PROTOCOL

TITLE:	**A PHASE III TRIAL OF CARBOPLATIN AND PACLITAXEL PLUS PLACEBO VERSUS CARBOPLATIN AND PACLITAXEL PLUS CONCURRENT AND EXTENDED BEVACIZUMAB IN CHINESE WOMEN WITH NEWLY DIAGNOSED, PREVIOUSLY UNTREATED, STAGE III OR STAGE IV EPITHELIAL OVARIAN, FALLOPIAN TUBE, OR PRIMARY PERITONEAL CANCER**
PROTOCOL NUMBER:	YO40268
VERSION NUMBER:	3
EUDRACT NUMBER:	To be determined
IND NUMBER:	113807
NCT NUMBER:	NCT03635489
TEST PRODUCT:	Bevacizumab (RO4876646)
MEDICAL MONITOR:	[redacted] M.D., Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	30 August 2017
DATE AMENDED:	Version 2: 23 August 2018 Version 3: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
04-Nov-2019 14:51:05	[redacted]	[redacted]

PROTOCOL AMENDMENT, VERSION 3: RATIONALE

Protocol YO40268 has been amended to align the tumor assessment and patient reported outcome (PRO) schedules with the follow-up schedules of patients with no documented disease progression. Additional updates to the protocol are provided. Changes to the protocol are summarized below:

- The pharmacy manual has been deleted as a source for further details regarding the administration, preparation, and storage of carboplatin and paclitaxel (Section 4.3.2.3).
- The use of Chinese herbal medicine with anti-cancer indication are permitted prior to screening. However, the use of these herbal therapies is still prohibited during the study (Section 4.4.2.1).
- To improve the collection of efficacy and safety data, the tumor assessment schedule has been updated to align with the follow-up schedule of patients with no documented disease progression (Section 4.5.5 and Appendix 1).
- The requirement that all ECGs be obtained prior to other procedures and after 3 hours of any meal has been removed (Section 4.5.7).
- The management of adverse events related to bevacizumab has been updated to align with the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0. A new Table 8, Causal Attribution Guidance, has been added (Section 5.1.4.2; Tables 3 and 8).
- The Medical Monitors and their contact information have been updated (Section 5.4.1).
- Language has been updated to indicate that therapeutic or elective abortions are not considered adverse events unless performed because of an underlying maternal or embryofetal toxicity. In such cases, the underlying toxicity should be reported as a serious adverse event. Language has also been added to clarify that all abortions are to be reported on the paper Clinical Trial Pregnancy Reporting Form (Section 5.4.3.2).
- To improve the collection of efficacy and safety data, the PRO assessment schedule has been updated to align with the follow-up schedule of patients with no documented disease progression (Appendix 1).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III TRIAL OF CARBOPLATIN AND PACLITAXEL PLUS PLACEBO VERSUS CARBOPLATIN AND PACLITAXEL PLUS CONCURRENT AND EXTENDED BEVACIZUMAB, IN CHINESE WOMEN WITH NEWLY DIAGNOSED, PREVIOUSLY UNTREATED, STAGE III OR STAGE IV, EPITHELIAL OVARIAN, FALLOPIAN TUBE OR PRIMARY PERITONEAL CANCER**
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I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form to the Sponsor or designee. Contact details will be provided to the Investigator prior to study start.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III TRIAL OF CARBOPLATIN AND PACLITAXEL PLUS PLACEBO VERSUS CARBOPLATIN AND PACLITAXEL PLUS CONCURRENT AND EXTENDED BEVACIZUMAB, IN CHINESE WOMEN WITH NEWLY DIAGNOSED, PREVIOUSLY UNTREATED, STAGE III OR STAGE IV, EPITHELIAL OVARIAN, FALLOPIAN TUBE OR PRIMARY PERITONEAL CANCER**
PROTOCOL NUMBER:	YO40268
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NCT NUMBER:	NCT03635489
TEST PRODUCT:	Bevacizumab (RO4876646)
PHASE:	Phase III
INDICATION:	Stage III or Stage IV Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy and safety of bevacizumab compared with placebo in combination with paclitaxel and carboplatin in Chinese patients with newly diagnosed, previously untreated FIGO Stage III with any gross (macroscopic or palpable) residual disease or FIGO Stage IV epithelial ovarian, primary peritoneal, or fallopian tube cancer.

Specific objectives and corresponding endpoints for the study are outlined in the table below.

In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., bevacizumab/placebo plus paclitaxel and carboplatin).

Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of bevacizumab versus placebo in combination with paclitaxel+carboplatin	• PFS after randomization, defined as the time from randomization to the first occurrence of disease progression or death from any cause during the study (whichever occurs first), as determined by the investigator according to RECIST v1.1

Objectives and Corresponding Endpoints (cont.)

Secondary Efficacy Objectives	Corresponding Endpoints
• To evaluate the efficacy of bevacizumab versus placebo in combination with paclitaxel+carboplatin	• OS after randomization, defined as the time from randomization to death from any cause • ORR, defined as a CR or PR, as determined by the investigator according to RECIST v1.1 for patients with measurable residual disease after primary surgery • DOR, defined for patients who had an OR and defined as the time from the first occurrence of a documented OR to disease progression, as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first for patients with measurable residual disease after primary surgery
• To evaluate patient-reported abdominal symptoms of OC associated with bevacizumab versus placebo in combination with paclitaxel+carboplatin, as measured by two items from the Abdominal/GI Symptom Scale of the EORTC QLQ-OV28	• Clinically meaningful improvement in patient-reported abdominal pain or bloating, defined as a $\geq$ 10-point decrease from the baseline score on either of the two items (Items 31 and 32) of the EORTC QLQ-OV28 Abdominal/GI Symptom Scale
• To evaluate patient-reported outcomes (PROs) of function and health-related quality of life (HRQoL) associated with bevacizumab versus placebo in combination with paclitaxel+carboplatin	• Clinically meaningful improvement in patient-reported function and HRQoL, defined as a $\geq$ 10-point increase from the baseline score on each of the function (physical, role, emotional, social) and global health status/HRQoL scales of the EORTC QLQ-C30
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate PROs of disease/treatment-related symptoms associated with bevacizumab versus placebo in combination with paclitaxel+carboplatin	• Mean and mean changes from the baseline score in disease and/or treatment-related symptoms by assessment timepoint and between treatment arms as assessed by all symptom items and/or scales of the EORTC QLQ-C30 and QLQ-OV28
• To evaluate any treatment burden associated with bevacizumab versus placebo in combination with paclitaxel+carboplatin	• Proportion of patients reporting each response option at each assessment timepoint by treatment arm for item GP5 from the FACT-G (“I am bothered by side effects of treatment.”)
• To evaluate and compare between treatment arms patients' health utility, as measured by the EQ-5D-5L to generate utility scores for use in economic models for reimbursement	• Health utility scores of the EQ-5D-5L questionnaire

Objectives and Corresponding Endpoints (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of bevacizumab versus placebo in combination with paclitaxel+carboplatin	• Occurrence and severity of adverse events, with severity determined according to NCI CTCAE v4.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results

CR = complete response; DOR = duration of response; EORTC = European Organization for Research and Treatment of Cancer; GI=gastrointestinal; HRQoL = health-related quality of life; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; OC = ovarian cancer; OR = objective response; OS = overall survival; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire Core 30; QLQ-OV28 = Quality of Life Questionnaire Ovarian Cancer Module 28; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Study Design

Description of Study

This is a Phase III, double-blind, two-arm, randomized study designed to evaluate the efficacy and safety of bevacizumab administered with paclitaxel plus carboplatin compared with placebo administered with paclitaxel plus carboplatin in Chinese patients with newly diagnosed, previously untreated FIGO Stage III with any gross (macroscopic or palpable) residual disease or FIGO Stage IV epithelial ovarian, fallopian tube, or primary peritoneal cancer. Approximately 100 patients are expected to be randomized.

