OS improved 5.3 months from 37.3 to 42.6 months, adding almost an additional half year of survival, which is considered of clinical relevance.

The PFS results are clearly in support of the primary endpoint. Median PFS improved from 10.2 to 13.8 months. The results are statistically significant and clinically relevant. The PFS findings are also overall in line with the PFS results in study AVF4095g, where the PFS by INV was 8.4 vs. 12.4 in the crb+gem and crb+gem+bev arm respectively. It is acknowledged that the chemotherapy backbone is different between studies AVF4095g and GOG-0213, but it is nonetheless encouraging to observe that the PFS results in the

bevacizumab arms are similar. PFS was primary endpoint in study AVF4095g that led to the extension of the indication to use bevacizumab in combination with carboplatin and gemcitabine in patients with platinum-sensitive disease.

3.3. Uncertainties and limitations about favourable effects

For the stratified efficacy analysis, instead of using treatment-free-interval data based on the randomization system as one of the stratification factors as used by the GOG, the MAH used the platinum-free-interval data based on the eCRF. The stratified OS analysis based on GOG's approach was performed as a sensitivity analysis. In this analysis using the stratification factors based on the registration form (during randomisation), the HR for OS was 0.838 (95% CI [0.693; 1.014]) and the log-rank test p-value was 0.0683. In the unstratified analysis, the HR for OS was 0.840 (95% CI [0.695; 1.015]) and the log-rank test p-value was 0.0698. The originally planned primary analysis of OS (GOG analysis) using the stratification factors based on the registration form (during randomization) would have been preferred in the primary analysis and has been reflected in the SmPC.

With regard to patients with prior bevacizumab exposure, it is important to emphasize that only 69 patients were included in this subgroup. There is also no clear benefit of treating patients with prior exposure to bevacizumab in first-line, with bevacizumab at first platinum-sensitive relapse. Even after additional presentation of data from three supportive studies, there was no strong scientific rationale to remove the limitation from the current SmPC.

3.4. Unfavourable effects

The safety of bevacizumab is well-known as a consequence of many years of use in the clinical setting. Bevacizumab, in combination with carboplatin and paclitaxel is also indicated for the front-line treatment of adult patients with advanced ovarian cancer. The median duration of exposure of carboplatin and paclitaxel/docetaxel was comparable between the two treatment arms. The median number of bevacizumab cycles was 16. The total dose of carboplatin and paclitaxel/docetaxel is also comparable between the two arms. Overall, it is considered that this allows a reasonable assessment of safety in this patient population.

The overall number of AEs was comparable between the two arms, however, there were more SAEs, Grade 3/4 AEs and discontinuations due to AEs in the crb+pac+bev arm. There were considerably more cases of non-CNS bleedings, hypertension, proteinuria and thromboembolic events. Neutropenia, wound healing complications and GI perforations were also reported more frequently in the bevacizumab arm. These events are expected and observed in clinical trials with bevacizumab. They are clinically manageable and are reflected in the SmPC, where precautionary measures are also provided.

The incidence of AEs leading to withdrawal of study treatment was higher in the Crb+Pac+Bev compared to the chemotherapy only arm. Regarding discontinuation, eighty-seven of 325 patients (27%) discontinued bevacizumab during the initial chemotherapy combination treatment phase with a median of 4 cycles of treatment. Additionally, 227 patients (70%) stopped bevacizumab during the maintenance phase with a median of 20 cycles.

3.5. Uncertainties and limitations about unfavourable effects

The majority of patients were below 65, white, ECOG 0 or 1. Very few patients were ECOG 3. These characteristics have been reflected in section 5.1 of the SmPC.

The incidence of AEs, SAEs, Grade 5 AEs, AEs leading to discontinuation of treatment, and AESIs was consistent with prior observations in patients aged > 65 years-old being treated with bevacizumab. However, the relatively small sample sizes preclude any very strong conclusions.

