26 February 2015
EMA/CHMP/205694/2015
Committee for Medicinal Products for Human Use (CHMP)

Extension of indication variation assessment report

Invented name: Avastin

International non-proprietary name: bevacizumab

Procedure No. EMEA/H/C/000582/II/0072

Marketing authorisation holder (MAH): Roche Registration Ltd

Note

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

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List of abbreviations

AE	adverse event
AEGT	adverse event group term
AESI	adverse event of special interest
ARDS	acute respiratory distress syndrome
AdEERS	adverse event expedited reporting system
ATE	arterial thromboembolic event
BPI	Brief Pain Inventory
Bv	bevacizumab
CHF	congestive heart failure
Cis	Cisplatin
CI	confidence interval
CNS	central nervous system
CR	complete response
CRADA	Cooperative Research and Development Agreement
CRF	Case Report Form
CSR	clinical study report
CT	computed tomography
CTC	Common Terminology Criteria
CTEP	Cancer Therapy Evaluation Program
CTSU	Cancer Trials Support Unit
CVA	cerebrovascular accident
Cx TOI	cervix trial outcome index
DCTD	Division of Cancer Treatment and Diagnosis
DIC	disseminated intravascular coagulation
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
DVT	deep venous thrombosis
EU	European Union
FACT-Cx	Functional Assessment of Cancer Therapy – Cervix
FACT-Ntx	Functional Assessment of Cancer Therapy – Neurotoxicity
FDA	Food and Drug Adminstration
FIGO	Féderation Internationale de Gynécologie et d'Obstétrique
GI	gastrointestinal
GOG	Gynecologic Oncology Group
GOG –Ntx4	Gynecologic Oncology Group-Neurotoxicity 4-item shortened subscale for patients with neurotoxicity
HPV	Human Papilloma Virus
HR	hazard ratio
HRQoL	health-related quality of life
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
LD	longest dimension
LVSD	left ventricular systolic dysfunction
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimum important difference
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria Adverse Event
NPT	non−protocol-specified cancer therapy
NSCLC	non − small cell lung cancer
ORR	objective response rate
OS	overall survival
Pac	Paclitaxel
PD	progressive disease
PFS	progression-free survival
PMB	Pharmaceutical Management Branch
PRES	posterior reversible encephalopathic syndrome

PS	performance status
q3w	every 3 weeks
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RPLS	reversible posterior leukoencephalopathy
SAP	Statistical Analysis Plan
SD	stable disease
SDC	Statistical and Data Center
SEDES	SDC Electronic Data Entry System
SEER	Surveillance, Epidemiology, and End Results
SLD	sum of the longest dimension
SMQ	Standardized MedDRA Query
TIA	transient ischemic attack
Top	Topotecan
US	United States
VEGF	vascular endothelial growth factor
VTE	venous thromboembolic event

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration Ltd submitted to the European Medicines Agency on 6 June 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product: **For presentations: See Annex A**	**International non-proprietary name:**
Avastin	bevacizumab

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	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

The Marketing authorisation holder (MAH) applied for a new indication: Bevacizumab, in combination with paclitaxel and cisplatin or paclitaxel and topotecan is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC.

The Package Leaflet was proposed to be updated in accordance.

Furthermore, the MAH took this opportunity to make minor editorial corrections in the SmPC.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

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 were:

Rapporteur: Christian Schneider Co-Rapporteur: Ingunn Hagen Westgaard

PRAC Rapporteur: Doris Stenver

Timetable	Actual dates
Submission date:	6 June 2014
Start of procedure:	27 June 2014
Rapporteur's preliminary assessment report circulated on:	18 August 2014
Co-Rapporteur's preliminary assessment report circulated on:	18 August 2014
PRAC Rapporteur's assessment report circulated on:	25 August 2014
PRAC Rapporteur's assessment report endorsed by PRAC on:	11 September 2014
Joint Rapporteurs' updated assessment report circulated on:	22 September 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 September 2014
MAH's responses submitted to the CHMP on:	18 November 2014
Joint Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	19 December 2014
PRAC Rapporteur's assessment report on the MAH's responses circulated on:	28 December 2014
PRAC Rapporteur's assessment report on the MAH's responses endorsed by PRAC on:	9 January 2015
Joint Rapporteurs' updated assessment report on the MAH's responses circulated on:	15 January 2015
Second request for supplementary information and extension of timetable adopted by the CHMP on:	22 January 2015
MAH's responses submitted to the CHMP on:	26 January 2015
Joint Rapporteurs' preliminary assessment report on the MAH's responses circulated on:	04 February 2015
PRAC Rapporteur's assessment report on the MAH's responses circulated on:	04 February 2015
PRAC Rapporteur's assessment report on the MAH's responses endorsed by PRAC on:	12 February 2015
CHMP opinion:	26 February 2015

2. Scientific discussion

2.1. Introduction

Problem Statement

Cervical cancer is the fourth most common cancer in women and seventh most common cancer overall. In 2012, approximately 528,000 new cervical cancer cases were diagnosed globally. Cervical cancer accounted for 7.5% of all female cancer deaths with approximately 266,000 deaths; the majority (87%) of these deaths occurs in developing countries (Globocan, 2012). In the European Union (EU), the crude incidence of cervical cancer is 13.2/100,000 and the crude mortality rate is 5.9/100,000 women/year.

The majority of invasive cervical cancers (70%) are caused by persistent infections with human papillomavirus (HPV) types 16 or 18. This has led to the development of vaccines against HPV16 and 18. The Féderation Internationale de Gynécologie et d'Obstétrique (FIGO) classified cervical cancer staging (stage I−IV) based on clinical examination including tumour size (IA,B), vaginal or parametrial involvement (stage IIA−IIIB), bladder or rectum extension (stage IVA), and distant metastases (stage IVB). Advanced stage disease is usually characterized by large central pelvic tumours which are necrotic and often the cause of significant bleeding as well as the involvement of adjacent pelvic organs (vagina, bladder, rectum, ureters). The mainstay of primary treatment for advanced disease (stage II−IV) is combination radiation therapy and radiation-sensitizing platinum-based chemotherapy (ESMO Clinical Practice Guideline, 2012).

Up to 50% of patients with advanced disease will have one or more recurrences, which are generally considered incurable, particularly if distant metastases, have developed; chemotherapy is usually recommended for these patients. In patients who present with distant metastasis (stage IVB), chemotherapy treatment is essentially palliative, and although the optimal regimen for chemotherapy has not been defined, cisplatin combination therapy is considered the standard of care (ESMO Clinical Practice Guideline, 2012). Carboplatin or non-platinum regimens (e.g., paclitaxel or topotecan) are options for patients who cannot tolerate cisplatin (Colombo et al. 2012).

About the product

Avastin contains bevacizumab, a recombinant humanised monoclonal antibody which bind to vascular endothelial growth factor (VEGF), the key driver of vasculogenesis and angiogenesis, and thereby inhibits the binding of VEGF to its receptors, Flt 1 (VEGFR-1) and KDR (VEGFR-2), on the surface of endothelial cells. Neutralising the biological activity of VEGF regresses the vascularisation of tumours, normalises remaining tumour vasculature, and inhibits the formation of new tumour vasculature, thereby inhibiting tumour growth.

Avastin was initially authorised in the EU on 12 January 2005 for the treatment of metastatic carcinoma of the colon or rectum in combination with fluoropyrimidine-based chemotherapy. It is currently approved in combination with other medicines to treat metastatic carcinoma of the colon or rectum (mCRC), metastatic breast cancer (mBC), Non-small cell lung cancer (NSCLC), advanced and/or metastatic renal cell cancer (mRCC), epithelial ovarian, fallopian tube and primary peritoneal cancer (see SmPC section 4.1 for full detailed indications).

As part of the present variation, the applicant applied for the following indication:

Bevacizumab, in combination with paclitaxel and cisplatin or paclitaxel and topotecan is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix.

The final indication approved by the CHMP is as follows:

Bevacizumab, in combination with paclitaxel and cisplatin or, alternatively, paclitaxel and topotecan in patients who cannot receive platinum therapy, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix (see SmPC Section 5.1).

The recommended dose of Avastin is 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion. It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity (see SmPC section 5.1).

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

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

2.3. Clinical aspects

2.3.1. Introduction

In support of this application the MAH provided data from study GOG-0240 which is a randomised, open-label, multicentre Phase III trial of bevacizumab in combination with chemotherapy (cisplatin plus paclitaxel versus the non-platinum doublet, topotecan plus paclitaxel) in women with persistent, recurrent, or stage IVB carcinoma of the cervix.

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 study

Table 1: Overview Study GOG-0240

Study No. (Phase)	Study Design	Population	Study objective	No. of Patients	Dose, Route, and Regimen
GOG-0240 (Phase III)	Randomized, multi-centre, active controlled, 2x2 factorial design	Patients with persistent, recurrent or Stage IV-B carcinoma of the cervix with: •Measurable disease •GOG PS 0	Primary objectives: • To determine if the addition of Bev to chemotherapy improves OS • To determine if the regimen of paclitaxel	N=452 (randomized 1:1:1:1)	Arm 1: cisplatin 50mg/m^2+paclitaxel 135 or 175 mg/m^2 Arm 2: cisplatin 50mg/m^2+paclitaxel 135 or 175 mg/m^2+bev 15 mg/kg Arm 3: Topotecan 0.75 mg/m^2, Days 1–3 +Paclitaxel 175 mg/m^2

		vs.1 •No prior chemotherapy other than with radiation •No prior anti-VEGF drug	and topotecan (non-platinum) improves OS in comparison to the standard cisplatin and paclitaxel regimen • To compare the frequency and severity of adverse events		Arm 4: Topotecan 0.75 mg/m^2, Days 1–3 +Paclitaxel 175 mg/m^2+ Bev 15 mg/kg

GOG PS= Gynecologic Oncology Group performance score; VEGF= vascular endothelial growth factor; bev=bevacizumab; OS=overall survival.

2.4. Clinical efficacy

2.4.1. Main study

GOG-0240

Study GOG-0240 (also known by Study ML01230) was a Phase III, randomized, open-label, multicenter study designed to evaluate the efficacy and safety of chemotherapy in combination with bevacizumab compared with chemotherapy alone in patients with persistent, recurrent, or stage IVB carcinoma of the cervix.

Methods

Study participants

The study enrolled patients (women aged ≥ 18 years) with persistent, recurrent or Stage IVB carcinoma of the cervix with measurable disease, a GOG PS 0 vs.1, no prior chemotherapy other than with radiation, and no prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents. Further details on inclusion and exclusion criteria are listed below:

Inclusion criteria:

- Patients had primary persistent, recurrent, or stage IVB squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix that was not amenable to curative treatment with surgery and/or radiation therapy.
- All patients had measurable disease. 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 had 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. Biopsy confirmation was required if the lesion(s) measured < 30 mm or if the treating physician determined it was clinically indicated. Patients had to have at least one "target lesion" to be used to assess response on this protocol as defined by RECIST. This lesion was to be the one that was biopsied if one was performed. Tumours within a previously irradiated field were designated as "non-target" lesions unless progression was documented or a biopsy was obtained to confirm persistence at least 90 days following completion of radiation therapy.

- Patients had adequate:

– Hematologic function: ANC ≥ 1500/µL; platelets ≥ 100,000/µL.

– Renal function: patients with serum creatinine ≤ ULN (NCI CTCAE Grade 0) or calculated creatinine clearance (Jeliffe Formula) ≥ 60 mL/min.

– Hepatic function: bilirubin ≤ 1.5 × institutional normal; SGOT, alkaline phosphatase ≤ 2.5 × institutional normal.

– Blood coagulation parameters (PTT, PT/INR): PT such that international normalized ratio (INR) is ≤ 1.5 (or an in-range INR, usually between 2 and 3, if a patient was on a stable dose of therapeutic warfarin for management of venous thrombosis including pulmonary thromboembolus) and a PTT < 1.2 times the upper limit of normal.

– Patients had to have a urine protein-creatinine ratio (UPC ratio) < 1.0.

- Patients had a GOG Performance Status of 0 or 1.
- Patients had recovered from the effects of surgery, radiation therapy, or chemoradiotherapy. At least 6 weeks must have elapsed from the last administration of chemoradiotherapy, and at least 3 weeks must have elapsed from the last administration of radiation therapy alone. At least 6 weeks must have elapsed from the time of any major surgical procedure prior to randomization.
- Patients signed an approved informed consent and authorization permitting release of personal health information.
- Patients were free of active infection requiring antibiotics.

Exclusion criteria:

• Patients with bilateral hydronephrosis that could not be alleviated by ureteral stents or percutaneous drainage.

• Patients previously treated with chemotherapy except when used concurrently with radiation therapy.

– Patients who had received concurrent paclitaxel and/or concurrent topotecan with radiation therapy were ineligible.

• Patients with craniospinal metastases.

• Patients with a concomitant malignancy other than non-melanoma skin cancer.

• Patients with a prior invasive malignancy (except non-melanoma skin cancer) who had any evidence of disease within the previous 5 years or whose prior malignancy treatment contraindicated the current protocol therapy.

• Patients with serious non-healing wound, ulcer, or bone fracture. This included history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess for which an interval of 3 to 6 months must have passed before study entry. In addition, the patient must have undergone correction (or spontaneous healing) of the perforation/fistula and/or the underlying process causing the fistula/perforation. Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection were eligible but required weekly wound examinations.

• Patients with active bleeding or pathologic conditions that carried a high risk of bleeding, such as known bleeding disorder, coagulopathy, or tumour involving major vessels.

• Patients with history or evidence upon physical examination of CNS disease, including primary brain tumour, seizures not controlled with standard medical therapy, any brain metastases, or history of

cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA), or subarachnoid haemorrhage within 6 months of the first date of treatment on this study.

• Patients with clinically significant cardiovascular disease. This included:

– Uncontrolled hypertension, defined as systolic > 150 mm Hg or diastolic > 90 mm Hg.

– Myocardial infarction or unstable angina > 6 months prior to registration.

– New York Heart Association (NYHA) Grade II or greater congestive heart failure

– Serious cardiac arrhythmia requiring medication. This did not include asymptomatic, atrial fibrillation with controlled ventricular rate.

– NCI CTCAE Grade ≥ 2 peripheral vascular disease (at least brief (< 24 hrs) episodes of ischemia managed non-surgically and without permanent deficit).

– History of CVA within 6 months.

• Patients with known hypersensitivity to Chinese hamster ovary (CHO) cell products or other recombinant human or humanized antibodies.

• Patients with or with anticipation of invasive procedures as defined below:

– Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to the first date of bevacizumab therapy.

– Major surgical procedure anticipated during the course of the study. This included, but was not limited to abdominal surgery (laparotomy or laparoscopy) prior to disease progression, such as colostomy or enterostomy reversal, interval or secondary cytoreductive surgery, or second look surgery.

– Core biopsy, within 7 days prior to randomization.

• Patients who were pregnant or nursing.

• Patients who have received prior therapy with any anti-VEGF drug, including bevacizumab.

• Patients with clinical symptoms or signs of GI obstruction and who required parenteral hydration and/or nutrition.

• Patients with medical history or conditions not otherwise previously specified that, in the opinion of the investigator, should exclude participation in this study.

• Patients with significant peripheral vascular disease.

• Patients with pre-existing Grade 2 or greater peripheral neuropathy.

Treatments

Patients were randomized to receive one of the following four treatment regimens:

• Regimen I: Cisplatin plus paclitaxel without bevacizumab

At the discretion of the investigator, patients received one of 3 options: paclitaxel 135 mg/m^2 IV over 24 hours on Day 1 and cisplatin 50 mg/m^2 IV on Day 2 every 3 weeks (q3w); or paclitaxel 175 mg/m^2 IV over 3 hours on Day 1 and cisplatin 50 mg/m^2 IV on Day 2 (q3w); or paclitaxel 175 mg/m^2 IV over 3 hours on Day 1 and cisplatin 50 mg/m^2 IV on Day 1 (q3w). The schedule was entered on the case report form (CRF) and remained constant for the duration of therapy.

• Regimen II: Cisplatin plus paclitaxel with bevacizumab

At the discretion of the investigator, patients received one of 3 options: paclitaxel 135 mg/ m^2 IV over 24 hours on Day 1 and cisplatin 50 mg/ m^2 IV on Day 2 plus bevacizumab 15 mg/kg IV on Day 2 (q3w); or paclitaxel 175 mg/ m^2 IV over 3 hours on Day 1 and cisplatin 50 mg/m^2 IV on Day 2 plus bevacizumab 15 mg/kg IV on Day 2 (q3w); or paclitaxel 175 mg/m^2 IV over 3 hours on Day 1 and cisplatin 50 mg/m^2 IV on Day 1 and bevacizumab 15 mg/kg IV on Day 1 (q3w). The schedule was entered on the CRF and remained constant for the duration of therapy.

• Regimen III: Topotecan plus paclitaxel without bevacizumab

Paclitaxel 175 mg/m^2 IV over 3 hours on Day 1 and Topotecan 0.75 mg/m^2 IV over 30 minutes on Days 1-3 (q3w).

• Regimen IV: Topotecan plus paclitaxel with bevacizumab

Paclitaxel 175 mg/m^2 IV over 3 hours on Day 1 and Topotecan 0.75 mg/m^2 IV over 30 minutes on Days 1-3 plus bevacizumab 15 mg/kg IV on Day 1 (q3w).

The patient's weight at screening was used to determine the bevacizumab dose to be used for the duration of the study. If a patient's weight changed by ≥10% during the course of the study, the bevacizumab dose was recalculated.

In all treatment regimens, cycles were repeated every 3 weeks, and patients continued on-study treatment until disease progression or unacceptable toxicities prohibited further therapy. If patients experienced a complete response (CR) on study they could receive an additional 2–3 cycles of therapy at their physician's discretion and then discontinue study therapy. Patients were followed until death, and even if the patient was taken off protocol therapy, all therapies and toxicities were reported on GOG forms until progression was documented.

The following dose modifications were permitted for components of chemotherapy in cases of tolerability or toxicity, although once a dose was reduced, no dose re-escalation was allowed:

• Cisplatin at an initial dose of 50 mg/m^2 was reduced to 37.5 mg/m^2, and then, if required, to 25 mg/m^2.

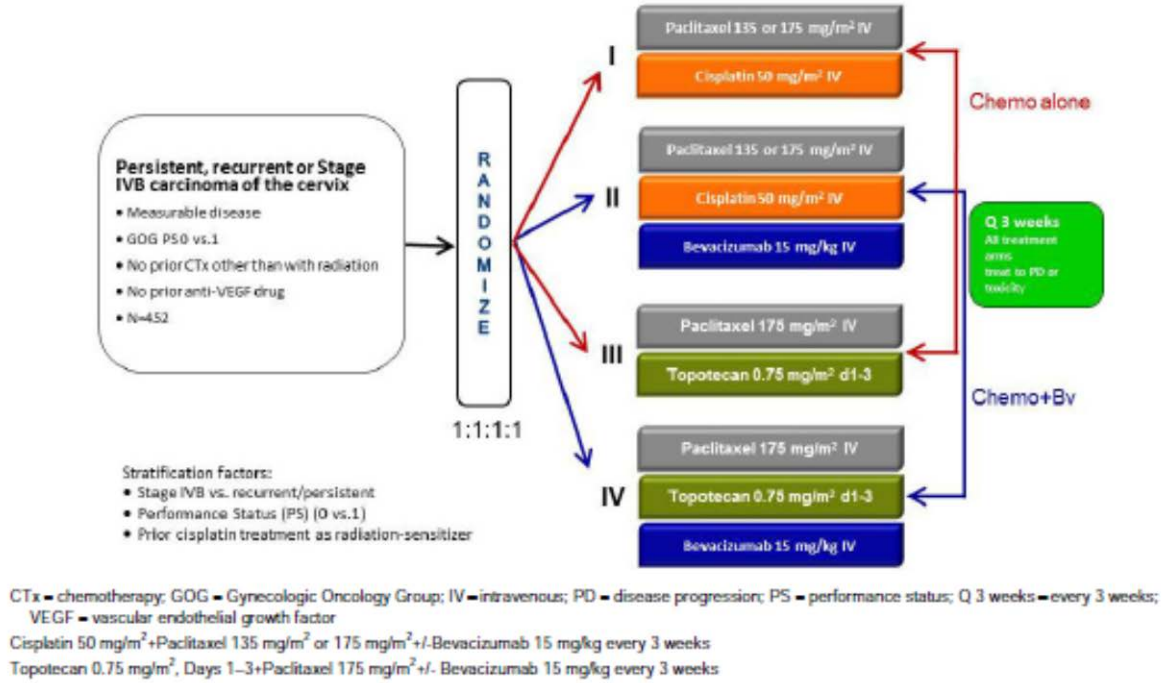
• Paclitaxel at an initial dose of 135 mg/m^2 (24-hour infusion schedule) was reduced to 110 mg/ m^2, and then, if required, to 90 mg/m^2.

• Paclitaxel at an initial dose of 175 mg/m^2 (3-hour infusion schedule) was reduced to 140 mg/m2, and then, if required, to 105 mg/m^2.

• Topotecan at an initial dose of 0.75 mg/m^2 was reduced to 0.6 mg/m^2, and then, if required, to 0.45 mg/m^2.

If a patient was unable to proceed with therapy despite two dose reductions as outlined, the patient was removed from the study.

The design of the study is presented in the Figure 1.



CTx = chemotherapy; GOG = Gynecologic Oncology Group; IV = intravenous; PD = disease progression; PS = performance status; Q 3 weeks = every 3 weeks; VEGF = vascular endothelial growth factor

Cisplatin 50 mg/m^2+Paclitaxel 135 mg/m^2 or 175 mg/m^2+/-Bevacizumab 15 mg/kg every 3 weeks

Topotecan 0.75 mg/m^2, Days 1–3+Paclitaxel 175 mg/m^2+/- Bevacizumab 15 mg/kg every 3 weeks

Figure 1: GOG-0240 Study design

Objectives

The primary objectives of Study GOG-0240 were:

• To determine if the addition of bevacizumab to chemotherapy improves OS in patients with persistent, recurrent, or stage IVB carcinoma of the cervix.