A patient-signed Informed Consent Form will be obtained before any study-specific procedures are undertaken.

After informed consent is obtained, patients who meet the eligibility criteria will be randomized in a 1:1 ratio to the bevacizumab and carboplatin plus paclitaxel arm or the placebo and carboplatin plus paclitaxel arm. Re-screening for any reason is not allowed.

Randomization will be stratified according to the following factors: FIGO stage and debulking status (Stage III optimally debulked versus Stage III suboptimally debulked versus Stage IV) and Eastern Cooperative Oncology Group (ECOG) Performance Status (0 vs. 1 or 2).

Patients will receive a maximum of six cycles of carboplatin/paclitaxel with either bevacizumab or placebo. Patients whose disease has not progressed after six cycles of chemotherapy with either bevacizumab or placebo will continue treatment with either bevacizumab or placebo until disease progression, unacceptable toxicity, or a maximum of 22 cycles, whichever occurs first. The details of each treatment arm are described below.

Number of Patients

Approximately 100 patients are expected to be enrolled in this study.

Target Population

The target population is patients with newly diagnosed, previously untreated, FIGO Stage III with any gross (macroscopic or palpable) residual disease or FIGO Stage IV epithelial ovarian, fallopian tube, or primary peritoneal cancer.

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment

- A histologic diagnosis of EOC, peritoneal primary carcinoma, or fallopian tube cancer, FIGO Stage III with any gross (macroscopic or palpable) residual disease or FIGO Stage IV defined surgically at the completion of initial abdominal surgery and with appropriate tissue available for histologic evaluation

  Patients with Stage III cancer for which the largest maximal diameter of any residual tumor implant at the completion of this initial surgery is no greater than 1 cm will be defined as having "optimally debulked" tumors. All others will be defined as "suboptimally debulked" tumors. Measurable disease on postoperative imaging studies is not required for eligibility.
- Patients with the following histologic epithelial cell types are eligible: serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner tumor, or adenocarcinoma not otherwise specified
- ECOG Performance Status 0, 1, or 2
- Life expectancy of at least 12 weeks
- Adequate hematological function indicated by all of the following:
  - ANC $\geq$ 1.5 $\times$109/L (ANC is not to be induced or supported by granulocyte colony-stimulating factors [G-CSFs])
  - Platelet count $\geq$ 100 $\times$ 109/L (without transfusion)
  - Hemoglobin $\geq$ 9.0 g/dL: Patients may receive RBC transfusions to attain this value.
- Adequate liver function indicated by all of the following:
  - Serum bilirubin $\leq$ 1.5 $\times$ the institutional upper limit of normal (ULN)

    Patients with known Gilbert disease who have serum bilirubin level $\leq$ 3 $\times$ ULN may be enrolled in the study.
  - AST, ALT, and alkaline phosphatase (ALP) $\leq$ 2.5 $\times$ ULN, with the following exceptions:

    Patients with documented liver metastases: AST and/or ALT $\leq$ 5 $\times$ ULN

    Patients with documented liver or bone metastases: ALP $\leq$ 5 $\times$ ULN
- Adequate renal function indicated by all of the following:
  - Serum creatinine (Scr) $\leq$1.5 ULN or calculated creatinine clearance (Ccr) $\geq$50 mL/min
  - Urinalysis for proteinuria $<$2+ unless a 24-hour urine protein $<$1 g is demonstrated
- Blood coagulation parameters: prothrombin time (PT) such that the international normalized ratio (INR) is $\leq$ 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 activated partial thromboplastin time (aPTT) is $\leq$ 1.5 $\times$ ULN. The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the enrolling institution), and the patient has been on a stable dose of anticoagulants for at least 2 weeks prior to randomization.
- Neurologic function: neuropathy (sensory and motor) of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 1 or better
- Enrollment between 1 and 12 weeks after initial surgery is performed for the combined purpose of diagnosis, staging, and cytoreduction

  Patients with measurable and non-measurable disease are eligible. Patients may or may not have cancer-related symptoms.
- Patients in this trial may receive ovarian estrogen with or without progestin replacement therapy as indicated at the lowest effective dose(s) for control of menopausal symptoms at any time, but not progestins for management of anorexia during study treatment or prior to disease progression

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of < 1% per year during the treatment period and for at least 6 months after the last dose of bevacizumab, paclitaxel, or carboplatin, whichever is later. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries, fallopian tubes, and/or uterus).

  Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of PRO questionnaires

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Current diagnosis of borderline epithelial ovarian tumor or recurrent invasive epithelial ovarian, primary peritoneal, or fallopian tube cancer treated with surgery only (such as patients with Stage IA or IB low-grade epithelial ovarian or fallopian tube cancers)

  Patients with a prior diagnosis of a borderline tumor that was surgically resected and who subsequently developed unrelated, new invasive epithelial ovarian, peritoneal primary, or fallopian tube cancer are eligible, provided that they have not received prior chemotherapy for any ovarian tumor.
- Prior radiotherapy to any portion of the abdominal cavity or pelvis

  Prior radiation for localized cancer of the breast, head and neck, or skin is permitted, provided that it was completed more than 3 years prior to randomization and the patient remains free of recurrent or metastatic disease.
- Prior chemotherapy for any abdominal or pelvic tumor, including neoadjuvant chemotherapy for ovarian, primary peritoneal, or fallopian tube cancer.

  Patients may have received prior adjuvant chemotherapy for localized breast cancer, provided that it was completed more than 3 years prior to randomization and that the patient remains free of recurrent or metastatic disease.
- Any prior targeted therapy (including, but not limited to, vaccines, antibodies, or tyrosine kinase inhibitors) or hormonal therapy for management of their epithelial ovarian or peritoneal primary cancer
- Synchronous primary endometrial cancer, or a history of primary endometrial cancer unless all of the following conditions are met:
  - Stage not greater than Stage IB
  - No more than superficial myometrial invasion, without vascular or lymphatic invasion
  - No poorly differentiated subtypes, including papillary serous, clear cell, or other FIGO Grade 3 lesions
- With the exception of non–melanoma-related skin cancers and other specific malignancies as noted above, patients with other invasive malignancies who had (or have) any evidence of the other cancer present within the last 5 years or whose previous cancer treatment contraindicates study treatment
- Prior or current treatment with any anti-angiogenic, including bevacizumab.
- Treatment with any other investigational agent or previous participation in another clinical trial within 30 days prior to randomization in this study.

- Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test result at screening, with the following exception:

  Patients with a past or resolved HBV infection, defined as having a negative HBsAg test result and a positive total hepatitis B core antibody (HBcAb) test result at screening, are eligible for the study if HBV DNA is negative or undetectable.
- Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test result and a positive HCV RNA test result at screening
- A positive test result for HIV
- Severe infections within 4 weeks prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Current or recent (within 10 days prior to randomization) use of aspirin ($>$ 325 mg/day) or other non-steroidal anti-inflammatory agents known to inhibit platelet function
- Serious non-healing wounds, ulcers, or bone fractures

  This includes history of abdominal fistula, GI perforation, or intra-abdominal abscess within 28 days prior to randomization. Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection are eligible but require weekly wound examinations.
- Active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorder, coagulopathy, or tumor involving major vessels
- History or evidence upon physical examination of CNS disease, including primary brain tumor, seizures not controlled with standard medical therapy, any brain metastases, or history of cerebrovascular accident (CVA; stroke), transient ischemic attack (TIA), or subarachnoid hemorrhage within 6 months of the first date of treatment on this study
- History of hypertensive crisis or hypertensive encephalopathy
- Patients with clinically significant cardiovascular disease; this includes the following:
  - Uncontrolled hypertension, defined as systolic $\geq$ 150 mmHg or diastolic $>$ 90 mmHg
  - Myocardial infarction or unstable angina $<$ 6 months prior to randomization
  - New York Heart Association (NYHA) Class II or greater congestive heart failure (CHF)
  - Serious cardiac arrhythmia requiring medication (This does not include asymptomatic, atrial fibrillation with controlled ventricular rate.)
  - NCI CTCAE Grade $\geq$2 peripheral vascular disease (at least brief [$<$ 24 hours] episodes of ischemia managed non-surgically and without permanent deficit)
  - History of CVA within 6 months prior to randomization
- Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies
- Have known sensitivity to any component of paclitaxel
- Patients scheduled to undergo an invasive procedure as defined below:

  Major surgical procedure within 28 days prior to the first date of bevacizumab/placebo therapy (Cycle 2) or anticipated during the course of the study. This includes, but is not limited to, abdominal surgery prior to disease progression, such as colostomy or enterostomy reversal, interval or secondary cytoreductive surgery, or second-look surgery.

  Core biopsy or other minor surgical procedures performed within 7 days prior to the anticipated first dose of bevacizumab/placebo therapy, with the following exception:

  The interval of time between placement of a central vascular access device (CVAD) (e.g., Port-A-Cath®) and the first dose of bevacizumab for a patient must be no shorter than 2 days with a well-healed incision

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 6 months after the last dose of bevacizumab, paclitaxel, or carboplatin, whichever is later

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to randomization.
- Patients with clinical symptoms or signs of GI obstruction and who require parenteral hydration and/or nutrition
- Evidence of any other disease, neurologic or metabolic dysfunction, physical examination finding, or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of any of the study drugs, puts the patient at higher risk for treatment-related complications, or may affect the interpretation of study results
- Requirement for treatment with any medicinal product that contraindicates the use of any of the study drugs, may interfere with the planned treatment, affects patient compliance, or puts the patient at high risk for treatment-related complications
- History or evidence of thrombotic disorders within the last 6 months prior to randomization

End of Study

The end of the study period is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for PFS analysis or safety follow-up is completed by the last patient, whichever occurs later. Additionally, the Sponsor may decide to terminate the study at any time.

Investigational Medicinal Products

The investigational medicinal product (IMP) for this study is bevacizumab.

Test Product (Investigational Drug)

Patients in the bevacizumab and chemotherapy arm will receive bevacizumab and paclitaxel/carboplatin combination therapy as follows:

- Chemotherapy:
  - Paclitaxel 175 mg/m2 IV over 3 hours on Day 1
  - Carboplatin area under the concentration–time curve (AUC) 6 IV administered over 30 minutes on Day 1 of each cycle
- Bevacizumab: Bevacizumab 15 mg/kg IV on Day 1 of Cycle 2 Q3W starting at Cycle 2 until disease progression, unacceptable toxicity, a maximum of 21 cycles, or withdrawal, whichever occurs first

Each chemotherapy cycle is to be repeated Q3W until disease progression, unacceptable toxicity, a maximum of six cycles, or withdrawal, whichever comes first.

Paclitaxel will be the first drug of the regimen to be administered to patients in each cycle in both arms, followed by carboplatin and then bevacizumab.

Comparator

Patients in the placebo and chemotherapy arm will receive placebo and paclitaxel/carboplatin combination therapy as follows:

- Chemotherapy:
  - Paclitaxel 175 mg/m2 IV over 3 hours on Day 1
  - Carboplatin AUC 6 mg/mL/min IV over 30 minutes on Day 1
- Placebo: Placebo IV on Day 1 Q3W starting at Cycle 2 until disease progression, unacceptable toxicity, a maximum of 21 cycles, or withdrawal, whichever occurs first

Each chemotherapy cycle will be repeated Q3W until disease progression, unacceptable toxicity, a maximum of six cycles, or withdrawal, whichever comes first.

Paclitaxel will be the first drug of the regimen to be administered in each cycle in both arms, followed by carboplatin and then placebo.

Non-Investigational Medicinal Products

Carboplatin and paclitaxel are the non-investigational medicinal products (NIMPs) for this study. Sites will obtain and utilize commercially available carboplatin and paclitaxel.

Statistical Methods

Primary Analysis

The primary efficacy endpoint is PFS, which will be assessed by the investigator using RECIST v1.1. The study is not fully powered for the primary endpoint; instead consistency with the global pivotal study (GOG218) will be considered for the primary endpoint.

PFS after randomization is defined as the time from randomization to the first documented occurrence of disease progression or death from any cause during the study (whichever occurs first), as determined by the investigator according to RECIST v1.1. Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment. Data for patients with no post-baseline tumor assessment will be censored at the date of randomization plus 1 day.

The primary endpoint of PFS will be analyzed between treatment and control arms based on the stratified log-rank test. The HR of PFS in the experimental arm compared with the control arm will be estimated using a stratified Cox regression model, and the 95% CI will be provided. The stratification factors will be those used during randomization, as recorded in eCRF. Results from an unstratified analysis will also be presented. Kaplan-Meier methodology will be used to estimate median PFS for each treatment arm, and Kaplan-Meier curves will be constructed to provide visual descriptions of the difference between the treatment and control arms.

The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS and OS for each treatment arm.

Determination of Sample Size

The purpose of this study is to confirm the efficacy and safety of bevacizumab in a population of Chinese women with advanced ovarian, fallopian tube, and primary peritoneal cancers who have not received prior chemotherapy for this disease, and to investigate the consistency in treatment effect between Chinese patients and the patients in global study for the purpose of registration in China. The primary efficacy results will be bridged with those of the pivotal Study GOG218.

A total of approximately 100 patients will be randomized in a 1:1 ratio to either the bevacizumab or placebo arms of the study. The final analysis of the primary endpoint of PFS will be performed when approximately 56 PFS events have occurred in the ITT population (56% of 100 patients), which will provide an 80% probability of demonstrating consistency with the global study.