3.6. Effects Table

Table 48: Effects Table for Avastin in combination in combination with paclitaxel and carboplatin for the treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer (data cut-off: 5 November 2014).

| Effect | Short Description | Unit | Treatment Crb+pac+ Bev | Control Crb+pac | Uncertainties/ Strength of evidence | References |
|--|--|-------------------------|------------------------|-------------------|--|-------------------------------------|
| Favourable Effects | | | | | | |
| OS | Time from randomization to the date of death from any cause | Median (Months) [95%CI] | 42.6 [37.8, 46.2] | 37.3 [33.3, 39.8] | OS improvement clinically relevant and statistically significant when data were derived from eCRF | See discussion on clinical efficacy |
| | | HR [95%CI] | 0.823 [0.680, 0.996] | | | |
| OS "GOG analysis" (sensitivity analysis) | | p-value | 0.0447 | | Not statistically significant in the originally planned primary analysis (GOG analysis stratification based on TFI on registration form) | |
| | | HR [95%CI] | 0.838 [0.693, 1.014] | | | |
| PFS | Time from randomization to first date of documented progression, or to death due to any cause. | p-value | 0.0683 | | | |
| | | HR [95%CI] | 0.613 [0.521, 0.721] | | | |
| OS (subgroup: prior bev treatment) | Time from randomization to the date of death from any cause | Median (Months) [95%CI] | 13.8 [12.9, 14.8] | 10.2 [9.7, 10.8] | PFS results in support of the primary endpoint | |
| | | HR [95% CI] | 0.613 [0.521, 0.721] | | | |
| PFS (subgroup: prior bev treatment) | Time from randomization to first date of documented progression, or to death due to any cause. | p-value | < 0.0001 | | | |
| | | HR [95% CI] | 0.764 [0.436, 1.340] | | | |
| OS (subgroup: prior bev treatment) | Time from randomization to the date of death from any cause | Median (Months) [95%CI] | 36.8 [27.0, 48.8] | 32 [27.0,37.3] | Not statistically significant. Limited number of patients. | |
| | | HR [95% CI] | 0.764 [0.436, 1.340] | | | |
| PFS (subgroup: prior bev treatment) | Time from randomization to first date of documented progression, or to death due to any cause. | Median (Months) [95%CI] | 10.7 [9.2,13.3] | 9.8 [8.9,11.1] | No data on possible resistance mechanism to bevacizumab in non-naïve patients | |
| | | HR [95% CI] | 0.841 [0.516, 1.373] | | | |

| Unfavourable Effects | | | | | | |
|--|--|------|-------------|-------------|------------------------------------|-----------------------------------|
| Grade \geq 3 AEs | | N(%) | 197 (60.6%) | 112 (33.7%) | No new safety concerns identified. | See discussion on clinical safety |
| SAE | | N(%) | 92 (28.3%) | 37 (11.1%) | | |
| Bleeding (non-CNS) | | N(%) | 137 (42.2%) | 36 (10.8%) | | |
| Hypertension | | N(%) | 135 (41.5%) | 10 (3.0%) | | |
| Proteinuria | | N(%) | 56 (17%) | 3 (<1%) | | |
| Neutropenia & associated complications | | N(%) | 40 (12.3%) | 26 (7.8%) | | |
| Arterial thromboembolic events | | N(%) | 22 (6.8%) | 6 (1.8%) | | |
| Wound healing complications | | N(%) | 10 (3.1%) | 2 (0.6%) | | |

Abbreviations: AEs (adverse events), HR (hazard ratio), PFS (progression free survival), OS (overall survival), SAE (serious adverse event). AE=occurring within first study treatment date and last study treatment date plus 30 days

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The observed improvement in median overall survival of almost half year is clinically relevant. These findings are further supported by the PFS results, which are in line with the PFS results observed in study AVF4095g that led to the extension of the indication to use bevacizumab in combination with carboplatin and gemcitabine in patients with platinum-sensitive disease. However, the added benefit comes at a cost. There are more SAE, AESI and discontinuations in the bevacizumab arm, but there are no new safety findings, and the safety profile is consistent with previous studies. The discontinuation rate of 25% is not unexpected in this setting and is also in line with previous findings.

3.7.2. Balance of benefits and risks

The benefit-risk balance is positive for Avastin in combination with carboplatin and paclitaxel in the treatment of adult patients with 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.

There were insufficient data to support a positive benefit-risk balance for Avastin in combination with carboplatin and gemcitabine or in combination with carboplatin and paclitaxel for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents. There is no clear benefit of treating patients with prior exposure to bevacizumab in first-line, with bevacizumab at first platinum-sensitive relapse while the risk of AEs remains. Furthermore, strong scientific rationale to support removing the limitation from the current SmPC has not been presented.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R of Avastin is positive in the following indication: in combination with carboplatin and paclitaxel, for treatment of adult patients with 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.

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

Extension of indication to include the use of Avastin in combination with paclitaxel and carboplatin for the for treatment of adult patients with 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. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated with efficacy and safety information from study GOG-0213. The Package Leaflet and RMP (v. 27.1) are updated in accordance.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Avastin is not similar to Yondelis and Lynparza within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.