• To determine if the regimen of paclitaxel and topotecan (non-platinum) improves OS in comparison to the standard cisplatin and paclitaxel regimen in patients with persistent, recurrent, or stage IVB of the cervix.

• To determine and compare the frequency and severity of adverse events (AEs) as assessed by CTCAE version 3.0 for the regimens administered in this study.

The secondary objectives included the estimation and comparison of the progression-free survival (PFS) and the proportion of tumour responses of patients treated with the regimens investigated on this study (reported herein using the GOG RECIST criteria). In addition, a secondary objective was to determine whether the addition of bevacizumab to chemotherapy, or the substitution of cisplatin with topotecan improves the health related quality of life (HRQoL) as measured by the FACT-Cx TOI and produces favourable toxicity profiles (with a particular focus on peripheral neuropathy as measured by the FACT/GOGNtx4 subscale and pain as measured by the BPI single item).

Finally exploratory endpoints included prognostic markers for predictive modelling the impact of smoking on prognosis and the rates of patients remaining stable, improving, or worsening as measured by the FACT-Cx TOI, the FACT/GOG-Ntx4, and BPI single-item (responder analyses).

Outcomes/endpoints

The primary endpoint of the study was Overall Survival (OS) defined as the time from randomization until death from any cause. For patients who had not died by the time of analysis, data were censored as of the last contact date at which the patient was known to be alive.

Secondary endpoints:

Progression free survival (PFS): defined as the time between the date of randomization and the date of first documented disease progression or death, whichever occurred first.

Objective response rate (ORR): defined as the percentage of patients who had objective response. Objective response was defined as a complete or partial overall response determined on two consecutive investigator assessments ≥ 4 weeks apart in patients with measurable disease at baseline. Patients without a post-baseline tumour assessment were considered non-responders.

ORR was assessed based on the investigator assessment using the GOG RECIST v1.0 criteria. There was no centrally, blinded review.

Quality of Life: HRQoL was measured by the FACT-Cx TOI. Measures selected included the FACT-Cx, the 4 sensory items of the FACT/GOG-Ntx4, and the "worst pain" single item from the BPI Short Form.

The FACT-Cx is the FACT-G (version 4) plus a cervix cancer-specific subscale. The primary HRQoL analysis used the Trial Outcomes Index (FACT-Cx TOI) which is a summary score of the items of the physical well-being, functional well-being, and of the cervix cancer subscales.

The FACT/GOG-Ntx is the FACT-G plus an 11-item subscale evaluating the symptoms and concerns associated with chemotherapy-induced neuropathy. The FACT/GOGNtx4 was included to assess the neurotoxicity that may result from the cisplatin-paclitaxel regimen.

The BPI is a 23-item, self-report instrument designed to assess pain in cancer and other diseases. HRQoL was collected at five timepoints: baseline, prior to Cycle 2 (3 weeks after Cycle 1), prior to Cycle 5 (12 weeks after Cycle 1), 6 months post-Cycle 1, and 9 months post-Cycle 1. All HRQoL forms were to be completed during protocol-based office visits (i.e., no mailed forms were used).

Sample size

The two primary hypotheses to be tested were whether the addition of bevacizumab improves survival and whether combining paclitaxel with topotecan instead of cisplatin improves survival. The study was designed to detect a 30% reduction in death associated with addition of either factor, corresponding to a hazard ratio (HR) of 0.7. In order to detect such a difference with 90% power (under the assumption of no interaction), it was required that at least 346 deaths were observed in the two levels for the factor being tested.

The total planned patient accrual was up to 450 patients.

Randomisation

Patients were randomly assigned to one of the four treatment arms in a 1:1:1:1 ratio. Randomisation was stratified by the following criteria: disease stage (persistent/recurrent vs. Stage IVB), performance status (0 vs. 1) and prior platinum therapy (yes vs. no).

Blinding (masking)

This was an open-label study.

Statistical methods

The two primary hypotheses to be tested were whether the addition of bevacizumab (Factor A) improves survival and whether combining paclitaxel with topotecan instead of cisplatin (Factor B) improves survival.

Table 2: Relationship between Factor A and B marginal survival functions used to assess hypothesis testing

			Factor B Level I cis + tax	Level II top + tax	
Factor A	Level I	no bev	cis + tax	top + tax	$S_{nobev}(t)$
	Level II	bev	cis + tax bev	top + tax bev	$S_{bev}(t)$
			$S_{cis+tax}(t)$	$S_{top+tax}(t)$	

Factor A was employed to investigate the effects of bevacizumab. Factor B was employed to investigate the regimen utilizing topotecan instead of cisplatin. The control arm was the administration of cisplatin and paclitaxel. Level I was considered to be the "non-experimental" level for each factor whereas Level II was the "experimental" level of each factor. The marginal survival of patients without bevacizumab treatment, S_{nobev} (t), was obtained by combining the patients who received the regimens across the first row. Likewise, an estimate of the marginal survival of patients who received bevacizumab treatment, S_{bev} (t), was obtained by combining the patients who received the regimens across the second row.

In the protocol, two efficacy analyses were initially planned for this study, an interim analysis at the time when 173 deaths had been observed in the entire study and a final analysis when 346 deaths were observed in the two levels for the factor being tested. To assess the null hypothesis of H_{01}: S_{bev} (t) = S_{nobev} (t), a one-sided stratified log-rank test was conducted at an overall 2.5% level of significance, using the spending function α(t*) = αt2 provided by Lan and DeMets (i.e., α = 0.025; z-scores are 2.498 at the interim [t = 0.5] and 2.018 at the final analysis [t = 1], corresponding to alpha spending of 0.00625 and 0.01875). The log-rank test was stratified on the prognostic factors listed in above Section Randomisation and the treatment levels for Factor B. A similar analysis was conducted to test H_{02}: $S_{cis + tax}$ (t) = $S_{top + tax}$(t), using a one-sided stratified log-rank test with an overall 2.5% level of significance, using the same alpha spending function.

The primary analysis of OS assumed no treatment interaction between chemotherapy and bevacizumab treatment. For each of the hypotheses, the comparison of OS between treatment arms was based on a two-sided stratified log-rank test at the 5% level of significance. The stratification factors were disease stage (persistent/recurrent vs. stage IVB), Performance Status (0 vs. 1), prior platinum therapy (yes vs. no), and the level of the other treatment assignment (experimental vs. reference). Results from an unstratified log-rank test were also presented. Kaplan-Meier methodology was used to estimate median OS for both treatment arms, and the 95% confidence intervals (Cis) for median OS were computed using Greenwood's formula. Kaplan-Meier curves were constructed to provide a visual depiction of the difference between the treatment arms. Estimates of the treatment effect were expressed as hazard

ratios (HRs) with use of a stratified Cox model with the same stratification variables used in the stratified log-rank test, including the 95% CIs. The unstratified HR was also presented.

A test for interaction between bevacizumab and chemotherapy treatment was conducted at the 10% level of significance against a two-sided alternative with a score test for interaction using a Cox proportional hazards model.

To further investigate the similarity of the two chemotherapy regimens, the ratio of the HRs was computed by comparing Cis+Pac+Bv group with Top+Pac+Bv group. The parameter estimates for the log HRs were taken from the stratified Cox regression models.

A sensitivity analysis was performed using an O'Brien Fleming boundary; this more conservative approach allowed comparison with the protocol-specified alpha spending function. Additionally, the significance level was adjusted to allow for the two primary hypotheses by applying a 2.5% two-sided alpha to the bevacizumab versus no bevacizumab comparison.

Additional Sensitivity Analyses of Primary Efficacy Endpoint:

Time to Censoring for Overall Survival: Kaplan-Meier curves of time to censoring were constructed to visually inspect any differences in follow-up between treatment arms.

Multivariate Cox Regression Models for Overall Survival: OS was also analyzed using a multivariate Cox regression model adjusted for treatment and the baseline prognostic factors that might be associated with OS. No covariate selection process was applied; all covariates were included in the model, regardless of statistical significance.

A sensitivity analysis was performed using an O'Brien Fleming boundary; this more conservative approach allowed comparison with the protocol-specified alpha spending function. Additionally, the significance level was adjusted for the two primary hypotheses by applying a 2.5% alpha (2-sided) to the bevacizumab versus no bevacizumab comparison.

OS was also analyzed using a multivariate Cox regression model adjusted for treatment and the baseline prognostic factors that might be associated with OS. No covariate selection process was applied; all covariates were included in the model, regardless of statistical significance.

To evaluate the robustness of the treatment effect observed in the primary efficacy analysis, subgroup analyses were performed, with the subgroups defined by demographic and baseline prognostic characteristics. The following demographic and baseline characteristics were considered: age (< 50, 50 – 65, > 65 years), race (White, non-White), baseline Performance Status (0, 1), smoking status (never, previous, current), FIGO stage (1, 2, 3, 4), histology (adenocarcinoma or unspecified/endometrioid/mucinous/serous adenocarcinoma, adenosquamous, clear cell or undifferentiated carcinoma, squamous cell carcinoma), disease status (persistent/recurrent, stage IVB), number of metastatic sites (1–2, >2), prior systemic chemotherapy (yes, no), prior adjuvant hormone therapy (yes, no), prior radiotherapy (yes, no), prior platinum therapy (yes, no), time to recurrence (< 6 months, 6 - 18 months, > 18 months), platinum-free interval (< 6 months, ≥ 6 months), site of recurrence within the field previously treated by radiation therapy (yes, no).

Descriptive summaries of OS were produced for each level of the categorical variables listed above for each treatment arm. These descriptive summaries consisted of the Kaplan-Meier estimates of median time to event and the unstratified HR and its 95% CI.

Adjustment for Covariates

The analyses of the time-to-event endpoints, including OS and PFS, were adjusted for the three stratification factors at randomization: disease stage (persistent/recurrent vs. stage IVB), Performance

Status (0 vs. 1), prior platinum therapy (yes vs. no), and the level of the other treatment assignment (experimental vs. reference). Specifically, the Cox proportional hazard regression model included the four covariates except when the results were generated for each of the 4 treatment arms. The stratified analysis provided an estimation of the HR taking into account the possible confounding effects from the stratification factors.

OS was also analyzed using a multivariate Cox regression model adjusted for treatment and the baseline prognostic factors that might be associated with OS. No covariate selection process was applied; all covariates were included in the model, regardless of statistical significance.

Handling of Dropout or Missing Data

For OS, data for patients who were lost to follow-up were analyzed as censored observations on the date of last contact. For PFS, data for patients who were lost to follow-up were analyzed as censored observations on the date of the last tumor assessment or if no post-randomization tumor assessment is available, at the date of randomization. For objective response, patients without a post-baseline tumor assessment were considered non-responders.

For HRQoL, each item in the FACT-Cx TOI and FACT/GOG-Ntx4 subscale were scored using a 5-point scale (0= not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; 4 = very much). Within an individual assessment, in order to address whether one or more items were not answered, a subscale score was computed as long as more than 50% of subscale items were answered. A subscale score S_i with N_i items was calculated as: Where δ_{ij} was equal to 1 when the j^{th} item had a valid response, otherwise it was equal to 0 and s_{ij} was the response score of the j^{th} item. The total FACT-Cx TOI score was the sum of the subscale scores if at least 80% of FACT-Cx TOI items provided valid answers.

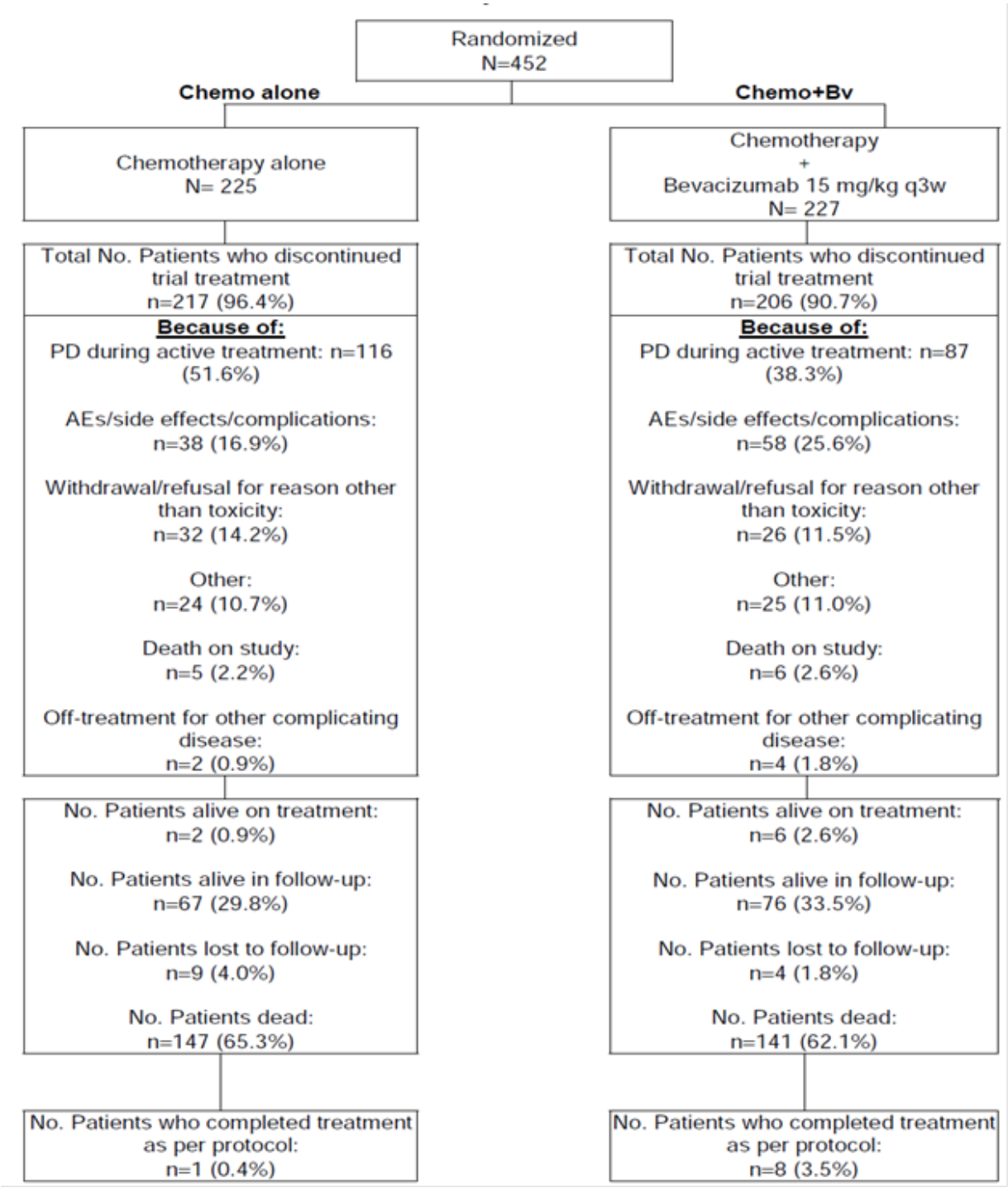
Interim Analyses and Data Monitoring

A DSMB was established to independently evaluate the safety of the patients participating in Study GOG-0240, which was designed, conducted, monitored, and analyzed by the GOG. The DSMB and DMC also met to review the results of the efficacy interim analysis.

Two efficacy analyses were performed. A first efficacy analysis, with a data cut-off in February 2012, occurred as pre-specified in the protocol when approximately 50% of the events (deaths) required for full information had been observed. A second efficacy analysis, with a data cut-off of 12 December 2012 was conducted at the request of the DSMB. This efficacy analysis, which was not pre-specified in the protocol, included 78% of the death events required for full information and is considered the final analysis.

Results

Participant flow



Recruitment

The study activation date was 4 April 2009 and the study closed to accrual as of 3 January 2012. Study GOG-0240 randomized 452 patients over approximately 33 months at 167 sites located in the US (n=434) and Spain (n=18).

Conduct of the study

The original protocol was activated and dated 10 March 2009. The protocol for Study GOG-0240 was amended 8 times on the following dates and in addition to minor clarifications, corrections, or editorial changes to the protocol and ICF documents, the following were included:

• 24 September 2009

- Only minor clarification corrections to the protocol and ICF were added.

• 1 July 2010

- For translational research, collection of archival tumour tissue was added.

- The appendix pertaining to the smoking questionnaire was deleted as it was available through SEDES. Reference to the smoking questionnaire stated that mandatory submission via SEDES was to occur.

- The CAEPR for bevacizumab was updated to version 2.1, which now included frequency data (the previous version did not have categories for Likely, Less Likely, or Rare but Serious).

- The addition that patients who experienced a CR may have received an additional 2-3 cycles of therapy at their physician's discretion before discontinuing study therapy.

• 22 December 2010

- Appendix VI, International Participation (Spain), was added, with information that PMB/NCI would not supply bevacizumab to GEICO sites.

- Updates to provide current information for IRB approval submissions to CTSU were included.

- Updates to provide current information for AdEERS expedited reports were included.

• 4 April 2011

- The following information was added to the procedures for AdEERS monitoring: AML/MDS events must be reported via AdEERS (in addition to routine AE reporting mechanisms). In NCI CTCAE v3.0, the event could be reported as: "Secondary malignancy-Other (specify)".

• 17 August 2011

- For reports through AdEERS, CTCAE v3.0 was to be used through 30 September 2011, and thereafter, CTCAE v4.0 was to be used. Sites were to report on the GOG CRFs using CTCAE v3.0.

• 26 October 2011

- For translational research, regarding the quick scan summary of the specimen requirements for GOG-0240, the information for WB02, WB03, and WB04 submissions was deleted. The requirement for Forms SP-WB02-0240, SPWB03- 0240, and SP-WB04-0240 were deleted.

• 6 December 2011

- The IND number was changed from 7921 to 113912.

- The CAEPR list for bevacizumab was updated to Version 2.2, October 21, 2011.

- The Agent Specific Adverse Event List (ASAEL) was renamed the Specific Protocol Exceptions to Expedited Reporting (SPEER), and included updates and changes to Added New Risk, Increase in Risk Attribution, Decrease in Risk Attribution, and Provided Further Clarification, as well as modification of SPEER reporting requirements.

• 25 May 2012

- The addition of the “Interim Analysis Report” and conclusions of this analysis were included in the protocol. The GOG’s DSMB reviewed the results and concluded:

- Topotecan was not a superior substitute for cisplatin with paclitaxel chemotherapy by OS in this group of patients and recommended that information be communicated to the physicians and patients participating in the study. The OS analysis did not indicate that the topotecan regimens performed worse than the cisplatin regimens. Given these results, patients who were receiving therapy with any of the four arms of GOG-0240 could remain on their current treatment assignment unless progression or unacceptable toxicity developed. As the protocol was closed to accrual, no treatment changes were incorporated.

- The results concerning the topotecan regimens in the GOG-0240 protocol were independent of the tolerability and efficacy of anti-angiogenesis therapy using bevacizumab in this study population and the study remained open awaiting results for the bevacizumab question.

Baseline data

The demographic and Baseline Characteristics are presented in Table 3.

Table 3: Demographic and Baseline Characteristics by Bevacizumab Treatment

	Chemo alone N = 225	Chemo+Bv N = 227
Age in years		
Mean	48.2	48.3
SD	12.10	11.69
Median	46.0	48.0
Min-Max	20 - 83	22 - 85
n	225	227
Age Category		
<50	131 (58.2%)	125 (55.1%)
50-65	73 (32.4%)	85 (37.4%)
>65	21 (9.3%)	17 (7.5%)
n	225	227
Race		
AMERICAN INDIAN/ALASKA NATIVE	2 (0.9%)	3 (1.3%)
ASIAN	7 (3.1%)	12 (5.3%)
BLACK	24 (10.7%)	36 (15.9%)
NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER	1 (0.4%)	-
UNKNOWN	9 (4.0%)	5 (2.2%)
WHITE	180 (80.0%)	171 (75.3%)
MISSING	2 (0.9%)	-
n	225	227
Ethnicity		
HISPANIC	28 (12.4%)	26 (11.5%)
NON-HISPANIC	185 (82.2%)	189 (83.3%)
UNKNOWN	12 (5.3%)	12 (5.3%)
n	225	227
Height in cm		
Mean	162.776	162.008
SD	7.1634	7.7762
Median	162.560	162.000
Min-Max	147.30 - 180.34	135.00 - 180.00
n	225	227
Weight in kg		
Mean	76.297	74.636
SD	23.5382	23.4776
Median	73.000	70.000
Min-Max	37.00 - 197.30	37.27 - 185.07
n	225	227
Performance Status		
0	132 (58.7%)	131 (57.7%)
1	93 (41.3%)	96 (42.3%)
n	225	227
Country		
Spain	11 (4.9%)	7 (3.1%)
USA	214 (95.1%)	220 (96.9%)
n	225	227
Smoking Status		
CURRENT	59 (26.2%)	69 (30.4%)
NEVER	85 (37.8%)	77 (33.9%)
PREVIOUS	79 (35.1%)	79 (34.8%)
MISSING	2 (0.9%)	2 (0.9%)
n	225	227
Previous Diagnosis of Cancer		
NO	215 (95.6%)	216 (95.2%)
YES	10 (4.4%)	11 (4.8%)
n	225	227

The disease characteristics are presented in Table 4.