Interim Analyses

There will be no planned interim analysis.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
ALP	alkaline phosphatase
aPTT	activated partial thromboplastin time
AUC	area under the concentration – time curve
BML	below measurable limit
BUN	blood urea nitrogen
Ccr	creatinine clearance
CHF	congestive heart failure
CR	complete response
CRF	Case Report Form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVA	cerebrovascular accident
DLT ANC	dose-limiting toxicity neutropenia
DLT PLT	dose-limiting toxicity thrombocytopenia
eCRF	electronic Case Report Form
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D-5L	EuroQol 5 Dimension, 5-Level Questionnaire
FACT-G	Functional Assessment of Cancer Therapy–General
FDA	Food and Drug Administration
FDG-PET	$^{(18)}$F-Fluorodeoxyglucose positron emission tomography
FIGO	International Federation of Gynecology and Obstetrics
G-CSF	granulocyte colony-stimulating factor
GCIG	International Gynecologic Cancer Intergroup
GFR	glomerular filtration rate
GI	gastrointestinal
GOG	Gynecologic Oncology Group
HR	hazard ratio
HRQoL	health-related quality of life

Abbreviation	Definition
ICH	International Conference for Harmonization
IMP	Investigational Medicinal Product
IND	Investigational New Drug (application)
INR	international normalized ratio
IRB	Investigational Review Board
IWRS	interactive Web-based response system
K_d	dissociation constant
LPLV	last patient, last visit
mCRC	metastatic colorectal cancer
MRI	magnetic resonance imaging
NaCl	sodium chloride
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	non–small cell lung cancer
NYHA	New York Heart Association
OC	ovarian cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
PT	prothrombin time
Q3W	every 3 weeks
RECIST v 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
SAiL	Safety of Avastin in Lung Cancer
Scr	serum creatinine
SD	stable disease
TIA	transient ischemic attack
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VEGF-A	vascular endothelial growth factor–A

1. BACKGROUND

1.1 BACKGROUND ON BACKGROUND ON OVARIAN, PRIMARY PERITONEAL, AND FALLOPIAN TUBE CANCERS

Ovarian, fallopian tube, and primary peritoneal cancers remain leading causes of cancer-related mortality among women worldwide. Globally, epithelial ovarian cancer (EOC) is the most common type of ovarian cancer. It affects 238,719 women annually and results in 140,200 cancer-related deaths, with an annual incidence of 52,100 (22,500 deaths) in China (Ferlay et al. 2013, Chen et al. 2016). EOC, fallopian tube cancer, and primary peritoneal cancer (commonly named as ovarian cancer thereafter) comprise tumors of extra-uterine Müllerian origin and share common clinical and biological behavior. They are typically grouped together in treatment paradigms and clinical investigations, as will be done in this current study.

The diagnosis of ovarian cancer (OC) at an early stage is uncommon because of its typically asymptomatic nature (Ebell et al. 2016). Even patients with more advanced-stage disease typically experience only vague non-specific symptoms that result in further delays in diagnosis. Thus, most patients with OC already have disseminated disease and advanced-stage disease upon initial diagnosis that make the likelihood of cure remote. The 5-year survival rate among patients with Stage I OC is $>$ 85% whereas the 5-year survival rates for patients with advanced Stage III or Stage IV OC are 39% and 17%, respectively (SEER database). Despite advances in perioperative and operative techniques, and a better understanding of the biology of OC, cure rates for OC have remained flat for more than a decade (Sopik et al. 2015).

The standard of care (SOC) for OC at initial diagnosis includes primary tumor reduction surgery, followed by platinum (carboplatin) and taxane (paclitaxel) systemic chemotherapy (McGuire 1996; Piccart 2000; Ozols et al. 2003, Ledermann et al. 2013). Recently, the Society of Gynecologic Oncology (SGO) identified the initiation of chemotherapy within 42 days following primary cytoreductive surgery as a quality indicator for improving OC care (https://www.sgo.org/quality-outcomes-and-research/quality-indicators/). Unfortunately, despite the high sensitivity of OC to initial platinum and taxane combination chemotherapy, the majority of women who are diagnosed with advanced-stage disease will relapse and ultimately succumb to their cancer. Many strategies that attempt to improve the clinical efficacy of first-line ovarian cancer (1LOC) cytotoxic chemotherapy regimens have been studied since carboplatin and paclitaxel were identified as the two key chemotherapies for OC. Adding a third cytotoxic agent to the carboplatin and paclitaxel doublet only increased hematologic toxicity, without commensurate increases in progression-free survival (PFS) and overall survival (OS), thus reinforcing the importance of carboplatin and paclitaxel as the frontline regimen (Bookman et al. 2009).

Despite the challenges observed with the manipulation or addition of cytotoxic chemotherapy agents to a carboplatin and paclitaxel doublet, the clinical experience with

biological agents, notably bevacizumab, has been more promising. Two randomized Phase III studies (Study Gynecology Oncology Group [GOG] 218; Study International Collaborative Ovarian Neoplasm [ICON]) of bevacizumab in patients with advanced OC who are treatment naive, demonstrated improvement in PFS (Burger et al. 2011, Perren et al. 2011). Study GOG218, which combined the standard dose of bevacizumab (15 mg/kg every 3 weeks [q3W]) with carboplatin and paclitaxel followed by bevacizumab monotherapy for 16 cycles, showed a significant improvement in the Response Evaluation Criteria in Solid Tumors (RECIST)-determined PFS (i.e., excludes the CA125 elevations and non–protocol-specified therapies), with a 35% reduction in the risk of progression or death and an increase of 6 months in the median PFS from 12 months to 18 months (Burger et al. 2011).

A pronounced benefit was also identified in Study BO17707 (ICON7) in a subgroup of patients who were at a particularly high risk for cancer recurrence. Patients who were treated with bevacizumab in this high-risk subgroup (i.e., International Federation of Gynecology and Obstetrics [FIGO] Stage IV disease or FIGO Stage III disease and >1.0 cm of residual disease after debulking surgery) experienced a reduction of 27% in their risk for progression that corresponded to an improvement of 5.5 months in their PFS (Perren et al. 2011). Furthermore, the treatment benefit in patients who were administered bevacizumab was evaluated in a subgroup analysis of Study GOG262, a Phase III study in which >80% of patients (including some in the neoadjuvant setting) were administered bevacizumab with chemotherapy (Chan et al. 2016). Although the primary objective of Study GOG262 was to test the clinical benefit of treatment with carboplatin combined with weekly paclitaxel or paclitaxel every 21days, an analysis of patients administered carboplatin and paclitaxel every 21 days showed a longer PFS when bevacizumab was added to the treatment compared with patients for whom it was not added (14.7 months vs. 10.3 months). This finding further supports the treatment benefit of the inclusion of bevacizumab in 1L OC treatment (Chan et al. 2016). Studies GOG218 and ICON7 led to the regulatory approval in the European Union (December 2011), the United States (June 2018), and other countries of bevacizumab combined with carboplatin and paclitaxel for the treatment of women with previously untreated OC at an advanced stage and is the recommendation by major guidelines as a new SOC.

Although surgery remains the cornerstone of 1L OC treatment, two seminal studies that evaluated the neoadjuvant approach compared with traditional primary surgery, followed by adjuvant chemotherapy, demonstrated similar duration in PFS and OS between the two approaches (Vergote et al. 2010; Kehoe 2016).

The current armamentarium of surgery, cytotoxic chemotherapy, and bevacizumab comprise key effective current treatment options for patients with OC. However, bevacizumab is not approved for the treatment of OC in China.

1.2 BACKGROUND ON BEVACIZUMAB

Bevacizumab is a recombinant humanized monoclonal antibody to VEGF composed of human IgG1 framework regions and antigen-binding complementary determining regions from a murine monoclonal antibody (VEGF A.4.6.1) that binds to and neutralizes human VEGF activity. Bevacizumab has a molecular mass of approximately 149 kDa and is glycosylated.

Bevacizumab recognizes all isoforms of VEGF with a dissociation constant (K_d) of approximately 8×10^{-10} M. It does not recognize other peptide growth factors tested (fibroblast growth factor, epidermal growth factor, hepatocyte growth factor, platelet-derived growth factor, and nerve growth factor). It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor environment. Additional anti-tumor activity may be obtained through the effects of bevacizumab on tumor vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells (Jain 2001).