Table 4: History of Cervical Cancer by Bevacizumab Treatment

	Chemo alone (N=225)		Chemo+Bv (N=227)	
Histology				
Adenocarcinoma Unsp.	45	(20.0%)	42	(18.5%)
Adenosquamous	21	(9.3%)	23	(10.1%)
Clear Cell Carcinoma	3	(1.3%)	1	(0.4%)
Endometrioid Adenocarcinoma	1	(0.4%)	0	(0.0%)
Mucinous Adenocarcinoma	2	(0.9%)	2	(0.9%)
Serous Adenocarcinoma	1	(0.4%)	1	(0.4%)
Squamous Cell Carcinoma	151	(67.1%)	158	(69.6%)
Undifferentiated Carcinoma	1	(0.4%)	0	(0.0%)
n	225	(100%)	227	(100%)
FIGO stage				
1	61	(27.9%)	52	(23.4%)
2	65	(29.7%)	59	(26.6%)
3	55	(25.1%)	58	(26.1%)
4	38	(17.4%)	53	(23.9%)
n	219	(100%)	222	(100%)
Disease Stage				
Persistent/Recurrent	188	(83.6%)	188	(82.8%)
Stage IVB	37	(16.4%)	39	(17.2%)
n	225	(100%)	227	(100%)
Primary Surgery				
Partial hysterectomy	0	(0.0%)	0	(0.0%)
Radical hysterectomy	35	(15.6%)	26	(11.5%)
Total hysterectomy	15	(6.7%)	15	(6.6%)
Radical trachelectomy	4	(1.8%)	3	(1.3%)
Bilateral salpingo-oophorectomy	32	(14.2%)	29	(12.8%)
Unilateral salpingo-oophorectomy	4	(1.8%)	5	(2.2%)
Omentectomy	5	(2.2%)	3	(1.3%)
Cervical conization	16	(7.1%)	11	(4.8%)
Para-aortic node sampling/dissection	26	(11.6%)	29	(12.8%)
Pelvic node sampling/dissection	51	(22.7%)	50	(22.0%)
Other	130	(57.8%)	150	(66.1%)
Number of Metastatic Sites				
1-2	162	(72.0%)	173	(76.2%)
>2	63	(28.0%)	54	(23.8%)
n	225	(100%)	227	(100%)
Sites of Involvement				
Ascites	10	(4.4%)	1	(0.4%)
Bladder	8	(3.6%)	5	(2.2%)
Bone	17	(7.6%)	14	(6.2%)
Cervix	81	(36.0%)	83	(36.6%)
CNS/Brain	0	(0.0%)	0	(0.0%)
Colon	7	(3.1%)	0	(0.0%)
Endometrium	4	(1.8%)	6	(2.6%)
Liver	30	(13.3%)	27	(11.9%)
Lung	61	(27.1%)	59	(26.0%)
Lymph node	113	(50.2%)	128	(56.4%)
Ovary	5	(2.2%)	3	(1.3%)
Parametrial involvement	6	(2.7%)	6	(2.6%)
Peritoneum	25	(11.1%)	16	(7.0%)
Pleural	2	(0.9%)	1	(0.4%)
Pleural effusion	6	(2.7%)	2	(0.9%)
Skin	0	(0.0%)	1	(0.4%)
Uterus	14	(6.2%)	14	(6.2%)
Other	90	(40.0%)	77	(33.9%)
Time to first recurrence/progression				
<6 months	30	(15.8%)	40	(20.6%)
6-18 months	81	(42.6%)	82	(42.3%)
>18 months	79	(41.6%)	72	(37.1%)
n	190	(100%)	194	(100%)
Platinum Free Interval				
<6 months	42	(27.5%)	57	(35.6%)
>=6 months	111	(72.5%)	103	(64.4%)
n	153	(100%)	160	(100%)
Site of Recurrence within the Field Previously Treated by Radiation Therapy				
NO	88	(48.6%)	99	(54.7%)
YES	93	(51.4%)	82	(45.3%)
n	181	(100%)	181	(100%)

Numbers analysed

Two analysis populations were defined for Study GOG-0240, the intent-to-treat (ITT) population and the safety population:

- ITT population (n=452), defined as all patients who were randomized to study treatment, irrespective of whether the assigned treatment was actually received.
- 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) during the study (n=440).

Outcomes and estimation

Primary endpoint

The efficacy results in terms of the primary endpoint of OS (cut-off date December 12, 2012; primary analysis) are presented in Table 5 and Figure 2.

Table 5: Overall Survival Stratified and Unstratified Analysis by Bevacizumab Treatment: ITT Population

Stratified Analysis

	Chemo alone (N=225)		Chemo+Bv (N=227)
Patients with event	147 (65.3 %)		141 (62.1 %)
Patients without events*	78 (34.7 %)		86 (37.9 %)
Time to event (months)			
Median#	12.9		16.8
95% CI for Median#	[10.9;15.0]		[14.1;19.0]
25% and 75%-ile	6.9;23.8		9.1;27.7
Range##	0.0 to 36.9		0.1 to 38.7
p-Value (Log-Rank Test)		0.0132	
Hazard Ratio		0.74	
95% CI		[0.58;0.94]	

Unstratified Analysis

	Chemo alone (N=225)		Chemo+Bv (N=227)
Patients with event	147 (65.3 %)		141 (62.1 %)
Patients without events*	78 (34.7 %)		86 (37.9 %)
Time to event (months)			
Median#	12.9		16.8
95% CI for Median#	[10.9;15.0]		[14.1;19.0]
25% and 75%-ile	6.9;23.8		9.1;27.7
Range##	0.0 to 36.9		0.1 to 38.7
p-Value (Log-Rank Test)		0.0471	
Hazard Ratio		0.79	
95% CI		[0.63;1.00]	

* censored
\# Kaplan-Meier estimate
including censored observations

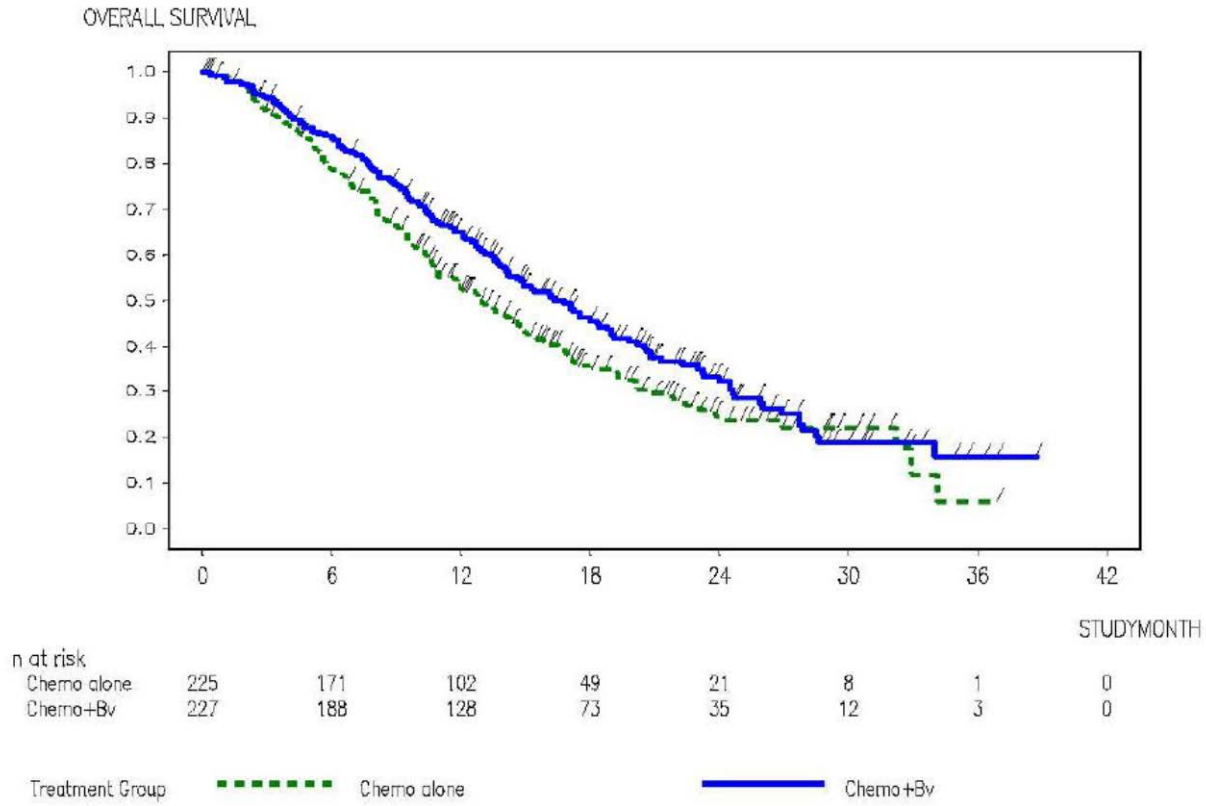


Figure 2: Kaplan-Meier Curve of Overall Survival by Bevacizumab Treatment

A follow up overall survival (OS) analysis with a clinical cut-off date of 7 March 2014, has been performed and results are presented in Table 6.

Table 6: Efficacy results from study GOG-0240 by Bevacizumab Treatment (ITT population)

	Chemo alone (N=225)		Chemo+Bv (N=227)
Patients with event	180 (80.0 %)		170 (74.9 %)
Patients without events*	45 (20.0 %)		57 (25.1 %)
Time to event (months)			
Median#	13.3		16.8
95% CI for Median#	[10.9;15.8]		[14.8;19.0]
25% and 75%-ile	6.9;26.9		9.2;34.0
Range##	0.0 to 52.2		0.1 to 55.9
p-Value (Log-Rank Test)		0.0126	
Hazard Ratio		0.76	
95% CI		[0.62;0.94]	

Note: log-rank test (stratified), p-value displayed for descriptive purpose only

A number of OS analyses have been submitted by the applicant and are presented in the following tables and figures.

Table 7: Overall Survival Stratified Analysis by Chemotherapy Backbone

	Cis+Pac+/-Bv (N=229)		Top+Pac+/-Bv (N=223)
Patients with event	141 (61.6 %)		147 (65.9 %)
Patients without events*	88 (38.4 %)		76 (34.1 %)
Time to event (months)			
Median#	15.5		13.3
95% CI for Median#	[13.6;19.2]		[11.8;16.2]
25% and 75%-ile	8.2;27.7		7.9;23.9
Range##	0.1 to 36.3		0.0 to 38.7
p-Value (Log-Rank Test)		0.2326	
Hazard Ratio		1.15	
95% CI		[0.91;1.46]	

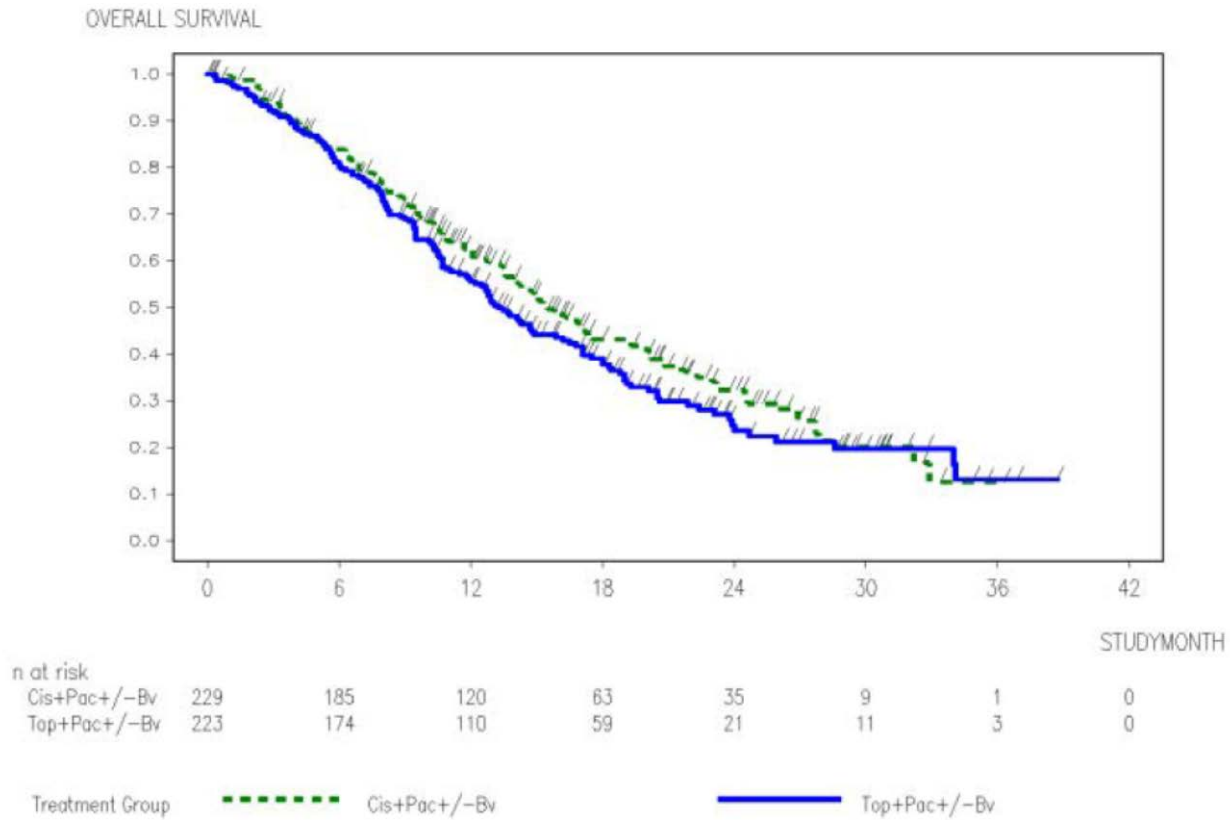


Figure 3: Kaplan-Meier Curve of Overall Survival by Chemotherapy Backbone

Table 8: Overall Survival Stratified Analysis by Trial Treatment (primary analysis and follow-up analysis)

Treatment Comparison	Other Factor	Overall survival – Primary analysis[1] Hazard Ratio (95% CI)	Overall survival - Follow-up analysis[2] Hazard Ratio (95% CI)
Avastin vs. No Avastin	Cisplatin+ Paclitaxel	0.72 (0.51, 1.02) (17.5 vs.14.3 months; p = 0.0609)	0.75 (0.55, 1.01) (17.5 vs.15.0 months; p = 0.0584)
	Topotecan+ Paclitaxel	0.76 (0.55, 1.06) (14.9 vs. 11.9 months; p = 0.1061)	0.79 (0.59, 1.07) (16.2 vs. 12.0 months; p = 0.1342)
Topotecan+ Paclitaxel vs. Cisplatin+ Paclitaxel	Avastin	1.15 (0.82, 1.61) (14.9 vs. 17.5 months; p = 0.4146)	1.15 (0.85, 1.56) (16.2 vs 17.5 months; p = 0.3769)
	No Avastin	1.13 (0.81, 1.57) (11.9 vs.14.3 months; p = 0.4825)	1.08 (0.80, 1.45) (12.0 vs 15.0 months; p = 0.6267)

[1] Primary analysis was performed with a data cut-off date of 12 December 2012 and is considered the final analysis

[2] Follow-up analysis was performed with a data cut-off date of 07 March 2014; all p-values are displayed for descriptive purpose only.

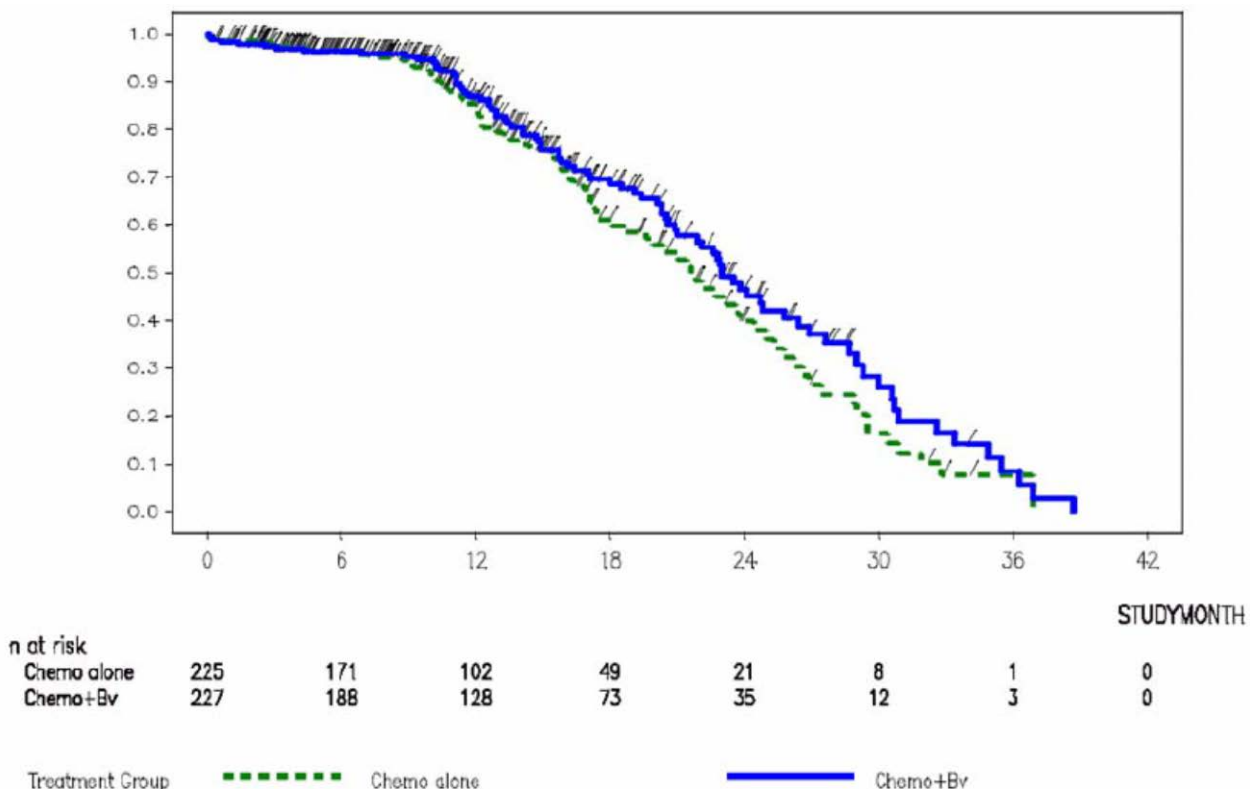


Figure 4: Kaplan-Meier Curve of the Time to Censoring for OS by Bevacizumab treatment

Table 9: Multiple Cox Regression for Overall Survival by Bevacizumab Treatment

Effect/ Covariate included in the Model	Hazard Ratio	95% CI for Hazard Ratio	p-Value
Bevacizumab	0.68	[0.53;0.87]	0.0019
Age (<50 vs all other)	0.66	[0.42;1.01]	0.0562
Age (50-65 vs all other)	0.50	[0.32;0.79]	0.0033
Race (white vs non-white)	0.88	[0.66;1.19]	0.4125
Performance status (1 vs 0)	1.70	[1.32;2.19]	<.0001
Never smoked vs all other	0.80	[0.59;1.08]	0.1448
Past smoker vs all other	0.96	[0.71;1.29]	0.7790
FIGO stage 1 vs all other	0.64	[0.40;1.04]	0.0711
FIGO stage 2 vs all other	0.95	[0.61;1.48]	0.8064
FIGO stage 3 vs all other	0.89	[0.57;1.41]	0.6224
Adenocarcinoma vs all other	1.28	[0.38;4.31]	0.6865
Adenosquamous vs all other	1.95	[0.57;6.72]	0.2909
Squamous Cell Carcinoma vs all other	1.51	[0.46;4.97]	0.4969
Disease status (RC vs Stage IVB)	1.15	[0.50;2.61]	0.7452
Number of metastatic sites (1-2 vs >2)	0.70	[0.53;0.93]	0.0151
Prior syst. chemoth. (yes vs no)	1.20	[0.15;9.60]	0.8603
Prior hormone therapy (yes vs no)	1.41	[0.43;4.64]	0.5738
Prior radiotherapy (yes vs no)	1.13	[0.54;2.38]	0.7448
Prior platinum therapy (yes vs no)	0.89	[0.12;6.67]	0.9076
TT 1st rec/prog (6-18 mo vs all other)	1.62	[1.08;2.43]	0.0194
TT 1st rec/prog (>18 mo vs all other)	0.91	[0.57;1.45]	0.6988
Platinum free intvl (<6 mo vs all other)	1.84	[1.31;2.59]	0.0005
Site rec after radioth (yes vs no/miss)	1.21	[0.93;1.59]	0.1567
Platinum Treated (yes vs no)	0.75	[0.59;0.96]	0.0225

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

Secondary endpoints

Progression-Free Survival

Table 10: Summary of Progression-Free Survival Stratified Analysis by Bevacizumab Treatment

	Chemo alone (N=225)		Chemo+Bv (N=227)
Patients with event	195 (86.7 %)		190 (83.7 %)
Patients without events*	30 (13.3 %)		37 (16.3 %)
Time to event (months)			
Median#	6.0		8.3
95% CI for Median#	[5.2;6.9]		[7.1;9.7]
25% and 75%-ile	2.7;10.5		4.3;13.6
Range##	0.0 to 31.1		0.0 to 35.5
p-Value (Log-Rank Test)		<.0001	
Hazard Ratio		0.66	
95% CI		[0.54;0.81]	

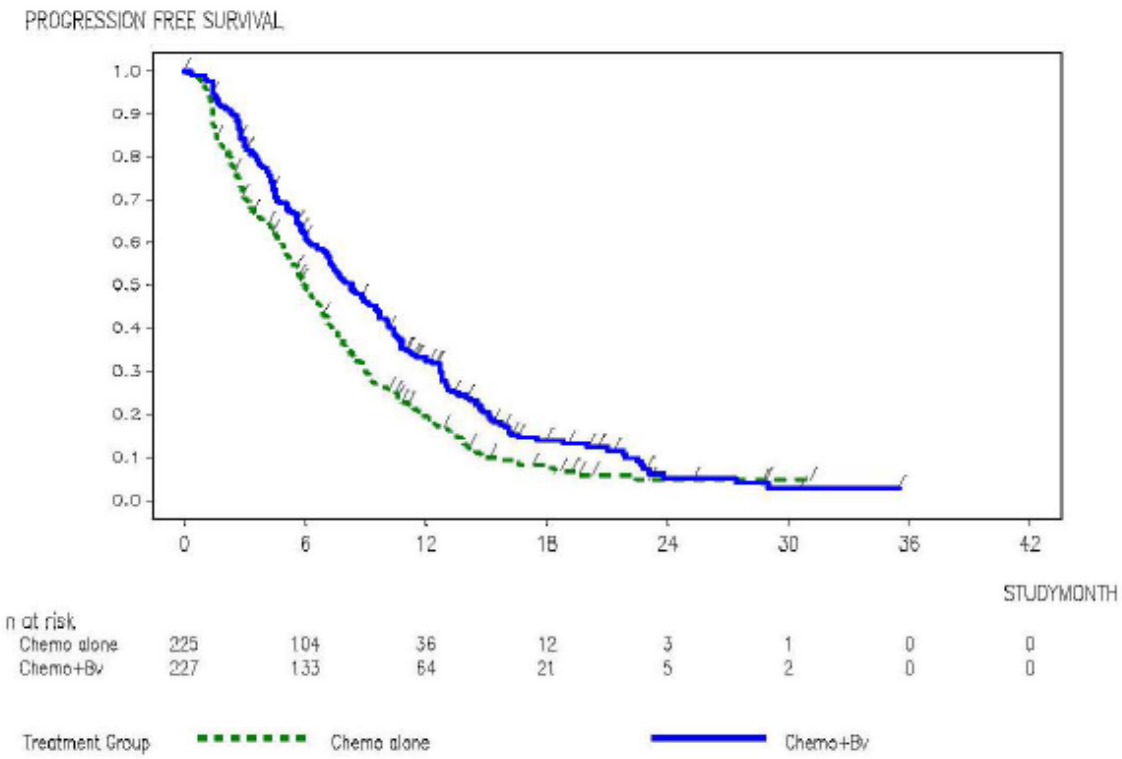


Figure 5: Kaplan-Meier Curve of Progression-Free Survival by Bevacizumab Treatment

Table 11: Progression-Free Survival Stratified Analysis by Chemotherapy Backbone

	Cis+Pac+/-Bv (N=229)		Top+Pac+/-Bv (N=223)
Patients with event	192 (83.8 %)		193 (86.5 %)
Patients without events*	37 (16.2 %)		30 (13.5 %)
Time to event (months)			
Median#	7.9		5.8
95% CI for Median#	[6.6;8.8]		[5.2;7.1]
25% and 75%-ile	4.2;12.8		2.8;11.6
Range##	0.0 to 35.5		0.0 to 30.6
p-Value (Log-Rank Test)		0.0290	
Hazard Ratio		1.26	
95% CI		[1.02;1.54]	

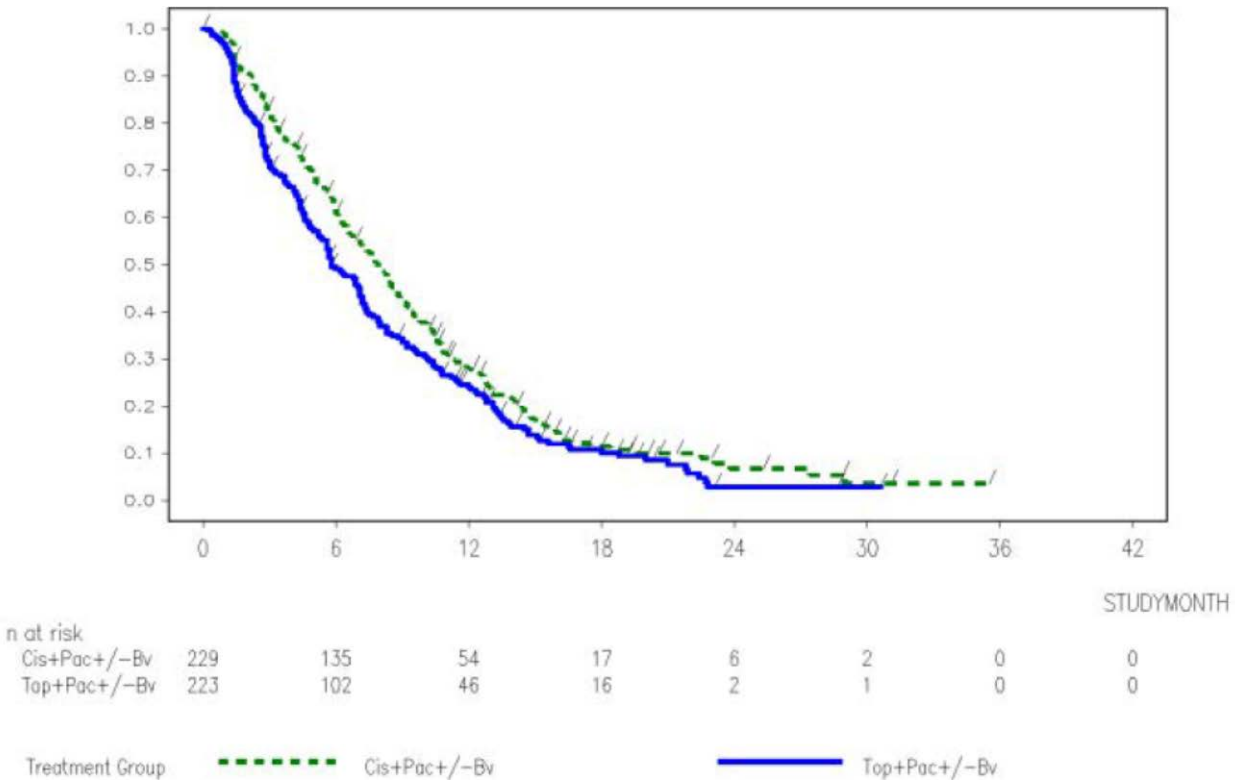


Figure 6: Kaplan-Meier Curve of Progression-Free Survival by Chemotherapy Backbone

Table 12: Progression-Free Survival Stratified Analysis by Trial Treatment

Treatment Comparison	Other Factor	Hazard Ratio (95% CI) Median PFS (months); p-values
Bevacizumab vs. No Bevacizumab	Topotecan+Paclitaxel	0.71 (0.53;0.95) 7.4 vs. 4.9; p=0.0226
	Cisplatin+Paclitaxel	0.57 (0.42;0.78) 9.1 vs. 6.9; p=0.0003
Topotecan+Paclitaxel vs. Cisplatin+Paclitaxel	Bevacizumab	1.34 (1.00, 1.79) 7.4 vs. 9.1; p=0.0513
	No Bevacizumab	1.20 (0.90, 1.60) 4.9 vs. 6.9; p=0.2135

Sensitivity analyses for PFS included censoring for NPT prior to disease progression, time to treatment failure, and subgroup analyses for patients who did or did not receive prior platinum chemotherapy.

Table 13: Progression-Free Survival Unstratified Analysis Censored for NPT Prior to Disease Progression by Bevacizumab Treatment

	Chemo alone (N=225)		Chemo+Bv (N=227)
Patients with event	180 (80.0 %)		175 (77.1 %)
Patients without events*	45 (20.0 %)		52 (22.9 %)
Time to event (months)			
Median#	6.0		8.3
95% CI for Median#	[5.2;6.9]		[7.1;9.7]
25% and 75%-ile	2.7;9.8		4.3;13.1
Range##	0.0 to 31.1		0.0 to 35.5
p-Value (Log-Rank Test)		0.0020	
Hazard Ratio		0.72	
95% CI		[0.59;0.89]	

Table 14: Progression-Free Survival Unstratified Analysis Censored for NPT Prior to Disease Progression by Chemotherapy Backbone Ancillary analyses

	Cis+Pac+/-Bv (N=229)		Top+Pac+/-Bv (N=223)
Patients with event	175 (76.4 %)		180 (80.7 %)
Patients without events*	54 (23.6 %)		43 (19.3 %)
Time to event (months)			
Median#	7.9		5.8
95% CI for Median#	[6.7;8.8]		[5.2;7.1]
25% and 75%-ile	4.3;12.7		2.8;11.5
Range##	0.0 to 35.5		0.0 to 30.6
p-Value (Log-Rank Test)		0.0455	
Hazard Ratio		1.23	
95% CI		[1.00;1.52]	

Table 15: Time to Treatment Failure Unstratified Analysis by Trial Treatment

	Cis+Pac (N=114)	Cis+Pac+Bv (N=115)	Top+Pac (N=111)	Top+Pac+Bv (N=112)
Patients included in analysis	114 (100.0 %)	114 (100.0 %)	111 (100.0 %)	112 (100.0 %)
Patients with event	113 (99.1 %)	107 (93.9 %)	107 (96.4 %)	110 (98.2 %)
Patients without events*	1 (0.9 %)	7 (6.1 %)	4 (3.6 %)	2 (1.8 %)
Time to event (months)				
Median#	4.4	4.5	3.9	4.9
95% CI for Median#	[3.7;5.5]	[3.9;5.3]	[2.8;4.6]	[3.8;5.7]
25% and 75%-ile	2.3;7.1	2.3;6.6	1.2;6.5	2.3;8.1
Range##	0.0 to 18.4	0.0 to 23.1	0.0 to 21.4	0.0 to 30.9
p-Value (Log-Rank Test)		0.3427	0.9343	0.0396
Hazard Ratio		0.88	1.01	0.76
95% CI		[0.67;1.15]	[0.77;1.32]	[0.58;0.99]

Table 16: Progression-Free Survival for Patients Who Did or Did Not Receive Prior Platinum Unstratified Analysis by Chemotherapy Backbone

Patients who received prior Platinum

	Cis+Pac+/-Bv (N=172)		Top+Pac+/-Bv (N=161)
Patients with event	148 (86.0 %)		142 (88.2 %)
Patients without events*	24 (14.0 %)		19 (11.8 %)
Time to event (months)			
Median#	7.6		5.6
95% CI for Median#	[6.0;8.8]		[4.5;6.4]
25% and 75%-ile	3.6;12.0		2.7;10.8
Range##	0.0 to 35.5		0.0 to 30.6
p-Value (Log-Rank Test)		0.0744	
Hazard Ratio		1.23	
95% CI		[0.98;1.55]	

Patients who did not receive prior Platinum

	Cis+Pac+/-Bv (N=57)		Top+Pac+/-Bv (N=62)
Patients with event	44 (77.2 %)		51 (82.3 %)
Patients without events*	13 (22.8 %)		11 (17.7 %)
Time to event (months)			
Median#	8.8		7.9
95% CI for Median#	[7.2;12.5]		[6.3;10.4]
25% and 75%-ile	5.9;15.1		4.2;13.3
Range##	1.0 to 31.1		0.6 to 23.1
p-Value (Log-Rank Test)		0.2112	
Hazard Ratio		1.29	
95% CI		[0.86;1.95]	

Overall Response Rate

Table 17: Best Overall Response (Derived) by Bevacizumab Treatment

	Chemo alone (N=225)		Chemo+Bv (N=227)
Responders$	76 (33.8 %)		103 (45.4 %)
Non-Responders	149 (66.2 %)		124 (54.6 %)
95% CI for Response Rates*	[27.6; 40.4]		[38.8; 52.1]
Difference in Response Rates		11.60	
95% CI for Difference in Response Rates#		[2.4; 20.8]	
p-Value (Chi-squared Test)		0.0117	
p-Value (2-sided Fishers Exact Test)		0.0126	
Complete Response (CR)	9 (4.0 %)		19 (8.4 %)
95% CI for CR Rates*	[1.8; 7.5]		[5.1; 12.8]
Partial Response (PR)	67 (29.8 %)		84 (37.0 %)
95% CI for PR Rates*	[23.9; 36.2]		[30.7; 43.6]
Stable Disease (SD)	74 (32.9 %)		62 (27.3 %)
95% CI for SD Rates*	[26.8; 39.4]		[21.6; 33.6]
Progressive Disease (PD)	56 (24.9 %)		29 (12.8 %)
95% CI for PD Rates*	[19.4; 31.1]		[8.7; 17.8]
Missing (No Response Assessment)	19 (8.4 %)		33 (14.5 %)

* 95% CI for one sample binomial using Pearson-Clopper method

Table 18: Best Overall Response (Derived) by Trial Treatment

	Cis+Pac (N=114)	Cis+Pac+Bv N=115)	Top+Pac (N=111)	Top+Pac+Bv (N=112)
Responders$	49 (43.0 %)	54 (47.0 %)	27 (24.3 %)	49 (43.8 %)
Non-Responders	65 (57.0 %)	61 (53.0 %)	84 (75.7 %)	63 (56.3 %)
95% CI for Response Rates*	[33.7; 52.6]	[37.6; 56.5]	[16.7; 33.4]	[34.4; 53.4]
Difference in Response Rates		3.97		19.43
95% CI for Difference in Response Rates#		[-9.4; 17.3]		[6.8; 32.1]
p-Value (Chi-squared Test)		0.5456		0.0022
p-Value (2-sided Fishers Exact Test)		0.5959		0.0029
Complete Response (CR)	5 (4.4 %)	10 (8.7 %)	4 (3.6 %)	9 (8.0 %)
95% CI for CR Rates*	[1.4; 9.9]	[4.2; 15.4]	[1.0; 9.0]	[3.7; 14.7]
Partial Response (PR)	44 (38.6 %)	44 (38.3 %)	23 (20.7 %)	40 (35.7 %)
95% CI for PR Rates*	[29.6; 48.2]	[29.4; 47.8]	[13.6; 29.5]	[26.9; 45.3]
Stable Disease (SD)	33 (28.9 %)	31 (27.0 %)	41 (36.9 %)	31 (27.7 %)
95% CI for SD Rates*	[20.8; 38.2]	[19.1; 36.0]	[28.0; 46.6]	[19.6; 36.9]
Progressive Disease (PD)	23 (20.2 %)	16 (13.9 %)	33 (29.7 %)	13 (11.6 %)
95% CI for PD Rates*	[13.2; 28.7]	[8.2; 21.6]	[21.4; 39.1]	[6.3; 19.0]
Missing (No Response Assessment)	9 (7.9 %)	14 (12.2 %)	10 (9.0 %)	19 (17.0 %)

Health-related quality of life (HRQOL)

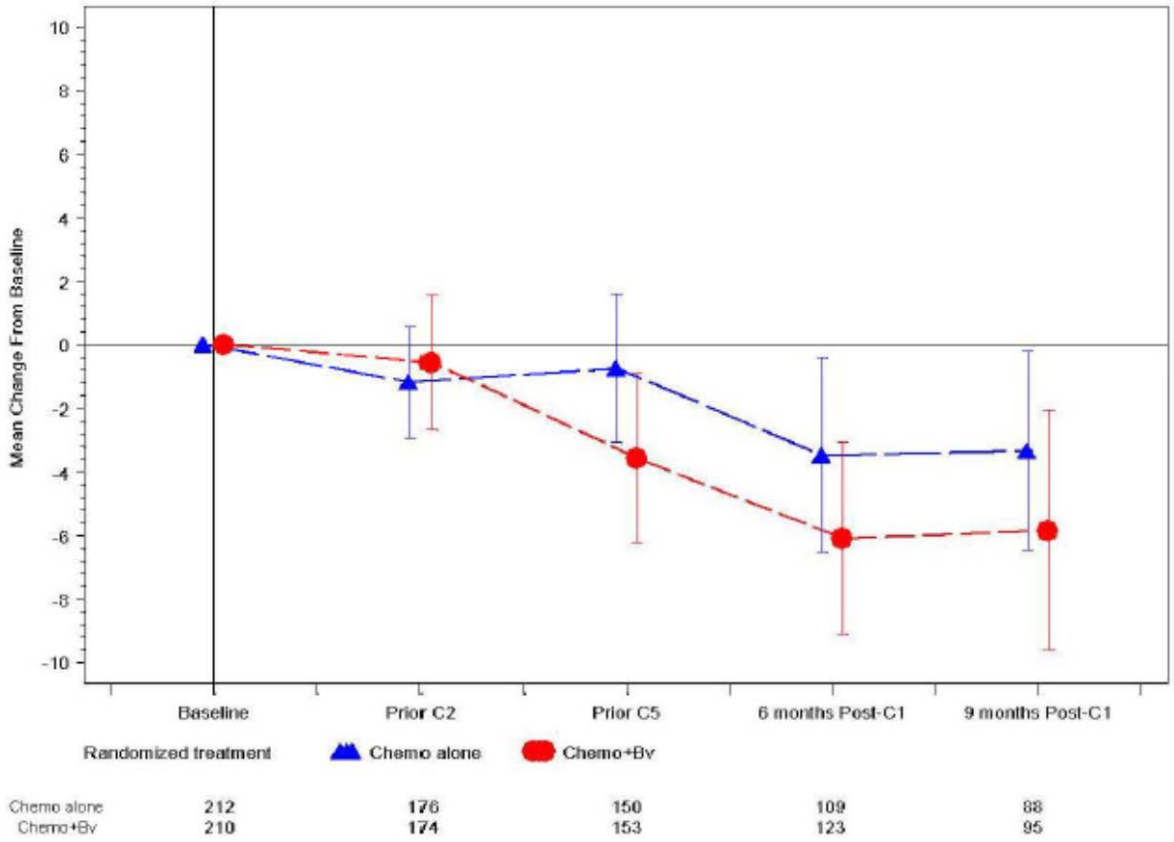


Figure 7: Plot of Change from Baseline in FACT-Cx TOI Score by Visit

Ancillary analyses

- Subgroup analyses

Subgroup analyses for PFS and OS are shown in the following figures.