Bevacizumab has shown benefit when added to chemotherapy in preclinical models of several tumors (Kim et al. 1993; Warren et al. 1995; Borgstrom et al. 1999). In animal models of subcutaneous human lung cancer (Calu-6 cell line), the combination of anti-VEGF and cisplatin resulted in markedly enhanced biologic activity compared with the activity of either agent alone (Kabbinavar et al. 1995).

Bevacizumab has already been tested in many Phase I, II, and III studies in patients with a variety of solid tumors, as a single agent or in combination with chemotherapy. Bevacizumab has been approved in many countries for the treatment of metastatic colorectal cancer (mCRC), locally recurrent or metastatic breast cancer (mBC), advanced, metastatic, or recurrent non–small cell lung cancer (NSCLC), advanced and/or metastatic renal cell cancer (mRCC), malignant glioma (WHO Grade IV), glioblastoma, epithelial ovarian, fallopian tube and primary peritoneal cancer, and cervical cancer.

To date, bevacizumab has been approved for two indications in China, mCRC and advanced, metastatic, or recurrent NSCLC.

Globally, it is estimated that a total of 32,237 patients have received bevacizumab through participation in clinical trials across cancer indications, of which 475 have been patients with OC (until 25 February 2016). It is estimated that 2,394,526 patients have been exposed to bevacizumab through participation in company-sponsored studies or through commercially available product (until 25 February 2016).

The safety profile of bevacizumab, when used in addition to carboplatin/paclitaxel chemotherapy in OC, was as expected based on the known toxicities of the individual components.

Refer to the Bevacizumab Investigator's Brochure for details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

For nearly two decades, surgery and platinum-based combination chemotherapy have been the standard first-line treatment for patients with advanced OC. Attempts to improve this standard two-drug chemotherapy by adding a third cytotoxic drug failed to affect either PFS or OS and resulted in an increase in toxic effects (du Bois et al. 2006; Pfisterer et al. 2006; Bookman et al. 2009; Hoskins et al. 2010).

Recently, two pivotal Phase III (GOG218 and ICON7) studies have demonstrated the benefit of bevacizumab use in addition to carboplatin plus paclitaxel chemotherapy in a predominantly Caucasian patient population with OC (Burger et al. 2011; Perren et al. 2011). The safety profile of bevacizumab, when used in addition to carboplatin/paclitaxel chemotherapy in OC, was as expected based on the known toxicities (see Section 1.2). As a result, bevacizumab in combination with carboplatin and paclitaxel, has been approved in the European Union for the front-line treatment of advanced (FIGO Stages IIIB, IIIC, and IV, 1988 edition) epithelial ovarian, fallopian tube, or primary peritoneal cancer and in the United States for advanced (Stage III or IV) ovarian cancer following initial surgical resection. The recommended dose regimen is 15 mg/kg administered Q3W for 15 months or until disease progression. Neither of the global Phase III trials included Chinese women with OC. Therefore, the efficacy and safety of bevacizumab in addition to paclitaxel and carboplatin in Chinese patients with OC have yet to be evaluated.

The purpose of this study is to confirm the efficacy and safety of bevacizumab in a randomized, double-blind, placebo-controlled, comparative setting in a population of Chinese women with advanced ovarian, fallopian tube, and primary peritoneal cancers who have not received prior chemotherapy for their disease. The benefit-risk profile for bevacizumab in combination with paclitaxel and carboplatin is expected to be in line with the positive benefit-risk observed in GOG218.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of bevacizumab compared with placebo in combination with paclitaxel and carboplatin in Chinese patients with newly diagnosed, previously untreated FIGO Stage III with any gross (macroscopic or palpable) residual disease or FIGO Stage IV epithelial ovarian, primary peritoneal, or fallopian tube cancer. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., bevacizumab/placebo plus paclitaxel and carboplatin).

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of bevacizumab versus placebo in combination with paclitaxel+carboplatin	• PFS after randomization, defined as the time from randomization to the first occurrence of disease progression or death from any cause during the study (whichever occurs first), as determined by the investigator according to RECIST v1.1 (see Appendix 2)
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of bevacizumab versus placebo in combination with paclitaxel+carboplatin	• OS after randomization, defined as the time from randomization to death from any cause • ORR, defined as a CR or PR, as determined by the investigator according to RECIST v1.1 for patients with measurable residual disease after primary surgery • DOR, defined for patients who had an OR and defined as the time from the first occurrence of a documented OR to disease progression, as determined by the investigator according to RECIST v1.1 or death from any cause, whichever occurs first for patients with measurable residual disease after primary surgery
• To evaluate patient-reported abdominal symptoms of OC associated with bevacizumab versus placebo in combination with paclitaxel+carboplatin, as measured by two items from the Abdominal/GI Symptom Scale of the EORTC QLQ-OV28	• Clinically meaningful improvement in patient-reported abdominal pain or bloating, defined as a ≥ 10-point decrease from the baseline score on either of the two items (Items 31 and 32) of the EORTC QLQ-OV28 Abdominal/GI Symptom Scale (see Appendix 5)
• To evaluate patient-reported outcomes (PROs) of function and health-related quality of life (HRQoL) associated with bevacizumab versus placebo in combination with paclitaxel+carboplatin	• Clinically meaningful improvement in patient-reported function and HRQoL, defined as a ≥ 10-point increase from the baseline score on each of the function (physical, role, emotional, social) and global health status/HRQoL scales of the EORTC QLQ-C30 (see Appendix 4)
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate PROs of disease/treatment-related symptoms associated with bevacizumab versus placebo in combination with paclitaxel+carboplatin	• Mean and mean changes from the baseline score in disease and/or treatment-related symptoms by assessment timepoint and between treatment arms as assessed by all symptom items and/or scales of the EORTC QLQ-C30 and QLQ-OV28
• To evaluate any treatment burden associated with bevacizumab versus placebo in combination with paclitaxel+carboplatin	• Proportion of patients reporting each response option at each assessment timepoint by treatment arm for item GP5 from the FACT-G (“I am bothered by side effects of treatment.”) (see Appendix 6)

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Efficacy Objectives (cont.)	Corresponding Endpoints (cont.)
• To evaluate and compare between treatment arms patients' health utility, as measured by the EQ-5D-5L to generate utility scores for use in economic models for reimbursement	• Health utility scores of the EQ-5D-5L questionnaire (see Appendix 7)
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of bevacizumab versus placebo in combination with paclitaxel+carboplatin	• Occurrence and severity of adverse events, with severity determined according to NCI CTCAE v4.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results

CR = complete response; DOR = duration of response; EORTC = European Organization for Research and Treatment of Cancer; GI=gastrointestinal; HRQoL = health-related quality of life; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; OC = ovarian cancer; OR = objective response; OS = overall survival; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire Core 30; QLQ-OV28 = Quality of Life Questionnaire Ovarian Cancer Module 28; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase III, double-blind, two-arm, randomized study designed to evaluate the efficacy and safety of bevacizumab administered with paclitaxel plus carboplatin compared with placebo administered with paclitaxel plus carboplatin in Chinese patients with newly diagnosed, previously untreated FIGO Stage III with any gross (macroscopic or palpable) residual disease or FIGO Stage IV epithelial ovarian, fallopian tube, or primary peritoneal cancer. Approximately 100 patients are expected to be randomized.

A patient-signed Informed Consent Form will be obtained before any study-specific procedures are undertaken.