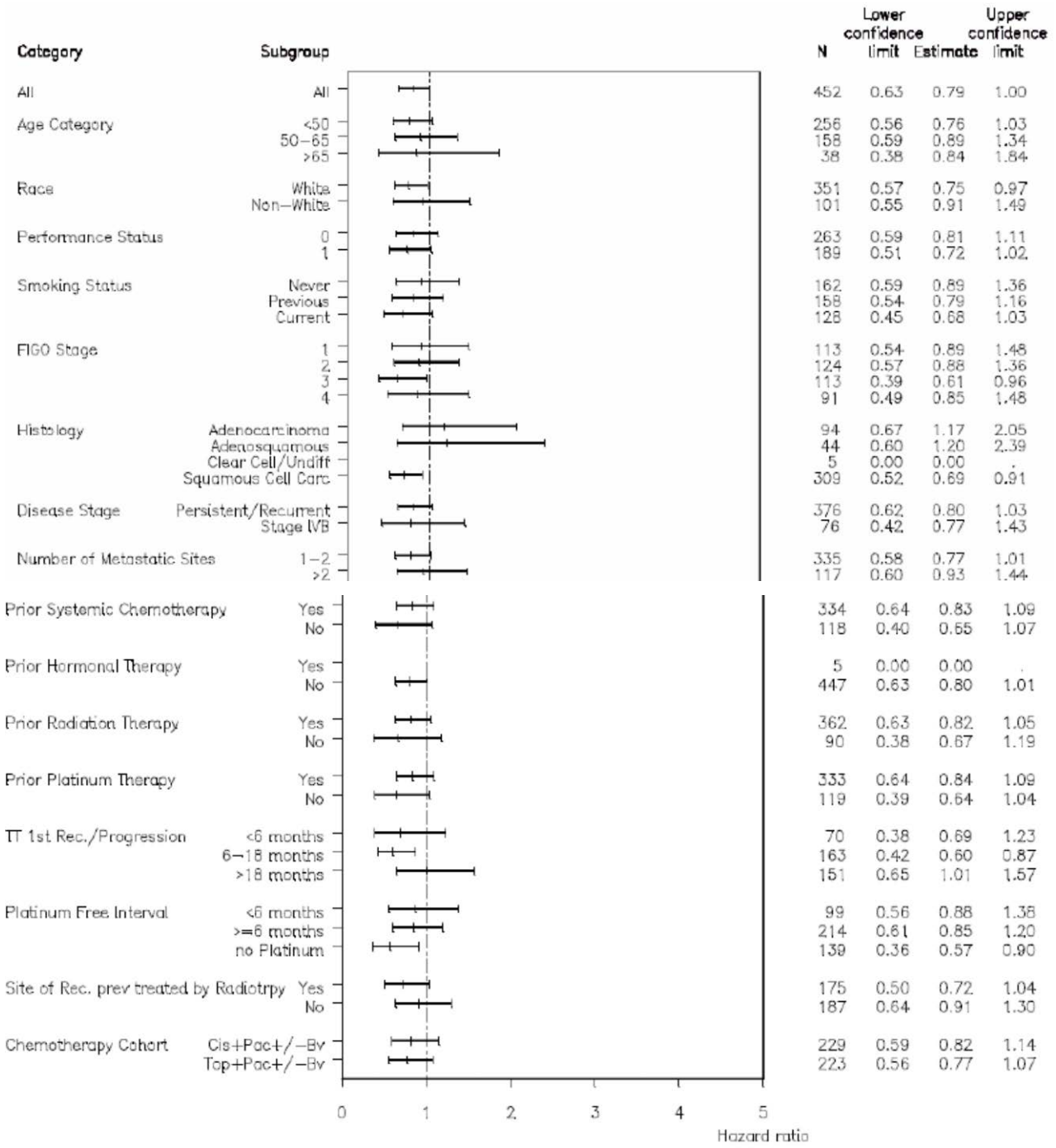


Figure 8: Forest Plot Overall Survival by Bevacizumab Treatment and Subgroup

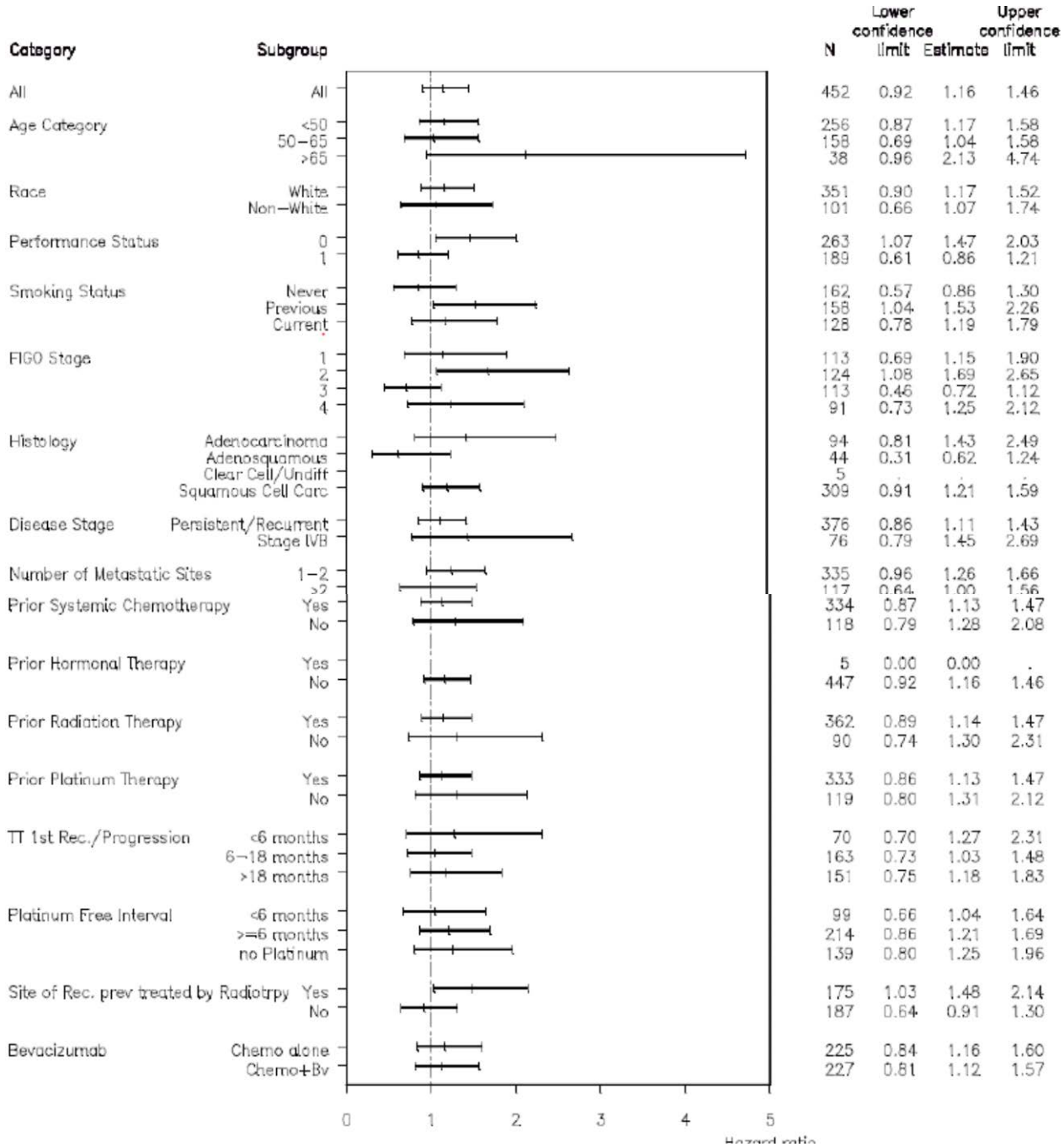


Figure 9: Forest Plot of Overall Survival by Chemotherapy Backbone and Subgroup

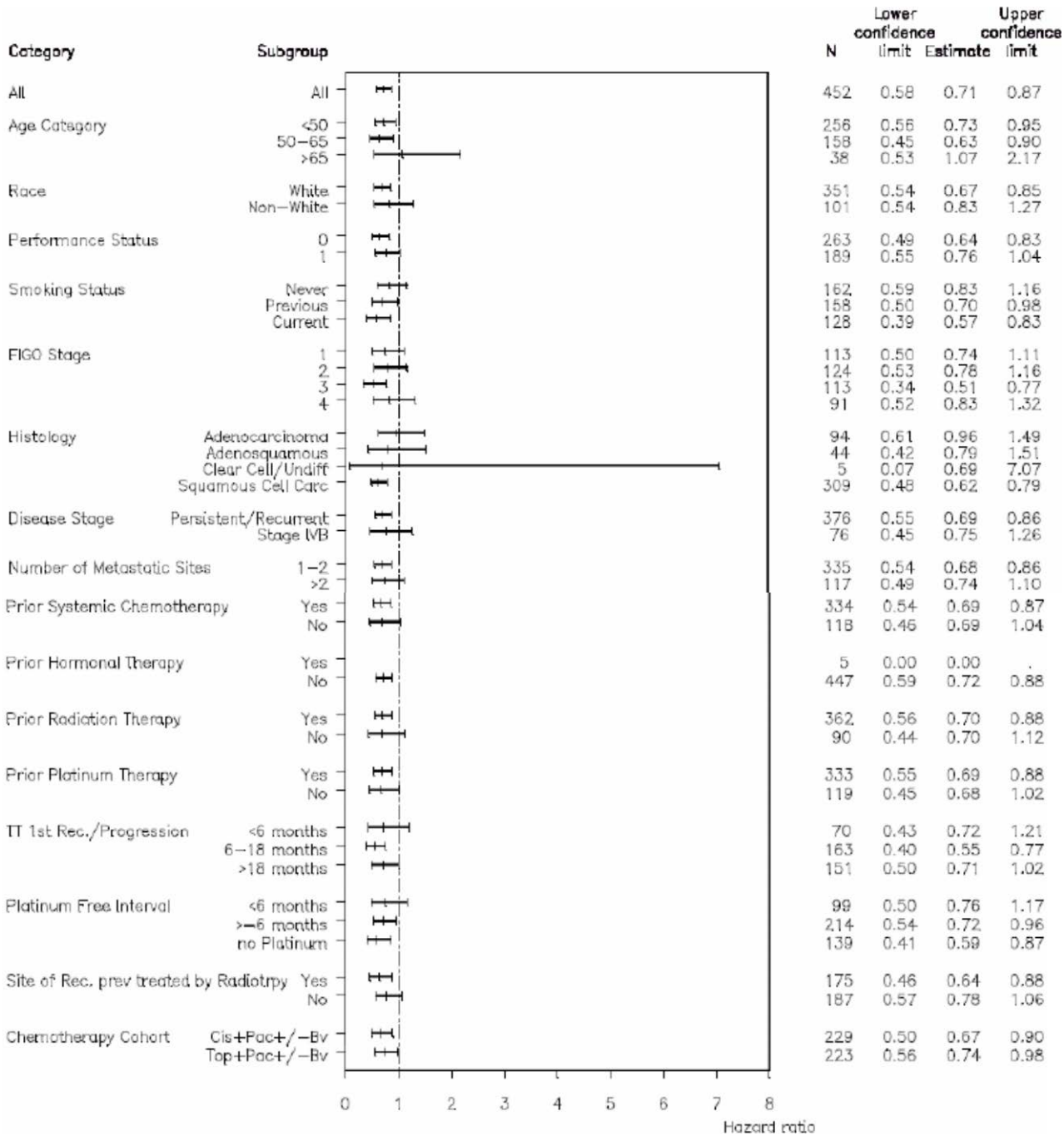


Figure 10: Forest Plot of PFS by Bevacizumab Treatment and Subgroup

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 19: Summary of Efficacy for trial Study GOG-0240

Title: Study GOG-0240 (also known by Study ML01230) is a Phase III, randomized, open-label, multicenter study designed to evaluate the efficacy and safety of chemotherapy in combination with bevacizumab compared with chemotherapy alone in patients with persistent, recurrent, or stage IVB carcinoma of the cervix		
Study identifier	GOG-0240 also known as study ML01230	
Design	Phase III, randomized, open-label, multicenter study	
	Period of trial Duration of main phase:	Study open to accrual 6 April 2009 to 3 January 2012 (last patient randomized) 6 April 2009 to 12 December 2012 (clinical database cutoff for all analyses)
	Duration of Extension phase:	Follow up analysis: clinical data cut-off 7 March 2014
Hypothesis	Superiority trial	
Treatments groups	Regimen I	Cisplatin + Paclitaxel At the discretion of the investigator, patients received one of 3 options: Pac 135 mg/m^2 IV over 24 hours on Day 1 and Cis 50 mg/m^2 IV on Day 2 (q3w); or Pac 175 mg/m^2 IV over 3 hours on Day 1 and Cis 50 mg/m^2 IV on Day 2 (q3w); or Pac 175 mg/m^2 IV over 3 hours on Day 1 and Cis 50 mg/m^2 IV on Day 1 (q3w) (114 randomized patients)
	Regimen II	Cisplatin + Paclitaxel + Bevacizumab At the discretion of the investigator, patients received one of 3 options: Pac 135 mg/m^2 IV over 24 hours on Day 1 and Cis 50 mg/m^2 IV on Day 2 plus Bv 15 mg/kg IV on Day 2 every 3 weeks (q3w); or Pac 175 mg/m^2 IV over 3 hours on Day 1 and Cis 50 mg/m^2 IV on Day 2 plus Bv 15 mg/kg IV on Day 2 (q3w); or Pac 175 mg/m^2 IV over 3 hours on Day 1 and Cis 50 mg/m^2 IV on Day 1 and Bv 15 mg/kg IV on Day 1 (q3w) (115 randomized patients)
	Regimen III	Topotecan + Paclitaxel Pac 175 mg/m^2 over 3 hours on Day 1 and Top 0.75 mg/m2 over 30 minutes on Days 1–3 (q3w) (111 randomized patients)

	Regimen IV	Topotecan + Paclitaxel + Bevacizumab Pac 175 mg/m^2 over 3 hours on Day 1 and Top 0.75 mg/m^2 over 30 minutes on Days 1−3 plus Bv 15 mg/kg IV on Day 1 (q3w) (112 randomized patients)
Endpoints and definitions	Overall survival	time from randomization until death from any cause
	Progression-Free Survival	time between the date of randomization and the date of first documented disease progression or death, whichever occurred first
	Objective Response Rate by Investigator Assessment	percentage of patients who had objective response defined as a complete or partial overall response determined on two consecutive investigator assessments ≥ 4 weeks apart, in patients with measurable disease at baseline
Database lock	17 October 2013	

Results and Analysis

Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat Population		
Descriptive statistics and estimate variability	**Treatment group**	**Chemo alone (pooled)**	**Chemo + Bv (pooled)**
	Number of subjects	225	227
	Median OS (months)	12.9 [10.9;15.0]	16.8 [14.1;19.0]
	Hazard ratio [95% CI]	0.74 [0.58;0.94] (p-value= 0.0132)	
	Median PFS (months)	6.0 [5.2;6.9]	8.3 [7.1;9.7]
	Hazard ratio [95% CI]	0.66 [0.54;0.81] (p-value <0.0001)	
	Best Overall Rate: Responders (%) [95% CI]	76 (33.8%) [27.6;40.4]	103 (45.4%) [38.8;52.1]

	Diff in rates[95% CI], p-value (chi-squared)	11.6[2.4;20.8] (p-value=0.0117)	
Analysis description	**Overall Survival Analysis by <u>Chemotherapy Backbone</u>**		
	Treatment group	Cisplatin + Paclitaxel +/- Bevacizumab	Topotecan + Paclitaxel +/- Bevacizumab
	Number of subject	229	223
	Median OS (months)	15.5 [13.6;19.2]	13.3 [11.8;16.2]
	Hazard ratio [95% CI]	1.15 [0.91;1.46] (p-value= 0.2326)	
	Median PFS (months)	7.9 [6.6;8.8]	5.8 [5.2;7.1]
	Hazard ratio [95% CI]	1.26 [1.02;1.54] (p-value=0.0290)	
	Best Overall Rate: Responders (%) [95% CI]	103 (45.0%) [38.4;51.7]	76(34.1%) [27.9;40.7]
	Diff in rates[95% CI], p-value (chi-squared)	-10.90[-20.1;-1.7] (p-value=0.0179)	
	Other: Overall Survival Analysis by Trial Treatment		
	Treatment comparison	Other factor	Hazard ratio [95%CI] Median OS (months);p-value
	Bevacizumab vs. No Bevacizumab	Topotecan + Paclitaxel	0.76 [0.55;1.06] 14.9 vs. 11.9; p=0.1061
		Cisplatin + Paclitaxel	0.72 [0.51;1.02] 17.5 vs.14.3; p=0.0609
	Topotecan + Paclitaxel vs. Cisplatin + Paclitaxel	Bevacizumab	1.15 [0.82;1.61] 14.9 vs. 17.5; p=0.4146
		No Bevacizumab	1.13 [0.81;1.57] 11.9 vs. 14.3; p=0.4825

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

Not applicable.

Clinical studies in special populations

No clinical studies in special populations have been submitted.

Supportive study

No supportive studies have been submitted.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

No dose-finding studies were submitted. In study GOG-0240, the dose of bevacizumab 15 mg/kg IV every 3 weeks (q3w) was selected as earlier evidence from Study GOG-0227C with bevacizumab monotherapy dosed at 15 mg/kg IV q3w in patients with recurrent cervical cancer demonstrated that bevacizumab was well tolerated and active. Furthermore, previous clinical trial experience in the metastatic cervical cancer setting demonstrated clinical activity and acceptable safety when bevacizumab was dosed at 15 mg/kg IV q3w in combination with cytotoxic chemotherapy. A dose of bevacizumab 10 mg/kg IV every 2 weeks (q2w) or bevacizumab 15 mg/kg IV q3w, which is equivalent to a dose of 5 mg/kg/week, is the most commonly used dose of bevacizumab that has been shown to be effective and safe when added to chemotherapy regimens in solid tumours.

Cisplatin plus paclitaxel (Cis+Pac) or topotecan plus paclitaxel (Top+Pac) were selected as chemotherapeutic combination partners since earlier studies provided evidence of higher response rates and longer duration of remission in advanced disease. Doses of chemotherapy were used in accordance with previous published studies and in accordance with approved labelling information. At the discretion of the investigator, patients received one of 2 options for their paclitaxel dosing regimen (paclitaxel 135 mg/m^2 IV over 24 hours or paclitaxel 175 mg/m^2 IV over 3 hours). Both doses of paclitaxel are considered equivalent; no evidence of a difference between short and long infusions in terms of OS, PFS, and tumour response was noted in a meta-analysis by the Cochrane Gynaecological Cancer Group, and in most cases a greater proportion of adverse events (AEs) and toxicity occurred in the 24-hour infusion group compared with the 3-hour group.

Study GOG-0240 was designed to test both the relative efficacy and safety of two chemotherapy combinations (i.e. cisplatin-paclitaxel versus topotecan-paclitaxel) that have never been directly compared in this setting, and the potential additional effect of adding bevacizumab to these two combinations. The study was generally well-conducted and enrolled 452 patients (women aged ≥18 years) with persistent, recurrent or Stage IVB carcinoma of the cervix with measurable disease, a GOG PS 0 vs.1, no prior chemotherapy other than with radiation and no prior anti-VEGF drug (see SmPC section 5.1).

The baseline characteristics were well-balanced, however, only few patients were over 65 years. Also, the majority of the patients had squamous cell carcinoma, persistent/recurrent disease, 1-2 metastatic sites, lymph node involvement, and more than 6 months of platinum free interval.

The comparison of chemotherapy + bevacizumab vs. chemotherapy is acknowledged. The comparison of topotecan + paclitaxel + bevacizumab vs. cisplatin + paclitaxel + bevacizumab is relevant and supported. Topotecan is an option for patients who cannot tolerate cisplatin, e.g. due to acquired drug resistance making platinum-based therapies less effective or due to unacceptable adverse events profile. The study design (2 x 2 factorial design) was pre-specified in the protocol and only powered for the pooled analysis. The factorial study design has shown to be very valuable for large mortality trials. More importantly, this study design depends on the assumption that there is no interaction between bevacizumab and the chemotherapy backbones. The HRs for bevacizumab vs. no bevacizumab and topotecan vs. cisplatin are considered comparable. There is no indication of any interaction.

The dose of bevacizumab, cisplatin, topotecan and paclitaxel all reflect current standards. The primary objective of the study was to demonstrate superiority with regard to OS. PFS and Overall Response were secondary endpoints. These secondary endpoints were assessed based only on investigator assessment using the GOG RECIST v1.0 criteria. Health-related quality of life (HRQoL) was also assessed using various scales. Interpretation of these secondary endpoints is hampered by the open-label nature of the study and the lack of a central, blinded review.

There were in general few protocol amendments and violations.

Regarding the release of results from the second interim analysis by the DSMB to both patients and investigators approximately 8-9 months before the data cut-off date, there seems to be no solid evidence for any operational bias. After this analysis it was communicated to both patients enrolled into the trial and all investigators that the topotecan-containing regimens were not superior to the cisplatin-containing regimens. No data on the potential additional effect of bevacizumab to either combination was released at that time. In addition, although the numbers were small, reasons for treatment discontinuation were comparable between the different treatment arms, and more or less comparable between the first Interim Analysis and the final analyses (data not shown).

Efficacy data and additional analyses

The primary endpoint of this study is OS, which is considered a robust and hard endpoint. The main analysis shows a HR=0.74 (95%CI: 0.58, 0.94; p=0.0132), with a difference in median OS of 3.9 months (12.9 months vs. 16.8 months) in favour of chemotherapy + bevacizumab. This improvement is larger than the findings from the OS analysis by backbone regimen (i.e. cisplatin + paclitaxel vs. topotecan + paclitaxel), which indicated that adding bevacizumab to either regimen leads to a non-statistically significant increase in OS of 3-3.2 months. The follow-up OS analyses were in line with the primary OS analyses (cut-off 12 December 2012), and provided evidence that the effect of bevacizumab is maintained when late events are taken into consideration.

The fact that adding bevacizumab results in a slightly lower median OS increase in the analysis by treatment arm compared with the pooled analysis (approximately 1 month) is mainly caused by the lower median OS of the topotecan containing regimens versus the cisplatin regimens. The topotecan containing regimens performed slightly worse compared with the cisplatin containing regimens (-2.2 months OS difference), though this difference was not statistically significant. These findings may trigger reservations against the pooling of the data, but this is not justified when taking the totality of data and evidence into consideration. Furthermore, the HRs in the individual chemotherapy arms were in line with the overall estimate.

Although a numerical difference in favour of cisplatin was observed in the OS analysis by chemotherapy, the number of responders was comparable between cisplatin + paclitaxel + bevacizumab and topotecan + paclitaxel + bevacizumab (ORR-analysis). Therefore, it is concluded that the combination of topotecan + paclitaxel + bevacizumab is a valuable alternative for patients that cannot be treated with cisplatin (see SmPC section 4.1).

Furthermore, ORR results are not in line with the OS results that were slightly more favourable in the cisplatin-arms (+/- bevacizumab) compared with the topotecan-arms (+/- bevacizumab) (see above). However, there are clear indications that the addition of bevacizumab to the topotecan + paclitaxel arm and the addition of bevacizumab to the cisplatin + paclitaxel arm resulted in rather similar benefits in ORR, PFS and OS.

The results of the OS subgroup analysis were in general consistent with the overall estimate although patients with squamous cell carcinoma seemed to have a better effect of bevacizumab compared with patients with adenocarcinoma and adenosquamous carcinoma. However, there is great uncertainty related to these data, which is reflected in the wide CIs. The subgroup analysis was of exploratory nature, the numbers were small and the issue of multiplicity was not controlled in this setting. Therefore, there is at present no convincing statistical evidence for any different responses to systemic therapy in patients with recurrent or metastatic cervical cancer based on histological subgroups.

The PFS results support OS and there seems to be no deterioration of QoL by the addition of bevacizumab to chemotherapy.

2.4.3. Conclusions on the clinical efficacy

The study GOG-0240 provides evidence for the effect of bevacizumab + chemotherapy in the treatment of patients with persistent, recurrent, or metastatic carcinoma of the cervix. An increase in median survival of 3.9 months is considered clinically relevant. OS by chemotherapy did not show any statistically significant result, but a numerical difference in favour of cisplatin was observed. However, the number of responders was comparable between cisplatin + paclitaxel + bevacizumab and topotecan + paclitaxel + bevacizumab arms. Therefore, it is concluded that the combination of topotecan + paclitaxel + bevacizumab is a valuable alternative for patients that cannot be treated with cisplatin (see SmPC section 4.1).

2.5. Clinical safety

2.5.1. Introduction

For the safety analyses, the clinical cut-off date for this report was 12 December 2012, with a database lock of 17 October 2013. The safety analyses were based on the safety population. The denominator used in the analyses was based on the treatment actually received by the patient rather than the treatment to which patients were randomized. From the randomized population, 12 patients did not receive any treatment, and 2 patients randomized to the bevacizumab arm did not receive any bevacizumab, so were part the chemotherapy alone arm for the safety analyses. The primary safety analyses were conducted to evaluate the safety of bevacizumab plus chemotherapy in comparison to chemotherapy alone. Additional analyses were performed to examine the safety of platinum vs. non-platinum treatment groups and by trial treatment arms.

Patient exposure

Chemotherapy + Bevacizumab exposure

The overall median duration of exposure (i.e., duration based on the start date of the first component and the last date of protocol therapy from the treatment completion form) was 17.9 weeks in the Chemo alone group and 20.7 weeks in the Chemo+Bv group (Table 20). The median duration of exposure of

bevacizumab was 17.6 weeks in the Chemo+Bv group, and the median durations of the individual chemotherapy components were comparable between the Chemo alone and Chemo+Bv groups or slightly longer in the Chemo+Bv group.

Table 20: Duration of Exposure to Trial Treatment by Bevacizumab Treatment

Duration (weeks)	Chemo alone (N=222)	Chemo+Bv (N=218)
Overall		
Mean	20.1	23.3
SD	16.03	19.20
Median	17.9	20.7
Min - Max	0.1 - 92.1	0.1 - 133.6
n	222	218
Bevacizumab		
Mean		21.1
SD		18.12
Median		17.6
Min - Max	-	0.1 - 133.3
n	0	218
Cisplatin		
Mean	19.4	20.5
SD	12.74	15.91
Median	18.1	19.1
Min - Max	0.1 - 51.3	0.1 - 115.1
n	113	109
Paclitaxel		
Mean	19.7	22.2
SD	15.84	17.46
Median	17.7	20.1
Min - Max	0.1 - 92.1	0.1 - 115.1
n	222	218
Topotecan		
Mean	20.0	23.4
SD	18.60	20.04
Median	16.3	21.1
Min - Max	0.1 - 92.1	0.1 - 133.3
n	107	109

Table 21: Total Dose by Bevacizumab Treatment

	Chemo alone (N=222)	Chemo+Bv (N=218)
Bevacizumab (mg)		
Mean		8271.3
SD		7354.42
25th percentile		3660.0
Median		6534.5
75th percentile		10500.0
Min		770.0
Max		60438.0
n	0	218
Cisplatin (mg)		
Mean	579.9	605.3
SD	337.15	406.13
25th percentile	308.5	330.0
Median	576.9	528.0
75th percentile	826.0	783.3
Min	79.0	78.0
Max	1369.0	2584.0
n	113	109
Paclitaxel (mg)		
Mean	2104.2	2241.7
SD	1570.88	1614.01
25th percentile	962.3	1165.0
Median	1794.5	1883.5
75th percentile	2772.0	2863.0
Min	7.0	211.0
Max	10500.0	10500.0
n	222	218
Topotecan (mg)		
Mean	28.9	38.1
SD	24.43	59.15
25th percentile	9.0	15.8
Median	25.1	25.2
75th percentile	36.0	40.0
Min	1.2	3.3
Max	135.0	488.8
n	107	109

Adverse events

An overview of the safety analysis comparing chemotherapy alone with bevacizumab plus chemotherapy (pooled analysis) is presented in table 22.

Table 22: Overall Safety by Bevacizumab Treatment

Adverse Event	Chemo alone (N=222) n (%)	Chemo+Bv (N=218) n (%)
All Adverse Events #:		
Pts w. AE	219 (98.6%)	216 (99.1%)
Pts w. Serious AE	81 (36.5%)	111 (50.9%)
Pts w. Grade 3/4/5 AE	127 (57.2%)	165 (75.7%)
Pts w. Grade 5 AE (Outcome Death)	5 (2.3%)	9 (4.1%)
Pts who Disc. Any Treatment due to AE	40 (18.0%)	56 (25.7%)
Deaths:		
All Deaths	145 (65.3%)	135 (61.9%)
Deaths not due to Progression	11 (5.0%)	10 (4.6%)
AE of Special Interest for Bevacizumab ##:		
Pts w. AE of Special Interest	37 (16.7%)	87 (39.9%)
Pts w. AE of Special Interest Grade 3/4/5	37 (16.7%)	82 (37.6%)
Pts w. Serious AE of Special Interest	33 (14.9%)	63 (28.9%)
Pts w. Bleeding (Grade >=3)	10 (4.5%)	15 (6.9%)
Pts w. Congestive heart failure/LVSD (Grade >=3)	0 (0.0%)	0 (0.0%)
Pts w. Febrile neutropenia (Grade >=3)	13 (5.9%)	12 (5.5%)
Pts w. Fistula/Abscess (non gastrointestinal)	5 (2.3%)	9 (4.1%)
Pts w. Gastrointestinal perforations	1 (0.5%)	22 (10.1%)
Pts w. Hypertension (Grade >=3)	1 (0.5%)	25 (11.5%)
Pts w. Posterior rev encephalopathy syndrome	0 (0.0%)	0 (0.0%)
Pts w. Proteinuria (Grade >=3)	0 (0.0%)	4 (1.8%)
Pts w. Thromboembolic event - arterial	7 (3.2%)	5 (2.3%)
Pts w. Thromboembolic event - venous (Grade >=3)	7 (3.2%)	18 (8.3%)
Pts w. Wound healing complication (Grade >=3)	0 (0.0%)	2 (0.9%)

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 30 days
Percentages are based on N

The safety analysis by trial treatment for the bevacizumab-containing arms compared with the chemotherapy alone arms is presented in Table 23.

Table 23: Overall Safety by Trial Treatment

Adverse Event	Cis+Pac (N=114) n (%)	Cis+Pac+Bv (N=109) n (%)	Top+Pac (N=108) n (%)	Top+Pac+Bv (N=109) n (%)
All Adverse Events #:				
Pts w. AE	112 (98.2%)	109 (100.0%)	107 (99.1%)	107 (98.2%)
Pts w. Serious AE	44 (38.6%)	50 (45.9%)	37 (34.3%)	61 (56.0%)
Pts w. Grade 3/4/5 AE	67 (58.8%)	85 (78.0%)	60 (55.6%)	80 (73.4%)
Pts w. Grade 5 AE (Outcome Death)	0 (0.0%)	4 (3.7%)	5 (4.6%)	5 (4.6%)
Pts who Disc. Any Treatment due to AE	29 (25.4%)	36 (33.0%)	11 (10.2%)	20 (18.3%)
Deaths:				
All Deaths	70 (61.4%)	66 (60.6%)	75 (69.4%)	69 (63.3%)
Deaths not due to Progression	4 (3.5%)	5 (4.6%)	7 (6.5%)	5 (4.6%)
AE of Special Interest for Bevacizumab ##:				
Pts w. AE of Special Interest	23 (20.2%)	45 (41.3%)	14 (13.0%)	42 (38.5%)
Pts w. AE of Special Interest Grade 3/4/5	23 (20.2%)	43 (39.4%)	14 (13.0%)	39 (35.8%)
Pts w. Serious AE of Special Interest	20 (17.5%)	36 (33.0%)	13 (12.0%)	27 (24.8%)
Pts w. Bleeding (Grade >=3)	5 (4.4%)	6 (5.5%)	5 (4.6%)	9 (8.3%)
Pts w. Congestive heart failure/LVSD (Grade >=3)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pts w. Febrile neutropenia (Grade >=3)	7 (6.1%)	3 (2.8%)	6 (5.6%)	9 (8.3%)
Pts w. Fistula/Abscess (non gastrointestinal)	4 (3.5%)	4 (3.7%)	1 (0.9%)	5 (4.6%)
Pts w. Gastrointestinal perforations	1 (0.9%)	12 (11.0%)	0 (0.0%)	10 (9.2%)
Pts w. Hypertension (Grade >=3)	1 (0.9%)	14 (12.8%)	0 (0.0%)	11 (10.1%)
Pts w. Posterior rev encephalopathy syndrome	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pts w. Proteinuria (Grade >=3)	0 (0.0%)	3 (2.8%)	0 (0.0%)	1 (0.9%)
Pts w. Thromboembolic event - arterial	5 (4.4%)	3 (2.8%)	2 (1.9%)	2 (1.8%)
Pts w. Thromboembolic event - venous (Grade >=3)	5 (4.4%)	14 (12.8%)	2 (1.9%)	4 (3.7%)
Pts w. Wound healing complication (Grade >=3)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.8%)

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 30 days
Percentages are based on N

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The most common (i.e., an incidence of ≥ 50%) AEs of any grade in any treatment group were AEs typically associated with components of the chemotherapy and included nausea, constipation, fatigue, peripheral sensory neuropathy, and alopecia. For chemo vs. chemo+Bv the frequencies of all these listed AEs were observed in the similar range. Analysed by chemotherapy backbone (Cis vs. Top regimens; e.g. Cis+Pac±Bv vs. Top+Pac±Bv), nausea, constipation and fatigue were observed at a higher frequency in the Cis regimen, except for peripheral sensory neuropathy which was observed in a similar frequency, and alopecia had a higher incidence in the Top-regimen.

Diarrhoea, abdominal pain, vomiting, oedema peripheral, headache, pain conditions (back pain, arthralgia, pain in extremity), decreased appetite, hyperglycaemia, hypomagnesaemia, dyspnoea, weight decreased, urinary tract infection, insomnia and hypertension were also among the most common AEs of any grade (occurring in ≥ 20% of patients in any treatment group), which are shown in Table 24.

The body systems in which patients most frequently reported at least one AE were gastrointestinal disorders, general disorders and administration site conditions, nervous system disorders, skin and subcutaneous tissue disorders, musculoskeletal and connective tissue disorders, and metabolism and nutrition disorders.

Hypertension (all grades) occurred in a higher proportion of patients in the bevacizumab-containing group (Chemo alone: 6% vs. Chemo + Bv: 29%), and analysed with regard to chemotherapy backbone,

hypertension (all grades) was reported more often in the Cis-regimen than in the Top-regimen (Cis+Pac ± Bv: 21% vs. Top+Pac± Bv: 14%).

Table 24: All Grade Adverse Events by Bevacizumab Treatment Occurring in ≥ 20% of Patients in Any Treatment Group

Time Window: First Study Treatment Date to Last Study Treatment Date plus 30 days

Body System/ Adverse Event	Chemo alone N = 222 No. (%)	Chemo+Bv N = 218 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	219 (99)	216 (99)
Total Number of AEs	2711	3361
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	191 (86)	189 (87)
NAUSEA	135 (61)	137 (63)
CONSTIPATION	110 (50)	106 (49)
DIARRHOEA	79 (36)	81 (37)
ABDOMINAL PAIN	72 (32)	75 (34)
VOMITING	71 (32)	74 (34)
Total Number of AEs	558	687
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total Pts With at Least one AE	184 (83)	189 (87)
FATIGUE	166 (75)	174 (80)
OEDEMA PERIPHERAL	49 (22)	33 (15)
Total Number of AEs	310	295
NERVOUS SYSTEM DISORDERS		
Total Pts With at Least one AE	161 (73)	155 (71)
PERIPHERAL SENSORY NEUROPATHY	140 (63)	134 (61)
HEADACHE	29 (13)	47 (22)
Total Number of AEs	257	288
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total Pts With at Least one AE	148 (67)	156 (72)
ALOPECIA	138 (62)	136 (62)
Total Number of AEs	226	242
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total Pts With at Least one AE	129 (58)	131 (60)
BACK PAIN	42 (19)	46 (21)
ARTHRALGIA	39 (18)	48 (22)
PAIN IN EXTREMITY	44 (20)	36 (17)
Total Number of AEs	227	254
METABOLISM AND NUTRITION DISORDERS		
Total Pts With at Least one AE	107 (48)	140 (64)
DECREASED APPETITE	57 (26)	75 (34)
HYPERGLYCAEMIA	43 (19)	56 (26)
HYPOMAGNESAEMIA	34 (15)	53 (24)
Total Number of AEs	291	412

Body System/ Adverse Event	Chemo alone N = 222 No. (%)	Chemo+Bv N = 218 No. (%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total Pts With at Least one AE	86 (39)	105 (48)
DYSPNOEA	53 (24)	50 (23)
Total Number of AEs	139	180
INVESTIGATIONS		
Total Pts With at Least one AE	65 (29)	100 (46)
WEIGHT DECREASED	15 (7)	45 (21)
Total Number of AEs	117	192
INFECTIONS AND INFESTATIONS		
Total Pts With at Least one AE	60 (27)	98 (45)
URINARY TRACT INFECTION	32 (14)	48 (22)
Total Number of AEs	89	157
VASCULAR DISORDERS		
Total Pts With at Least one AE	54 (24)	103 (47)
HYPERTENSION	14 (6)	63 (29)
Total Number of AEs	68	124
PSYCHIATRIC DISORDERS		
Total Pts With at Least one AE	62 (28)	76 (35)
INSOMNIA	33 (15)	43 (20)
Total Number of AEs	98	119

Investigator text for Adverse Events encoded using MedDRA version 16.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
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All AEs with an incidence difference ≥ 5% between groups by Bv treatment are shown in Table 25.

Table 25: Adverse Events with an Incidence Difference of ≥5% between Treatment Arms by Bevacizumab Treatment

Time Window: First Study Treatment Date to Last Study Treatment Date plus 30 days

Body System/ Adverse Event	Chemo alone N=222 No. (%)	Chemo+Bv N=218 No. (%)
METABOLISM AND NUTRITION DISORDERS		
DECREASED APPETITE	57 (25.7)	75 (34.4)
HYPERGLYCAEMIA	43 (19.4)	56 (25.7)
HYPOMAGNESAEMIA	34 (15.3)	53 (24.3)
HYPONATRAEMIA	22 (9.9)	41 (18.8)
HYPOALBUMINAEMIA	24 (10.8)	35 (16.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
FATIGUE	166 (74.8)	174 (79.8)
OEDEMA PERIPHERAL	49 (22.1)	33 (15.1)
INVESTIGATIONS		
WEIGHT DECREASED	15 (6.8)	45 (20.6)
BLOOD CREATININE INCREASED	22 (9.9)	35 (16.1)
INFECTIONS AND INFESTATIONS		
URINARY TRACT INFECTION	32 (14.4)	48 (22.0)
INFECTION	10 (4.5)	21 (9.6)
VASCULAR DISORDERS		
HYPERTENSION	14 (6.3)	63 (28.9)
THROMBOSIS	6 (2.7)	21 (9.6)
NERVOUS SYSTEM DISORDERS		
HEADACHE	29 (13.1)	47 (21.6)
DYSARTHRIA	2 (0.9)	17 (7.8)
GASTROINTESTINAL DISORDERS		
STOMATITIS	22 (9.9)	33 (15.1)
PROCTALGIA	2 (0.9)	14 (6.4)
ANAL FISTULA	-	13 (6.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
NEUTROPENIA	14 (6.3)	28 (12.8)
LYMPHOPENIA	12 (5.4)	25 (11.5)
PSYCHIATRIC DISORDERS		
ANXIETY	23 (10.4)	36 (16.5)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
PELVIC PAIN	18 (8.1)	30 (13.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
EPISTAXIS	4 (1.8)	37 (17.0)
RENAL AND URINARY DISORDERS		
PROTEINURIA	7 (3.2)	22 (10.1)

Percentages are based on N
Investigator text for Adverse Events encoded using MedDRA version 16.0.
Multiple occurrences of the same adverse event in one individual counted only once.

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(PDRD)

Grade ≥ 3 Adverse Events

More patients experienced at least one Grade ≥ 3 AE in the Chemo + Bv group (75.7%) compared with the Chemo alone group (57.2%); the numbers for Grade ≥ 3 AE in the bevacizumab-containing treatment

arms (Cis + Pac + Bv: 78.0%; Top + Pac + Bv: 73.4%) compared to the Chemo alone treatment arms (Cis + Pac: 58.8%; Top + Pac: 55.6%).

The most frequently reported Grade ≥ 3 AEs (≥ 5% in either treatment group) are shown in Table 26, of which abdominal pain and fatigue were overall the most frequently reported.

The most frequent of Grade ≥ 3 AEs (≥ 10% in either treatment arm, by trial treatment) reported in patients were abdominal pain, nausea, fatigue, urinary tract infection, hypokalaemia, hypertension, thrombosis, and peripheral sensory neuropathy.

The Grade ≥ 3 AEs with a difference of ≥ 2% between treatment groups showing the greatest difference in incidence were hypertension (Chemo alone: 0.5% vs. Chemo+Bv: 11.5%), thrombosis (2.7% vs. 8.3%), infection (1.8% vs. 6.4%), fatigue (9.9% vs. 14.2%), and pelvic pain (1.4% vs. 5.5%). Other Grade ⩾ 3 AE with a ⩾ 2% higher incidence in the Bv arm compared to the chemo alone arm were: abdominal pain (9.9% vs 11.9%), diarrhoea (2.7% vs 5.5%), anal fistula (- vs 3.7%), proctalgia (- vs 2.8%) (these two latter are observed in the Bv group only), urinary tract infection (6.3% vs 8.3%), cellulitis (0.5% vs 3.2%), hypokalaemia (4.5% vs 7.3%), hyponatremia (1.4% vs 3.7%), dehydration (0.5% vs 4.1%), neutropenia (4.1% vs 7.8%), lymphopenia (3.2% vs 6.0%) and back pain (3.2% vs 5.5%).

The incidences of Grade ≥ 3 pelvic pain, dyspnoea, hypertension, and thrombosis were higher (≥ 5%) in the Cis+Pac+Bv arm compared with the Cis+Pac arm, and the incidence of nausea was higher in Cis+Pac arm compared with the Cis+Pac+Bv arm. In contrast, the incidences of Grade ≥ 3 abdominal pain, infection, dehydration, fatigue, and hypertension were higher (≥ 5%) in the Top+Pac+Bv arm compared with Top+Pac arm, and no AE had a higher incidence in the Top+Pac arm compared with the Top+Pac+Bv arm (data not shown).

Table 26: Grade 3– 5 Adverse Events by Bevacizumab Treatment Occurring in ≥ 5% of Patients in Either Treatment Group

Time Window: First Study Treatment Date to Last Study Treatment Date plus 30 days

Body System/ Adverse Event	Chemo alone N = 222 No. (%)	Chemo+Bv N = 218 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	127 (57)	165 (76)
Total Number of AEs	334	539
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	42 (19)	66 (30)
ABDOMINAL PAIN	22 (10)	26 (12)
NAUSEA	15 (7)	11 (5)
VOMITING	9 (4)	10 (5)
DIARRHOEA	6 (3)	12 (6)
INFECTIONS AND INFESTATIONS		
Total Pts With at Least one AE	26 (12)	43 (20)
URINARY TRACT INFECTION	14 (6)	18 (8)
INFECTION	4 (2)	14 (6)
METABOLISM AND NUTRITION DISORDERS		
Total Pts With at Least one AE	24 (11)	44 (20)
HYPOKALAEMIA	10 (5)	16 (7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total Pts With at Least one AE	29 (13)	36 (17)
FATIGUE	22 (10)	31 (14)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Total Pts With at Least one AE	27 (12)	37 (17)
NEUTROPENIA	9 (4)	17 (8)
FEBRILE NEUTROPENIA	13 (6)	12 (6)
LYMPHOPENIA	7 (3)	13 (6)
VASCULAR DISORDERS		
Total Pts With at Least one AE	15 (7)	47 (22)
HYPERTENSION	1 (<1)	25 (11)
THROMBOSIS	6 (3)	18 (8)
NERVOUS SYSTEM DISORDERS		
Total Pts With at Least one AE	22 (10)	28 (13)
PERIPHERAL SENSORY NEUROPATHY	11 (5)	14 (6)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total Pts With at Least one AE	18 (8)	30 (14)
BACK PAIN	7 (3)	12 (6)
PAIN IN EXTREMITY	7 (3)	10 (5)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
Total Pts With at Least one AE	8 (4)	21 (10)
PELVIC PAIN	3 (1)	12 (6)

Grade 5 Adverse Events

Five patients (2.3%) in the Chemo alone group and 9 patients (4.1%) in the Chemo + Bv group experienced Grade 5 AEs.

Among patients in the Chemo alone group (all in Top+Pac), 5 patients experienced Grade 5 AEs:

- Top+Pac: death, epistaxis, lung disorder, febrile neutropenia and pelvic infection.

In the Chemo + Bv group, 9 patients experienced a total of 11 Grade 5 AEs: 5 patients were in the Top + Pac + Bv arm and 4 patients in the Cis + Pac + Bv arm:

- Top+Pac+BV: one patient (neutropenia and cellulitis), one patient (neutropenia and pneumonia), one patient each large intestine perforation, acute respiratory distress syndrome, sudden death. Neutropenia was the only Grade 5 AE reported in more than 1 patient.
- Cis+Pac+BV: multi-organ failure, disease progression, ileal perforation, and dyspnoea.

Adverse Events of Special Interest (AESIs)

Adverse events that were previously seen to have a higher incidence during bevacizumab treatment were subject to a separate analysis.

These AESIs were: Arterial thromboembolic events (ATEs) any grade, Bleeding (Grade ≥ 3), Congestive heart failure (CHF)/left ventricular systolic dysfunction (LVSD) (Grade ≥ 3), Febrile neutropenia (Grade ≥ 3), Fistula/abscess [non-GI (any grade)], Gastrointestinal perforation, including fistula/abscess (any grade), Hypertension (Grade ≥ 3), Proteinuria (Grade ≥ 3), Reversible posterior leukoencephalopathy syndrome (RPLS) or posterior reversible encephalopathy syndrome (PRES) (any grade), Venous thromboembolic event (VTE; Grade ≥ 3) and Wound healing complications (Grade ≥ 3).

The following AESIs were observed at higher incidences in the bevacizumab-containing arms compared with the corresponding chemotherapy alone arms: Grade ≥ 3 hypertension, any grade GI perforation, Grade ≥ 3 VTEs, Grade ≥ 3 bleeding, any grade fistula/abscess (non-GI), Grade ≥ 3 proteinuria, and Grade ≥ 3 wound healing complication.

Bleeding (≥grade 3), gastrointestinal perforations, hypertension (≥grade 3) and venous thrombotic events (grade ≥3) were more frequently observed in the cisplatin + paclitaxel + bevacizumab (5.5%, 11%, 12.8% and 12.8%, respectively) and topotecan + paclitaxel + bevacizumab (8.3%, 9.2%, 10.1% and 3.7%, respectively) arms, compared with cisplatin + paclitaxel (4.4%, 0.9%, 0.9% and 4.4%, respectively) and topotecan + paclitaxel arms (4.6%, 0%, 0% and 1.9%, respectively).