After informed consent is obtained, patients who meet the eligibility criteria will be randomized in a 1:1 ratio to the bevacizumab and carboplatin plus paclitaxel arm or the placebo and carboplatin plus paclitaxel arm. Re-screening for any reason is not allowed.

Randomization will be stratified according to the following factors: FIGO stage and debulking status (Stage III optimally debulked versus Stage III suboptimally debulked versus Stage IV) and Eastern Cooperative Oncology Group (ECOG) Performance Status (0 vs. 1 or 2).

Patients will receive a maximum of six cycles of carboplatin/paclitaxel with either bevacizumab or placebo. Patients whose disease has not progressed after six cycles of chemotherapy with either bevacizumab or placebo will continue treatment with either bevacizumab or placebo until disease progression, unacceptable toxicity, or a maximum of 22 cycles, whichever occurs first. The details of each treatment arm are described below.

3.1.2 Bevacizumab and Chemotherapy

Patients in the bevacizumab and chemotherapy arm will receive bevacizumab and paclitaxel/carboplatin combination therapy as follows:

- Chemotherapy:
  - Paclitaxel 175 mg/m^2 IV over 3 hours on Day 1
  - Carboplatin area under the concentration–time curve (AUC) 6 IV administered over 30 minutes on Day 1 of each cycle
- Bevacizumab: Bevacizumab 15 mg/kg IV on Day 1 of Cycle 2 Q3W starting at Cycle 2 until disease progression, unacceptable toxicity, a maximum of 21 cycles, or withdrawal, whichever occurs first

Each chemotherapy cycle is to be repeated Q3W until disease progression, unacceptable toxicity, a maximum of six cycles, or withdrawal, whichever comes first.

Paclitaxel will be the first drug of the regimen to be administered to patients in each cycle in both arms, followed by carboplatin and then bevacizumab.

3.1.3 Placebo and Chemotherapy

Patients in the placebo and chemotherapy arm will receive placebo and paclitaxel/carboplatin combination therapy as follows:

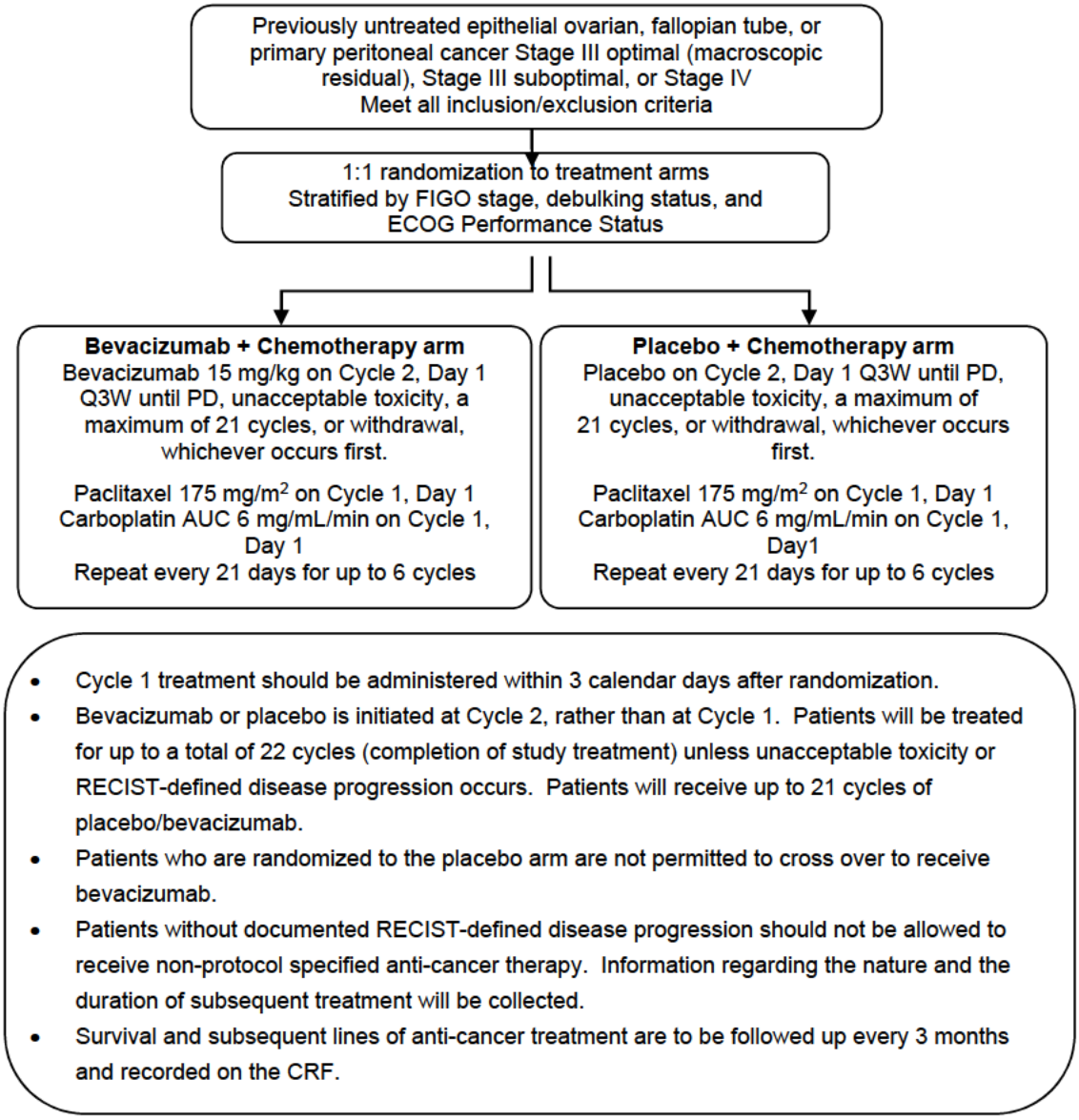
- Chemotherapy:
  - Paclitaxel 175 mg/m2 IV over 3 hours on Day 1
  - Carboplatin AUC 6 mg/mL/min IV over 30 minutes on Day 1
- Placebo: Placebo IV on Day 1 Q3W starting at Cycle 2 until disease progression, unacceptable toxicity, a maximum of 21 cycles, or withdrawal, whichever occurs first

Each chemotherapy cycle will be repeated Q3W until disease progression, unacceptable toxicity, a maximum of six cycles, or withdrawal, whichever comes first.

Paclitaxel will be the first drug of the regimen to be administered in each cycle in both arms, followed by carboplatin and then placebo.

A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



AUC = area under the concentration – time curve; CRF = Case Report Form; FIGO = International Federation of Gynecology and Obstetrics; ECOG = Eastern Cooperative Oncology Group; PD = progressive disease; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors.

3.2 END OF STUDY

The end of the study period is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for PFS analysis or safety follow-up is completed by the last patient, whichever occurs later. Additionally, the Sponsor may decide to terminate the study at any time (see Section 4.6.3).

Treatment will continue until disease progression, unacceptable toxicity, completion of the study treatment, patient or physician decision to discontinue, death, or withdrawal, whichever occurs first. Tumor response data collection will continue if a patient prematurely ends treatment, provided there is no confirmed radiographic disease progression. Tumor response data collection will also continue beyond the completion of the study treatment until radiographic disease progression is confirmed. Follow-up data, including OS and initiation of subsequent anti-cancer therapies, will continue for each patient until patient death or study closure.