The incidence of GI perforations (mostly GI vaginal fistulae such as rectovaginal fistulae) in bevacizumab-treated patients was higher than that seen in clinical trials of bevacizumab to date. In addition, further to the MAH medical review and reclassification of PE cases to VTEs, the Grade ≥ 3 VTE rate was higher than previously observed in bevacizumab-treated patients.

Bevacizumab has a well-known safety profile, which includes hypertension, proteinuria, wound healing complications, mucocutanous bleeding, ATEs, VTEs, GI-perforations and fistula. These adverse drug reactions were also observed in study GOG-0240. Overall, there were more AEs in the chemo + bevacizumab arm as expected. However, the majority of the AEs are manageable.

Arterial Thromboembolic Events (ATEs)

ATEs of any grade were reported in 7 patients (3.2%) in the Chemo alone group and 5 patients (2.3%) in the Chemo + Bv group. Grade 4 acute myocardial infarction was reported in 1 patient in the Chemo alone

group. ATEs of any grade were reported in similar proportions between the Top + Pac and Top + Pac + Bv arms and in more patients in the Cis + Pac arm compared with the Cis + Pac + Bv arm.

Medical review of embolism events in AdEERS reports, and the comments recorded in CRFs, revealed that all Grade 4 emboli were pulmonary emboli. With the pulmonary emboli re-categorized as Grade ≥ 3 VTEs, only one ATE (acute myocardial infarction) was reported, which occurred in the Chemo alone group (Cis + Pac arm).

Bleeding (Grade ≥3)

A total of 10 patients (4.5%) in the Chemo alone group and 15 patients (6.9%) in the Chemo + Bv group experienced Grade ≥ 3 bleeding events. These were reported in similar proportions in the Cis+Pac (5 pts) and Cis+Pac+Bv (6 pts) arms and in more patients in the Top+Pac+Bv arm (9 pts) compared with the Top + Pac arm (5 pts).

The most frequently reported bleeding events included haemorrhage urinary tract (Chemo alone: 3 patients vs. Chemo + Bv: 5 patients), rectal haemorrhage (Chemo alone: 3 patients vs. Chemo + Bv: 3 patients), and vaginal hemorrhage (Chemo alone: 1 patient vs. Chemo + Bv: 5 patients). In the Chemo alone group, 1 patient each experienced ureteric haemorrhage and GI anastomotic leak. Upon medical review, it was determined that a rectovaginal fistula was reported as a GI anastomotic leak, and this patient was therefore also assigned to the GI perforation category.

More patients in the Top + Pac + Bv arm developed urinary tract haemorrhage compared with the Top + Pac arm, and more patients in the Cis + Pac + Bv arm developed vaginal haemorrhage compared with the Cis + Pac arm.

Across both treatment groups, the majority of patients (22 of 25) who experienced a bleeding event experienced Grade 3 events. Two patients, both of whom were in the Chemo + Bv group experienced Grade 4 events; one patient (in Cis+Pac+Bv) developed a vaginal haemorrhage and one patient (in Top+Pac+Bv) developed an upper GI haemorrhage. One patient in the Chemo alone group (Top+Pac) experienced a Grade 5 epistaxis event.

Congestive Heart Failure/Left Ventricular Systolic Dysfunction (Grade ≥3)

No patient in either the Chemo alone or Chemo + Bv groups experienced CHF/LVSD.

Febrile Neutropenia (Grade ≥3)

A similar proportion of patients in the Chemo alone (5.9%) and Chemo + Bv (5.5%) groups experienced Grade ≥ 3 febrile neutropenia events. Grade 3 febrile neutropenia events were reported in 9 patients (4.1%) in the Chemo alone group and 12 patients (5.5%) in the Chemo + Bv group. With regards to Cisplatin; in more patients in the Cis + Pac arm compared with the Cis + Pac + Bv arm (7 vs. 3) and for Topotecan: in more patients in the Top + Pac + Bv arm compared with the Top + Pac arm (9 vs. 6) experienced Grade ≥ 3 febrile neutropenia events.

The majority (22 of 25) of patients experienced Grade 3 febrile neutropenia. Three patients (1.4%) in the Chemo alone group, (i.e. 2 patients in the Cis + Pac arm and 1 patient in the Top + Pac arm) experienced Grade 4 febrile neutropenia events. In the Top + Pac arm, 1 patient experienced a Grade 5 febrile neutropenia event.

Fistula or Abscess (Non-Gastrointestinal)

A total of 5 patients (2.3%) in the Chemo alone group and 9 patients (4.1%) in the Chemo + Bv group experienced fistula or abscess (primarily reported as non-GI) events of any grade and were reported in similar numbers of patients in the Cis+Pac and Cis+Pac+Bv arms (4 in each arm), and more patients in the Top+Pac+Bv arm compared with the Top+Pac arm (5 vs. 1).

Fistula and abscess (primarily reported as non-GI) events were further defined following medical review. Medical review of the non-GI fistula and abscess events identified 2 out of 5 events in the Chemo alone group, and 5 out of 9 events (3 reported as vaginal, 1 reported as enterovaginal, and 1 reported as vesical fistula) in the Chemo + Bv group as GI vaginal fistulae (i.e., fistulae between any part of the GI tract, such as the anus, ileum, rectum, or colon, and vagina)..

The majority of patients (10 of 14) experienced vaginal fistula AEs. Medical review of the events reported as vaginal fistula, female genital tract fistulae or vesical fistulae revealed 7 out of 14 involved vagina and GI tract.

Two patients had Grade 2 events (1 each in the Cis+Pac arm and the Top+Pac+Bv arm). A total of 7 patients had Grade 3 vaginal fistula events, of which 3 were reported in patients in the Cis+Pac arm, 3 were reported in patients in the Cis + Pac + Bv arm, and 1 was reported in 1 patient in the Top + Pac + Bv arm. One patient in the Top + Pac + Bv arm experienced a Grade 4 vaginal fistula event.

One patient in the Top + Pac arm and 1 patient in the Top + Pac + Bv arm developed female genital tract fistula events, both of which were Grade 3. Two patients experienced vesical fistula events; 1 patient in the Cis + Pac+Bv arm had a Grade 2 event and 1 patient in the Top + Pac + Bv arm had a Grade 3 event.

Gastrointestinal Perforation

GI perforation events of any grade were reported more frequently in patients in the Chemo + Bv group (22 patients; 10.1%) compared with the Chemo alone group (1 patient; 0.5%). One patient in the Chemo alone group experienced a Grade 3 GI anastomotic leak.

Total Events Including GI-Vaginal Fistulae

GI Perforation Events

Of 22 patients (10.1%) with GI perforation SMQ defined events in the chemotherapy (Chemo) + bevacizumab (Bv) group, 15 patients (7.0%) had GI-vaginal fistulae (see Table 27). In the Chemo alone group, one patient (0.5%) had a GI perforation SMQ defined event; this event was a GI-vaginal fistula.

Table 27: Total Gastrointestinal Perforation SMQ Defined Events

Adverse Events	Chemo alone (N=222)	Chemo+Bv (N=218)
Total GI Perforation SMQ	1 (0.5%)	22 (10.1%)
GI-vaginal fistulae	*1 (0.5%)*	*15 (7.0%)*
Rectovaginal fistulae	*1*	*12*
Ileo-recto-vaginal or entero-vaginal fistulae		*2*
Recto-vaginal-vesical fistula		*1*

GI=gastrointestinal; SMQ=standardized MedDRA query.

Non-Gastrointestinal Abscess/Fistula

Of 9 patients (4.1%) with abscess/fistulae in the Chemo + Bv group, 5 patients (2.2%) had GI-vaginal fistulae and 4 patients (1.8%) had abscess/fistulae that did not involve the GI tract. In the Chemo alone group, 5 patients (2.3%) had abscess/fistulae, of which 2 patients (0.9%) had GI-vaginal fistulae and 3 patients had abscess/fistulae that did not involve the GI tract (1.4%).

Total GI-Vaginal Fistulae

Summing the GI-vaginal fistulae reported in both the GI perforation SMQ category (i.e., rectovaginal fistulae, ileo-recto-vaginal or entero-vaginal fistula, and recto-vaginal-vesical fistula in Table 27) and the abscess/fistula AEGT category (i.e., recto- or entero-vaginal fistulae) and counting the three events that

were included in both categories only once, the incidences of GI-vaginal fistulae were 8.3% (18/218) in the Chemo + Bv group and 0.9% (2/222) in the Chemo alone group.

Events Excluding GI-Vaginal Fistulae

GI Perforation Events

In the Chemo + Bv group, 7 patients (3.2%) had GI perforation SMQ defined events that involved only the GI tract (5 intestinal or rectal perforation; 1 peritonitis; 1 rectal fistula), and in the Chemo alone group, no patient had a GI perforation SMQ defined event that involved only the GI tract.

Non-Gastrointestinal Abscess/Fistula

In the Chemo + Bv group, 4 patients (1.8%) had abscess/fistulae that did not involve the GI tract, all of which were vaginal or vesicovaginal fistulae, and in the Chemo alone group, 3 patients (1.4%) had abscess/fistulae that did not involve the GI tract, all of which were vaginal or vesicovaginal fistulae.

In conclusion, when comparing chemotherapy (Chemo) alone versus chemotherapy + bevacizumab (Chemo + Bv), the incidences of GI perforation SMQ (excluding GI-vaginal fistula) events are 0% vs. 3.2%, GI-vaginal fistulae 0.9% vs. 8.3%, and non-GI fistula (excluding GI-vaginal fistula) 1.4% vs. 1.8%.

GI perforation events by chemo arm

With regard to trial treatment (individual treatment arms), GI perforation events of any grade were reported in similar proportions of patients in Cis+Pac+Bv (11.0%) and Top+Pac+Bv (9.2%) arms; 1 patient (0.9%) in the Cis+Pac arm and no patient in the Top+Pac arm developed GI perforation events. In the Cis + Pac arm, 1 patient experienced a Grade 3 GI anastomotic leak.

Across bevacizumab-containing treatment arms, the majority of patients (13 of 23) developed anal fistula events. Grade 1 or 2 events were experienced by 2 patients in the Cis+Pac+Bv arm and 3 patients in the Top+Pac+Bv arm. Grade 3 events occurred in 5 patients in the Cis+Pac+Bv arm and 3 patients in the Top+Pac+Bv arm.

One patient in the Cis+Pac+Bv arm and 1 patient in the Top+Pac+Bv arm developed Grade 3 ileal fistulas. Two patients both in the Cis+Pac+Bv arm experienced Grade 3 rectal perforation events.

In the Top+Pac+Bv arm, 1 patient developed Grade 3 colonic fistula, and 1 patient developed Grade 3 peritonitis. In the Cis+Pac+Bv arm, 1 patient experienced a Grade 3 small intestinal perforation. No patient in any treatment arm experienced Grade 4 GI perforation events.

There were 2 Grade 5 events; 1 patient in the Cis+Pac+Bv arm developed an ileal perforation and 1 patient in the Top+Pac+Bv arm developed a large intestine perforation.

After medical review, as previously mentioned, only the following AE terms (fistula [i.e., anal, ileal, and colonic] and anastomotic leak) were found to have a different underlying medical condition. GI Perforation standardized MedDRA Query (SMQ), non-GI fistula and abscess, ATE and VTE adverse event group terms (AEGTs) were medically reviewed in more detail because of the different clinical significance of GI perforation compared to rectovaginal fistula and of pulmonary emboli compared to ATE events.

Summary of prior cancer treatment for cervical cancer

A summary of prior cancer treatment for cervical cancer, by bevacizumab treatment, for patients who developed GI perforations, GI-vaginal fistulae, and non-GI fistulae was provided.

The proportion of patients with or without prior radiation therapy was balanced across Chemo alone and Chemo + Bv groups. All patients who developed GI perforation or GI-vaginal fistula had prior radiation.

The rates of GI perforation in patients with prior radiation were 0% and 4.1% in the Chemo alone group and Chemo + Bv group, respectively. The rates of GI-vaginal fistula in patients with prior radiation were 1.1% and 10.5% in the Chemo alone group and Chemo + Bv group, respectively. There were no patients without prior radiation therapy, either in the Chemo alone group or the Chemo + Bv group, who developed GI perforation or GI-vaginal fistula.

For those patients with prior radiation therapy, the rates of non-GI fistula were the same (1.7%) in the Chemo alone group and Chemo + Bv group. For those patients without prior radiation therapy, the rates of non-GI fistula were 0% and 2.2% in the Chemo alone group and Chemo + Bv group, respectively.

The rates of GI perforation in the Chemo + Bv group were 2.6% vs. 3.6% in patients with recurrence within the field of prior radiation and outside the field of prior radiation, respectively. As mentioned above, there was no GI perforation event in patients who did not have prior radiation or bevacizumab treatment.

The rates of non-GI fistula in the Chemo alone group were 3.2% vs. 0% in patients with recurrence within the field of prior radiation and outside the field of prior radiation, respectively. The rates of non-GI fistula in the Chemo + Bv group were 0% vs. 2.9% in patients with recurrence within the field of prior radiation and outside the field of prior radiation, respectively.

The rates of GI-vaginal fistula in the Chemo alone group were 1.1% vs. 0.8% in patients with recurrence within the field of prior radiation and outside the field of prior radiation, respectively. The rate of GI-vaginal fistula in the Chemo + Bv group was higher in patients with recurrence within the field of prior radiation (16.7%) compared with patients with recurrence outside the field of prior radiation (3.6%). The rate in patients with recurrence within the field of prior radiation was also higher in the bevacizumab-treated patients compared with the Chemo alone treated patients (16.7% Chemo + Bv vs. 1.1% Chemo alone).

Hypertension (Grade ≥3)

Grade ≥ 3 hypertension AEs were reported in more patients in the Chemo + Bv group (11.5%) – and in a similar proportion of patients in the Cis + Pac + Bv (12.8%) and Top + Pac + Bv (10.1%) - arms compared with the Chemo alone group (0.5%). One patient in the Chemo alone (Cis + Pac arm) group developed Grade 3 hypertension. All events were Grade 3 hypertension events. No patient in the Chemo + Bv group discontinued treatment because of hypertension.

Proteinuria (Grade ≥3)

Grade ≥ 3 proteinuria events were reported in 4 patients (1.8%) in the Chemo+Bv group – i.e. in 3 patients (2.8%) in the Cis + Pac + Bv arm and 1 patient (0.9%) in the Top + Pac + Bv arm. All incidences of proteinuria were Grade 3. No patient in the either chemo alone (Cis + Pac or Top + Pac arms) group experienced proteinuria events.

Reversible Posterior Leukoencephalopathy Syndrome or Posterior Reversible Encephalopathy Syndrome (RPLS or PRES)

No patient in any treatment arm experienced posterior reversible encephalopathy syndrome. Neither PRES nor RPLS are AE terms available in NCI CTCAE v.3. Therefore, no patient in either the Chemo alone or Chemo+Bv groups could be reported as PRES/RPLS. Medical review of 1 patient in the Chemo + Bv group (Cis + Pac + Bv arm) with symptomatic leukoencephalopathy who experienced Grade 4 confusional state and Grade 3 seizure revealed MRI findings consistent with PRES/RPLS.

Venous Thromboembolic Event (Grade ≥3)

Grade ≥ 3 VTEs were reported in more patients in the Chemo + Bv group (8.3%) compared with the Chemo alone group (3.2%). Among the four treatment arms, there were unequally distributed as a higher proportion of patients in the Cis+Pac+Bv arm (12.8%) compared with the Cis + Pac arm (4.4%), Top+Pac+Bv arm (3.7%) or the Top+Pac arm (1.9%).

All thrombosis events were Grade 3. One patient in the Chemo alone group (Cis+Pac arm) had a reported Grade 4 pulmonary embolism (PE). No patient experienced a Grade 5 VTE.

A medical review of Grade ≥ 3 VTEs was performed. After medical review, 11 cases of pulmonary embolism that were reported as emboli (unqualified) and initially classified under the ATE category were reclassified in the (Grade ≥ 3) VTE category.

Wound Healing Complications or Dehiscence (Grade ≥3)

Grade ≥ 3 wound healing complication events were reported in 2 patients (0.9%) in the Chemo + Bv group (both patients were in the Top + Pac + Bv cohort) and no patient in the Chemo alone group. The 2 patients were both in the Top + Pac + Bv arm and experienced Grade 3 wound complication events.

Serious adverse event / deaths / other significant events

Serious adverse events

A total of 81 patients (36.5%) in the Chemo alone group and 111 patients (50.9%) in the Chemo+Bv group experienced SAEs. Serious adverse events (SAEs) reported in ≥ 5% of patients in either treatment arm are shown in Table 28.

Table 28: Serious Adverse Events by Trial Treatment Occurring in ≥ 5% Patients in Either Treatment Arm

Time Window: First Study Treatment Date to Last Study Treatment Date plus 30 days

Body System/ Adverse Event	Cis+Pac N = 114 No. (%)	Cis+Pac+Bv N = 109 No. (%)	Top+Pac N = 108 No. (%)	Top+Pac+Bv N = 109 No. (%)
ALL BODY SYSTEMS				
Total Pts with at Least one AE	44 (39)	50 (46)	37 (34)	61 (56)
Total Number of AEs	132	214	98	207
GASTROINTESTINAL DISORDERS				
Total Pts With at Least one AE	16 (14)	29 (27)	13 (12)	27 (25)
ABDOMINAL PAIN	7 (6)	10 (9)	6 (6)	11 (10)
NAUSEA	9 (8)	8 (7)	2 (2)	10 (9)
VOMITING	8 (7)	11 (10)	3 (3)	7 (6)
DIARRHOEA	5 (4)	8 (7)	2 (2)	5 (5)
CONSTIPATION	3 (3)	6 (6)	2 (2)	6 (6)
ANAL FISTULA	-	5 (5)	-	5 (5)
Total Number of AEs	38	69	22	62
INFECTIONS AND INFESTATIONS				
Total Pts With at Least one AE	12 (11)	17 (16)	12 (11)	23 (21)
URINARY TRACT INFECTION	7 (6)	7 (6)	7 (6)	10 (9)
INFECTION	1 (<1)	6 (6)	2 (2)	7 (6)
Total Number of AEs	16	26	13	29
VASCULAR DISORDERS				
Total Pts With at Least one AE	10 (9)	21 (19)	5 (5)	9 (8)
THROMBOSIS	4 (4)	13 (12)	2 (2)	3 (3)
Total Number of AEs	10	24	5	9
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
Total Pts With at Least one AE	9 (8)	9 (8)	11 (10)	14 (13)
NEUTROPENIA	4 (4)	7 (6)	5 (5)	7 (6)
FEBRILE NEUTROPENIA	6 (5)	2 (2)	5 (5)	7 (6)
Total Number of AEs	11	10	13	16
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Total Pts With at Least one AE	6 (5)	12 (11)	7 (6)	16 (15)
FATIGUE	-	5 (5)	2 (2)	12 (11)
PYREXIA	4 (4)	5 (5)	2 (2)	1 (<1)
Total Number of AEs	7	14	8	17
METABOLISM AND NUTRITION DISORDERS				
Total Pts With at Least one AE	5 (4)	11 (10)	4 (4)	8 (7)
DEHYDRATION	2 (2)	4 (4)	-	5 (5)
HYPOKALAEMIA	2 (2)	5 (5)	1 (<1)	2 (2)
Total Number of AEs	8	18	4	15
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Total Pts With at Least one AE	5 (4)	7 (6)	6 (6)	6 (6)
DYSPNOEA	2 (2)	5 (5)	2 (2)	1 (<1)
Total Number of AEs	5	8	8	7

Investigator text for Adverse Events encoded using MedDRA version 16.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.

Source: GOG-0240 CSR, ae11ser_s002.

Deaths

As of the clinical cut-off date (12 December 2012), a total of 145 patients (65.3%) in the Chemo alone group and 135 patients (61.9%) in the Chemo+Bv group had died. The majority of deaths were due to cervical cancer, with comparable frequencies in both the Chemo alone group (58.6%) and in the Chemo+Bv group (54.6 %).

A summary of the primary cause of death in these patients by trial treatment is provided in Table 29.

Table 29: Deaths and Primary Cause of Death by Trial Treatment

	Cis+Pac (N=114)		Cis+Pac+Bv (N=109)		Top+Pac (N=108)		Top+Pac+Bv (N=109)	
Number of patients with death record	70	(61.4%)	66	(60.6%)	75	(69.4%)	69	(63.3%)
Due to other cause	1	(0.9%)	0	(0.0%)	4	(3.7%)	1	(0.9%)
Due to protocol treatment	0	(0.0%)	1	(0.9%)	1	(0.9%)	3	(2.8%)
Due to this disease	64	(56.1%)	57	(52.3%)	66	(61.1%)	62	(56.9%)
Due to this disease/Due to other cause	2	(1.8%)	3	(2.8%)	1	(0.9%)	1	(0.9%)
Due to this disease/Unknown	0	(0.0%)	0	(0.0%)	1	(0.9%)	1	(0.9%)
Unknown	3	(2.6%)	3	(2.8%)	2	(1.9%)	1	(0.9%)
Unknown/Due to other cause	0	(0.0%)	1	(0.9%)	0	(0.0%)	0	(0.0%)
Unknown/Due to this disease	0	(0.0%)	1	(0.9%)	0	(0.0%)	0	(0.0%)

Percentages are based on N

Program : $PROD/cdpt3682/ml01230/died_10.sas / Output : $PROD/cdpt3682/i01230a/reports/died_10_S001.lst

The total number of patients who died from a cause different from “due to this disease” was very similar between the Chemo alone group and Chemo + Bv group: 15 (6.8%) vs. 16 (7.3%). A higher percentage of patients died more than 90 days after the last dose of study treatment in the Chemo alone group (4.1% in the Chemo alone group vs. 2.8% in the Chemo + Bv group) and a higher percentage died ≤ 90 days after the last dose of study treatment in the Chemo + Bv group (2.7% in the Chemo alone group vs. 4.6% in the Chemo + Bv group), although the percentages are very small. Among patients who died more than 90 days after the last dose of study treatment, the most frequent reason was “unknown” (5 [2.3%] patients in the Chemo alone group vs. 3 [1.4%] in the Chemo + Bv group). Among patients who died ≤ 90 days after the last dose of study treatment, the most frequent reason for death was “due to other cause” for patients in the Chemo alone group (4 [1.8%] patients) and “due to protocol treatment” for patients in the Chemo + Bv group (4 [1.8%] patients).