If a patient discontinues and/or withdraws from the study treatment, tumor response data as well as follow-up and/or surveillance data (e.g., OS, subsequent anti-cancer therapies) will continue to be monitored and collected until patient death or study closure.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Dose and Schedule

Bevacizumab dosing has been extensively investigated in several trials. Bevacizumab 15 mg/kg in combination with paclitaxel and carboplatin chemotherapy was selected for the Phase III study GOG218, which demonstrated a PFS benefit and acceptable toxicity. Based on the results from this trial, the European Medicines Agency (EMA) approved bevacizumab in combination with carboplatin and paclitaxel for the front-line treatment of advanced (FIGO Stages IIIB, IIIC, and IV) epithelial ovarian, fallopian tube, and primary peritoneal cancers and the U.S. Food and Drug Administration (FDA)-approved bevacizumab in combination with chemotherapy (carboplatin and paclitaxel), followed by bevacizumab as a single agent, for the treatment of women with advanced (Stage III or IV) ovarian cancer following initial surgical resection.

The pharmacokinetics of bevacizumab have been well characterized based on data from 18 clinical studies across multiple indications in more than 1900 patients (Han et al. 2016), which includes 35 Chinese patients from a Phase I study (BP20689). Race and indication (tumor-type) were not found to be pharmacokinetic (PK)-associated covariates that affected bevacizumab exposure. Bevacizumab has an elimination half-life of approximately 20 days resulting in extended plasma persistence, which supports a Q3W dosing schedule. A bevacizumab dose regimen of 15 mg/kg Q3W enables therapeutic levels of bevacizumab to be maintained in excess of VEGF-A concentrations during treatment cycles.

In the Chinese Phase I study (BP20689), the PK profile of bevacizumab in Chinese patients was similar to that of the PK profile in Caucasian patients, resulting in comparable exposures when administered at the same dose (see Section 1.3.1 Pharmacology of Bevacizumab in the Investigator's Brochure). In other cancer trials, such as Safety of Avastin in Lung Cancer (SAiL), which included Chinese patients, results in the Chinese subgroup suggested that the efficacy and tolerability of bevacizumab 15 mg/kg Q3W was similar to that observed in the entire study population (Tsai et al. 2011).

Therefore, the dose regimen of 15-mg/kg bevacizumab Q3W in combination with paclitaxel plus carboplatin in this study has been selected on the basis of robust clinical evidence with the objective to confirm the efficacy and safety of bevacizumab in Chinese patients with advanced OC.

3.3.2 Delay of Initial Treatment with Bevacizumab

Owing to a concern for potential wound healing complications related to bevacizumab in this trial, bevacizumab/placebo therapy will begin at the start of Cycle 2 of carboplatin and paclitaxel combination chemotherapy.

3.3.3 Rationale for Patient Population

This study will enroll Chinese patients with newly diagnosed, previously untreated, FIGO Stage III with any gross (macroscopic or palpable) residual disease or FIGO Stage IV epithelial ovarian, fallopian tube, or primary peritoneal cancer (i.e., cancers of extra-uterine Müllerian origin). The eligibility criteria for this study include patients who are at the highest risk for a poor clinical outcome and, therefore, represent those in great need for new, more effective treatments.

Because of its predisposition to present in an advanced stage with large tumor volume, EOC, fallopian tube carcinoma, and primary peritoneal carcinoma remain the leading cause of death among all gynecologic malignancies with poor 5-year OS rates of 39% (Stage III) and 17% (Stage IV) (Goff et al. 2012; Ferlay et al. 2013; American Cancer Society 2016; Siegel et al. 2016). Furthermore, certain tumor characteristics, such as postoperative macroscopic residual disease and Stage IV disease, portend especially poor prognosis and a high risk for recurrence. Despite effective cytotoxic agents therapy, recurrence rates remain high for patients with advanced stage OC, thereby highlighting the need to avail novel and durable therapies for these patients and thus justifying their inclusion in this study.

Both GOG218 and ICON7 studies included previously untreated epithelial ovarian, primary peritoneal, or fallopian tube cancer, Stage III optimal (macroscopic or palpable residual), Stage III suboptimal, and Stage IV patients. ICON7 also included high-risk FIGO Stage I and IIA patients. Although both studies showed benefit in PFS, there were more data supporting bevacizumab's effect in patients with Stage III and IV disease, and

the EMA approval is for this population. Therefore, the Stage III and IV patient population was chosen by the Sponsor as the target group in this trial.

3.3.4 Rationale for Control Group

For nearly two decades, the standard treatment for women with advanced OC has been surgery and platinum-based chemotherapy. Attempts to improve the efficacy of this standard two-drug chemotherapy by adding a third cytotoxic drug failed to affect either PFS or OS and resulted in an increase in toxic effects (du Bois 2006; Pfisterer et al. 2006; Bookman et al. 2009; Hoskins et al. 2010). Although intraperitoneal chemotherapy has extended OS from 12 months to 17 months, it is an option only for women with advanced OC who have a small amount of residual disease after surgery (Armstrong et al. 2006). One trial in Japan demonstrated an alternative regimen with weekly paclitaxel administration, which provided a sustained significant improvement in PFS for patients receiving dose-dense therapy compared with conventional treatment (Katsumata et al. 2009, 2013).

The fifth GCIG Ovarian Cancer Consensus Conference (Karam et al. 2017) recommended that the control arm in international clinical trials of first-line chemotherapy of OC should be six cycles of combination IV chemotherapy with carboplatin (AUC 5 to AUC 6 mg/mL/min) and paclitaxel (175 mg/m^2 given as a 3-hour infusion) administered Q3W. Carboplatin and paclitaxel, given in this manner, are considered the international standard of care (Aabo et al. 1998; du Bois 2001; McGuire and Markman 2003; Stuart et al. 2011). This regimen was also regarded as the Category 1 recommendation in China editions of the NCCN guidelines for epithelial ovarian cancer (Version 2, 2015), which is the most commonly used regimen in China.

3.3.5 Rationale for Patient-Reported Outcome Assessments

Abdominal symptoms (e.g., bloating, increased abdominal size, and abdominal pain) are ranked as the top symptoms in terms of frequency, severity, and duration by patients with OC and represent a significant burden in women with newly diagnosed advanced disease (Olson et al. 2001; Goff et al. 2004; Matsuo et al. 2011; Friedlander and King 2013; Donovan et al. 2014). Prioritizing measurement of patient-reported abdominal symptoms is important because these common advanced symptoms are most likely to be affected by early treatment and are critical in the assessment of clinical benefit (Donovan et al. 2014; Herzog et al. 2014). In this study, improvements in the symptoms of bloating and abdominal pain will be assessed with the use of the valid and reliable European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Ovarian Cancer Module 28 (EORTC QLQ-OV28) to provide a direct measure of clinical benefit in this patient population (Cull et al. 2001; Greimel et al. 2003).

The EORTC QLQ-OV28 includes a seven-item abdominal/gastrointestinal (GI symptom scale (Items 31–37; see Appendix 5). Improvement in abdominal symptoms as

identified by Item 31 ("Did you have abdominal pain?") and Item 32 ("Do you have a bloated feeling in your abdomen/stomach?") will be assessed as a key secondary endpoint to document the effect of bevacizumab on two of the most predominant and burdensome symptoms of advanced OC (Cella et al. 2003). Instead of analyzing the entire abdominal/GI scale, this secondary endpoint definition is based on an analysis of the two single items that identify and assess two distinct symptoms that are the most clinically relevant and important to newly diagnosed patients with advanced OC (Olson et al. 2001; Cella et al. 2003; Goff et al. 2004; Matsuo et al. 2011; Goff 2012; Friedlander and King 2013; Donovan et al. 2014).