The total number of patients who died from a cause different from “due to this disease” was very similar between the two chemotherapy backbones: 15 (6.7%) in the Cis + Pac +/- Bev group and 16 (7.4%) in the Top + Pac +/- Bev group. A higher percentage of patients died more than 90 days after the last dose of study treatment in the Cis + Pac +/- Bev group (9 [4.0%] patients in the Cis + Pac +/- Bev group vs. 6 [2.8%] in the Top + Pac +/- Bev group) and ≤90 days after the last dose of study treatment in the Top + Pac +/- Bev group (6 [2.7%] patients in the Cis + Pac +/- Bev group vs. 10 [4.6%] in the Top + Pac +/- Bev group), although the percentages are very small.

In the trial-treatment-arm comparison, the total number of patients who died from a cause different from “due to this disease” was very small and ranged from 6 patients in the Cis + Pac arm to 9 patients in both the Cis + Pac + Bv and Top + Pac arms. A higher percentage of deaths in each treatment arm occurred > 90 days after the last study treatment except in the Top + Pac + Bv arm (> 90 days: 4 [3.5%] in Cis + Pac, 5 [4.6%] in both the Cis + Pac + Bv and Top + Pac arms, and 1 [0.9%] in the Top + Pac + Bv arm). The number of patients who died ≤ 90 days after the last dose of study treatment from a cause different from “due to this disease” were 2 [1.8%] in the Cis + Pac arm, 4 [3.7%] in both the Cis + Pac + Bv and Top + Pac arms, and 6 [5.5%] in the Top + Pac + Bv arm

Laboratory findings

Laboratory tests related to AEs included haemoglobin, peripheral ANC/granulocytes count, peripheral platelet count, and peripheral white blood cell (WBC) count. Nearly all patients experienced a Grade 1–4 laboratory test result for a test related to AEs, with similar incidences between bevacizumab treatment groups (Chemo alone: 95.0% vs. Chemo + Bv: 95.9%).

Across both treatment groups, fewer patients experienced Grade 1 or 2 abnormal laboratory test results for tests related to AEs, and the majority of patients with abnormal laboratory test results for tests related

to AEs experienced Grade 3 abnormal test results (Chemo alone: 37.4% vs. Chemo + Bv: 36.2%) or Grade 4 (Chemo alone: 26.6% vs. Chemo + Bv: 39.9%) events.

The incidences of Grade 1 or 2 laboratory test results for tests related to AEs were comparable between treatment groups. The incidences of worst grade (Grade 2–4) laboratory parameters during the study were comparable between the Chemo alone and Chemo + Bv groups for the laboratory parameters granulocytes, hemoglobin, platelets, and WBC.

Clinically significant findings in vital signs, physical findings, and other observations related to safety were reported as AEs.

Safety in special populations

Adverse Events by Age Group

Adverse events by age were evaluated using the following age groups: < 65 years and ≥ 65 years. The majority of patients were aged < 65 years (Chemo alone: 200 of 222 patients [90.1%] vs. Chemo + Bv: 199 of 218 patients [91.3%]), with fewer patients aged ≥ 65 (Chemo alone: 22 patients [9.9%] vs. Chemo + Bv: 19 patients [8.7%]).

AEs reported with higher incidences in both treatment groups in patients aged ≥ 65 years compared to patients aged < 65 years include the following; dyspnoea; blood creatinine; neutropenia; palpitations; hypomagnesaemia; dehydration; hyperkalaemia and muscular weakness.

Adverse Events by Race

The majority of patients in Study GOG-0240 (safety population) were White, with 177 (79.7%) White and 45 (20.3%) non-White patients in the Chemo alone treatment group and 164 (75.2%) White and 54 (24.8%) non-White patients in the Chemo + Bv treatment group.

AEs reported with higher incidences in both treatment groups in Non-white versus White patients include the following; increased blood alkaline phosphatase; hyperkalaemia; metabolic disorder; peripheral motor neuropathy; muscular weakness and hyperhidrosis.

Safety related to drug-drug interactions and other interactions

There is no new information specific to bevacizumab with regard to interactions.

Discontinuation due to adverse events

Forty patients (18.0%) in the Chemo + Bv group and 56 patients (25.7%) in the Chemo alone group experienced AEs leading to discontinuation of study treatment regimen. The most frequent body systems reported in patients who discontinued were nervous system disorders and general disorders and administration site conditions.

The AEs with the highest number of patients who discontinued study treatment were neuropathy peripheral (Chemo alone: 4% (9 pts) vs. Chemo + bevacizumab: 3% (6 pts)) and unevaluable event (2% (4 pts) *vs.* 4% (9 pts)), drug hypersensitivity [3% (6 pts) *vs.* <1% (1 patient)] and peripheral sensory neuropathy (3 pts in each group). No patient in the Chemo + bevacizumab group discontinued treatment because of hypertension.

33% in the cisplatin + paclitaxel + bevacizumab arm discontinued treatment compared to 18.3% in the topotecan + paclitaxel + bevacizumab arm.

Post marketing experience

The post–marketing experience with bevacizumab is collected on the basis of safety data contained in ten previously scheduled Periodic Safety Update Reports (PSURs). The total number of patients exposed to bevacizumab in the post marketing setting from the International Birth Date (IBD) up to 9 January 2014 is estimated to be approximately 1,558,181 patients across indications.

The majority of the known off-label use of bevacizumab involves intravitreal administration for the treatment of age-related macular degeneration (AMD). Safety concerns associated with this off-label use are primarily related to bevacizumab injection into the eye, which is not an approved method of administration for this product. Systemic events have also been observed with this route of administration.

2.5.2. Discussion on clinical safety

Adverse events by chemotherapy versus chemotherapy+bevacizumab

There were more adverse events (AEs) in the chemotherapy+bevacizumab treatment arm, which is not unexpected. Conversely, there were more deaths in the chemotherapy alone treatment arm.

The most common AEs were those related to chemotherapy in general, e.g. fatigue. However, there was an excess of hyperglycaemia, hypomagnesia, hyponatraemia, fatigue, epistaxis, decreased weight, infections, neutropenia, pain, GI perforations (including perforations/fistulae to the vagina and anus) and hypertension in the chemotherapy + bevacizumab arm. There were one Grade 3 and one Grade 4 hypomagnesaemia in the chemotherapy + bevacizumab group. In general, hypomagnesaemia were more common in the cisplatin arms. With regard to hyperglycaemia, there were 5 Grade 3 AEs in the chemotherapy alone group vs. 9 Grade 3 AEs in the chemotherapy + bevacizumab group. There was no Grade 4 or 5 AE. No meaningful difference can be detected between the cisplatin and topotecan arms. Hyperglycaemia is a well-known risk that is already reflected in section 4.8 of the SmPC.

The frequency of fistula is considerable higher in study GOG-0240 than what has been observed in previous trials with bevacizumab. When comparing chemotherapy (Chemo) alone versus chemotherapy +/- bevacizumab (Chemo +/- Bv), the incidences of GI perforation SMQ (excluding GI vaginal fistula) events were 0% vs. 3.2%, GI vaginal fistulae 0.9% vs. 8.3%, and non-GI vaginal, vesical, or female genital tract fistulae 1.4% vs. 1.8%. As currently reflected in the SmPC, patients may be at an increased risk for the development of gastrointestinal perforation when treated with bevacizumab. Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab are also at increased risk of gastrointestinal-vaginal fistulae (see SmPC sections 4.4. and 4.8).

The only predictor is previous radiation therapy. Prior radiation is a risk factor for the development of GI-vaginal fistulae and GI perforation and all patients who developed GI perforation or GI-vaginal fistulae had a history of prior pelvic radiation (see SmPC sections 4.4 and 4.8). The frequency of GI-vaginal fistulae in the group treated with chemotherapy + bevacizumab was higher in patients with recurrence within the field of prior radiation (16.7%) compared with patients with recurrence outside the field of prior radiation (3.6%). The corresponding frequencies in the control group receiving chemotherapy alone were 1.1% vs. 0.8%, respectively. Recurrence of cancer within the field of prior radiation is an additional important risk factor for the development of GI-vaginal fistulae (see SmPC sections 4.4 and 4.8). Patients who develop GI-vaginal fistulae may also have bowel obstructions and require surgical intervention as well as diverting ostomies (see SmPC section 4.8).

There are more Grade 5 AEs in the chemo+bev arm, where some of the events are probably related to the treatment. However, the events are well-known are reflected in the current SmPC. Having the severity of

the disease in mind and that these events are well-known, well-characterised and often manageable, there is no reason for any major concern.

More AESI occurred in the chemo + bev arm. There were more events of bleeding in the chemo + bev arm, but no clear pattern can be observed except for vaginal haemorrhage. Grade 3-5 bleeding reactions have been reported in up to 8.3% of patients treated with bevacizumab in combination with paclitaxel and topotecan compared with up to 4.6% of patients treated with paclitaxel and topotecan (see section 4.8).

More non-GI fistula were observed in the chemo+bev arm and none of the events were Grade 5 (see SmPC section 4.8).

The most striking difference is seen with regard to gastrointestinal perforations, where 4 patients in the chemo + bev arm experienced Grade 5 AEs. The majority of the GI perforations were anal fistula. There were more VTEs in the chemo + bev arm, and it seems as if the risk of thromboembolic events is higher in the cis + pac + bev arm. Grade 3-5 venous thromboembolic events have been reported in up to 15.6% of patients treated with bevacizumab in combination with paclitaxel and cisplatin compared with up to 7.0% of patients treated with paclitaxel and cisplatin. Patients treated for persistent, recurrent, or metastatic cervical cancer with bevacizumab in combination with paclitaxel and cisplatin may be at increased risk of venous thromboembolic events (See SmPC sections 4.4 and 4.8).

Grade 3-5 infections were reported in up to 24% of patients treated with bevacizumab in combination with paclitaxel and topotecan compared with up to 13% of patients treated with paclitaxel and topotecan.

Cellulitis, lymphopenia, proctalgia, back pain, pelvic pain and weight decreased were reported in higher frequencies in study GOG-0240 in the chemo + bevacizumab arm vs the chemo arm. Therefore, these have been included as adverse drug reactions in the SmPC with their respective frequencies. In addition, the frequencies of abdominal pain and fistula have been updated in the SmPC (see SmPC section 4.8).

Adverse events by chemotherapy arm

Looking at data by chemotherapy arm, there seems to be slightly more infections in the top + pac +/- bev group, which is expected, as infections and neutropenia are very common AEs in patients treated with topotecan. In the cis + pac +/- bev arm there seems to be more gastrointestinal disorder, hypokalaemia and vascular disorders. Again, this pattern is also recognisable.

Only 5 of the Grade 5 AEs occurred in the top + pac + bev arm, while all 4 Grade 5 AEs in the cisplatin group were observed in the cis + pac + bev arm. In conclusion, topotecan seems to offers a valuable treatment option for patients that cannot be treated with cisplatin, e.g. due to acquired drug resistance making platinum-based therapies less effective or due to unacceptable AEs profile.

The safety analysis by trial treatment revealed that there are slightly more SAEs and deaths in the in top + pac + bev arm. However, on the other hand, there are more discontinuations in the cis + pac + bev arm. There seems to be more cases of gastrointestinal disorders, vascular disorders (primarily hypertension and thrombosis) and pain (pelvic pain) in the cis + pac + bev arm, while there are slightly more cases of infection in the top + pac + bev arm. The combination of cisplatin + paclitaxel and bevacizumab results in the increased risk of thromboembolic events (see above and SmPC section 4.8). There is an increased risk of infections, when bevacizumab is combined with topotecan+paclitaxel (see above and SmPC section 4.8).

Overall, there were more deaths in the chemo alone arm and the majority of deaths were related to the disease. Exploratory analyses of non-PD related deaths ≤ 90 days and >90 days after the last dose of study treatment, showed no substantial differences in non-PD related deaths when looking at data by bevacizumab treatment, by chemotherapy backbone and by trial treatment. The numbers were in general

low and prevent any reasonable conclusion, but there is no indication of any long-term differences in non-PD deaths.

In the evaluation of data based on age and race, an increased number of deaths in non-white was observed, but the subgroup analysis of OS showed no significant difference between white and non-white. The proportion of non-PD related deaths and Grade 5 AEs were not higher in the non-white patients treated with bev+chemo compared to non-white patients treated with chemo alone. Furthermore, there seems to be some differences in baseline characteristics between white and non-white that could explain the difference: Non-white patients were more likely to be black and have PS=1, which both are indicative of a poorer prognosis.

Finally, more patients in the chemo + bev discontinued treatment (18% vs 26%) compared to the chemo alone arm. However, the overall discontinuation rates are considered reasonable and acceptable.

2.5.3. Conclusions on clinical safety

In conclusion, the safety results of chemo + bevacizumab and chemo alone are as they can be expected. However, GI perforation (including vaginal fistulae), Grade ⩾3 VTE and Grade ⩾3 bleeding rates in patients treated with bevacizumab were higher than those observed in clinical trials of bevacizumab to date.

Overall, the level of discontinuation is considered acceptable in all treatment arms, where the two topotecan arms perform better. The comparison of cisplatin + paclitaxel + bevacizumab and topotecan + paclitaxel + bevacizumab revealed some differences with regards to safety/AEs, but all were manageable. Thus, topotecan is considered an option for patients that cannot be treated with cisplatin.

Based on the safety data from study GOG-0240, the following new adverse drug reactions have been included in section 4.8 of the SmPC: cellulitis, lymphopenia, back pain, pelvic pain, weight decreased, and proctalgia. In addition the frequencies of abdominal pain and fistula have been updated to very common and common respectively.

2.5.4. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

The RMP has been updated to reflect the new indication. No significant changes were made to the sections on safety concerns and pharmacovigilance plan. The routine risk minimisation measures have been updated to reflect the new warnings and safety data presented in the SmPC.

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

The PRAC considered that the risk management plan version 17.0 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. Particularly, the existing warnings with regard to gastrointestinal perforations, fistulae, venous thromboembolism and infections have been updated. The Package Leaflet has been updated accordingly.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Study GOG-0240 showed that the addition of bevacizumab to chemotherapy resulted in a statistically and clinically relevant difference with regard to the primary endpoint of OS. The primary analysis showed a HR=0.74 (95%CI: 0.58, 0.94; p=0.0132), with a difference in median OS of 3.9 months (12.9 months vs. 16.8 months) in favour of chemotherapy + bevacizumab (i.e. cisplatin + paclitaxel + bevacizumab and topotecan + paclitaxel + bevacizumab arms combined).

The effect was confirmed by a similar difference in median PFS. The pooled PFS analysis showed a statistically significant increase in PFS with a HR of 0.66 (95% CI: 0.54, 0.81; log-rank p-value <0.0001) in patients treated with chemotherapy + bevacizumab. The observed improvement in the median time to progression or death was 2.3 months: 8.3 months in the chemotherapy + bevacizumab group versus 6.0 months in the chemotherapy alone group.

In the pooled analysis, ORR was significantly higher (p=0.0117) in the chemotherapy + bevacizumab group (45.4%) compared with the chemotherapy alone group (33.8%).

In addition, HRQoL data did not indicate any major deterioration of QoL by adding bevacizumab to chemotherapy.

Uncertainty in the knowledge about the beneficial effects

PFS and ORR data were only based on non-blinded investigator assessments, but these endpoints were secondary.

Release of the second interim analysis report by the DSMB to investigators and patients approximately 8-9 months before the data cut-off date in December 2012 may have introduced an operational bias in the study, but there is no evidence to substantiate this concern. In this report, it was namely concluded that topotecan was not a superior substitute for cisplatin with paclitaxel chemotherapy by OS.

It is noted that patients with squamous cell carcinoma seems to have a better effect of bevacizumab compared with patients with adenocarcinoma and adenosquamous carcinoma. However, the subgroup analysis was exploratory of nature, the numbers were small and the issue of multiplicity was not controlled in this setting. Therefore no conclusion can be drawn based on this date. In addition, the results of the OS subgroup analysis were in general consistent with the overall estimate.

Risks

Unfavourable effects

Bevacizumab has a well-known safety profile, which includes hypertension, proteinuria, wound healing complications, mucocutanous bleeding, ATEs, VTEs, GI-perforations and fistula. These adverse drug reactions were also observed in study GOG-0240. Overall, there were more AEs in the chemo + bevacizumab arm as expected. However, the majority of the AEs are manageable.

There were more VTEs in the chemo + bevacizumab arm, and it seems as if the risk of thromboembolic events was higher in the cisplatin + paclitaxel + bevacizumab arm, while there were slightly more cases of infections in the topotecan + paclitaxel + bevacizumab arm. Also, of the AEs of special interest, bleeding (≥grade 3), gastrointestinal perforations, hypertension (≥grade 3) and venous thrombotic events (grade ≥3) were more frequently observed in the cisplatin + paclitaxel + bevacizumab and topotecan + paclitaxel + bevacizumab arms, compared with cisplatin + paclitaxel and topotecan + paclitaxel arms.

When comparing the two cisplatin containing regimens, the SAEs with a higher incidence (difference ≥ 5%) in the bevacizumab arm were: thrombosis, infection, anal fistula and fatigue.

For the two topotecan regimens, the SAEs with a higher incidence (difference ≥ 5%) in the bevacizumab arm arms were: fatigue, nausea, dehydration, and anal fistula.

Uncertainty in the knowledge about the unfavourable effects

With regard to excess risk of death observed in non-white patient, the subgroup analysis of OS did not show any significant difference between white and non-white. There is considerable uncertainty related to these data and no conclusion can be made at this stage. In addition, there seems to be some differences in baseline characteristics between white and non-white that could explain the difference.

There were more deaths in the chemo alone arm and the majority of deaths were related to the disease. Exploratory analyses of non-PD related deaths ≤ 90 days and >90 days after the last dose of study treatment showed no substantial differences in non-PD related deaths. The numbers were in general low and prevent any reasonable conclusion, but there is no indication of any long-term differences in non-PD deaths.

Balance

Importance of favourable and unfavourable effects

In a patient population with persistent, recurrent or stage IVB disease, which is associated with poor outcome, the treatment difference observed in terms of OS in the chemo + bevacizumab arm is clinically relevant and important. This finding is supported by sensitivity analysis and PFS data.

In the chemo + bevacizumab arm no detrimental effect could be seen with regard to HRQoL, which is an important aspect to consider in this late-stage disease, where current treatment options could be perceived as palliative.

The addition of bevacizumab to chemotherapy also led to slightly more thromboembolic events and fistulae (vaginal), but these are not considered to outweigh the difference seen in median survival.

Overall, based on the results form study GOG-0240 it is concluded that chemo + bevacizumab is considered superior to chemotherapy alone, and the benefit-risk balance is positive. An improvement of OS with 3.9 months is important in this patient population which have not had such clinically significant result for almost a decade.

Benefit-risk balance

Overall, the benefit-risk balance of bevacizumab in combination with chemotherapy in the treatment of patients with persistent, recurrent or stage IVB cervical cancer is considered positive.

Discussion on the benefit-risk assessment

Patients with persistent, recurrent or stage IVB disease have a very poor outcome and treatment is often palliative. Chemotherapy, though essentially palliative, is usually recommended for these patients, and although the optimal regimen for chemotherapy has not been defined, cisplatin combination therapy is considered the standard of care. Results from a more recent study suggested that cisplatin plus paclitaxel was the preferred regimen in this setting and possibly superior to topotecan plus cisplatin combination in terms of OS, PFS and ORR (Monk et al. 2009; Cella et al. 2010). Based on these findings, the cisplatin plus paclitaxel combination is now considered as the preferred regimen in recent treatment guidelines (ESMO Clinical Practice Guideline, 2012), but there is still a clear need for more effective and better tolerable treatment options in this setting.

In light of this, a statistically significant reduction in the risk of death of 26% (HR of 0.74 (95% CI: 0.58, 0.94) of adding bevacizumab to chemotherapy with a corresponding improvement in median OS of 3.9 months is considered clinically relevant. Open-label studies have their limitations, and with regard to PFS, where there was no independent review of data, the importance of this endpoint is considered to be limited and the results are only seen as supportive. However, there is no evidence of any operational bias with regard to the PFS data. The same can be claimed with regard to HRQoL, but most importantly no detrimental effect was observed.

The addition of bevacizumab to chemotherapy leads to more thromboembolic events in the cisplatin + paclitaxel + bevacizumab arm and infections in the topotecan + paclitaxel + bevacizumab arm. Furthermore, GI perforation (including vaginal fistulae), Grade ≥3 VTE and Grade ≥3 bleeding rates in patients treated with bevacizumab were higher than those seen in clinical trials of bevacizumab to date. However, these events did not have a negative impact on OS and can be managed in the clinical setting.

4. Recommendations

Outcome

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

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

Extension of Indication to include treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix for Bevacizumab in combination with paclitaxel and cisplatin or paclitaxel and topotecan. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet is updated in accordance.

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

5. EPAR changes

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

Scope

Extension of Indication to include treatment of adult patients with persistent, recurrent, or metastatic carcinoma of the cervix for Bevacizumab in combination with paclitaxel and cisplatin or paclitaxel and topotecan. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet is updated in accordance.

Summary

Please refer to the scientific discussion Avastin-H-C-582-II-72.