To provide supplementary information to describe clinical benefit in the patient population and support and inform on the benefit-risk assessment of bevacizumab therapy, a global assessment of the impact of treatment on patients' functioning and health-related quality of life (HRQoL) will be conducted and analyzed as secondary efficacy endpoints with the functional (role, physical, emotional, and social) and global health status/HRQoL scale scores of the validated, reliable EORTC Quality of Life Questionnaire Core 30 (QLQ-C30) (Aaronson et al. 1993). In addition, an exploratory efficacy endpoint has been specified to evaluate any treatment burden patients may experience with the addition of bevacizumab, which will be assessed by analyzing the proportion of patients who select each response option at each assessment timepoint by treatment arm for the single item GP5 ("I am bothered by side effects of treatment") from the physical well-being subscale of the validated and reliable Functional Assessment of Cancer Therapy–General (FACT-G) Quality of Life Instrument–Version 4 (Cella et al. 1993; Webster et al. 1999). Patients will also complete the validated EuroQol 5 Dimension, 5-Level Questionnaire (EQ-5D-5L) (Herdman et al. 2011; Janssen et al. 2013; see Appendix 7) to generate utility scores to inform pharmacoeconomic evaluations. As such, the utility results will not be included in the Clinical Study Report (CSR).

Given the duration of treatment and the potential for long-term treatment impact, all patient-reported outcome (PRO) measures will be assessed at specified timepoints while patients are receiving treatment and during the follow-up period after treatment discontinuation as defined in the schedule of activities (see Appendix 1).

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 100 patients with newly diagnosed, previously untreated, FIGO Stage III with any gross (macroscopic or palpable) residual disease or FIGO Stage IV epithelial ovarian, fallopian tube, or primary peritoneal cancer will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form

- Age $\geq$ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- A histologic diagnosis of EOC, peritoneal primary carcinoma, or fallopian tube cancer, FIGO Stage III with any gross (macroscopic or palpable) residual disease or FIGO Stage IV defined surgically at the completion of initial abdominal surgery and with appropriate tissue available for histologic evaluation

  Patients with Stage III cancer for which the largest maximal diameter of any residual tumor implant at the completion of this initial surgery is no greater than 1 cm will be defined as having "optimally debulked" tumors. All others will be defined as "suboptimally debulked" tumors. Measurable disease on postoperative imaging studies is not required for eligibility.
- Patients with the following histologic epithelial cell types are eligible: serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner tumor, or adenocarcinoma not otherwise specified
- ECOG Performance Status 0, 1, or 2
- Life expectancy of at least 12 weeks
- Adequate hematological function indicated by all of the following:
  - ANC $\geq 1.5 \times 10^9$/L (ANC is not to be induced or supported by granulocyte colony-stimulating factors [G-CSFs])
  - Platelet count $\geq 100 \times 10^9$/L (without transfusion)
  - Hemoglobin $\geq$ 9.0 g/dL: Patients may receive RBC transfusions to attain this value.
- Adequate liver function indicated by all of the following:
  - Serum bilirubin $\leq$ 1.5 $\times$ the institutional upper limit of normal (ULN)

    Patients with known Gilbert disease who have serum bilirubin level $\leq$ 3 $\times$ ULN may be enrolled in the study.
  - AST, ALT, and alkaline phosphatase (ALP) $\leq$ 2.5 $\times$ ULN, with the following exceptions:

    Patients with documented liver metastases: AST and/or ALT $\leq$ 5 $\times$ ULN

    Patients with documented liver or bone metastases: ALP $\leq$ 5 $\times$ ULN
- Adequate renal function indicated by all of the following:
  - Serum creatinine (Scr) $\leq$1.5 ULN or calculated creatinine clearance (Ccr) $\geq$50 mL/min
  - Urinalysis for proteinuria $<$2+ unless a 24-hour urine protein $<$1 g is demonstrated

- Blood coagulation parameters: prothrombin time (PT) such that the 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 activated partial thromboplastin time (aPTT) is $\leq 1.5 \times$ ULN. The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the enrolling institution), and the patient has been on a stable dose of anticoagulants for at least 2 weeks prior to randomization.
- Neurologic function: neuropathy (sensory and motor) of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Grade 1 or better
- Enrollment between 1 and 12 weeks after initial surgery is performed for the combined purpose of diagnosis, staging, and cytoreduction

  Patients with measurable and non-measurable disease are eligible. Patients may or may not have cancer-related symptoms.
- Patients in this trial may receive ovarian estrogen with or without progestin replacement therapy as indicated at the lowest effective dose(s) for control of menopausal symptoms at any time, but not progestins for management of anorexia during study treatment or prior to disease progression
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of $< 1\%$ per year during the treatment period and for at least 6 months after the last dose of bevacizumab, paclitaxel, or carboplatin, whichever is later. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries, fallopian tubes, and/or uterus).

  Examples of contraceptive methods with a failure rate of $<$ 1% per year include bilateral tubal ligation, male sterilization, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, including the completion of PRO questionnaires

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Current diagnosis of borderline epithelial ovarian tumor or recurrent invasive epithelial ovarian, primary peritoneal, or fallopian tube cancer treated with surgery only (such as patients with Stage IA or IB low-grade epithelial ovarian or fallopian tube cancers)

  Patients with a prior diagnosis of a borderline tumor that was surgically resected and who subsequently developed unrelated, new invasive epithelial ovarian, peritoneal primary, or fallopian tube cancer are eligible, provided that they have not received prior chemotherapy for any ovarian tumor.

- Prior radiotherapy to any portion of the abdominal cavity or pelvis

  Prior radiation for localized cancer of the breast, head and neck, or skin is permitted, provided that it was completed more than 3 years prior to randomization and the patient remains free of recurrent or metastatic disease.

- Prior chemotherapy for any abdominal or pelvic tumor, including neoadjuvant chemotherapy for ovarian, primary peritoneal, or fallopian tube cancer.

  Patients may have received prior adjuvant chemotherapy for localized breast cancer, provided that it was completed more than 3 years prior to randomization and that the patient remains free of recurrent or metastatic disease.

- Any prior targeted therapy (including, but not limited to, vaccines, antibodies, or tyrosine kinase inhibitors) or hormonal therapy for management of their epithelial ovarian or peritoneal primary cancer
- Synchronous primary endometrial cancer, or a history of primary endometrial cancer unless all of the following conditions are met:
  - Stage not greater than Stage IB
  - No more than superficial myometrial invasion, without vascular or lymphatic invasion
  - No poorly differentiated subtypes, including papillary serous, clear cell, or other FIGO Grade 3 lesions
- With the exception of non–melanoma-related skin cancers and other specific malignancies as noted above, patients with other invasive malignancies who had (or have) any evidence of the other cancer present within the last 5 years or whose previous cancer treatment contraindicates study treatment
- Prior or current treatment with any anti-angiogenic, including bevacizumab.
- Treatment with any other investigational agent or previous participation in another clinical trial within 30 days prior to randomization.

- Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test result at screening, with the following exception:

  Patients with a past or resolved HBV infection, defined as having a negative HBsAg test result and a positive total hepatitis B core antibody (HBcAb) test result at screening, are eligible for the study if HBV DNA is negative or undetectable.
- Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test result and a positive HCV RNA test result at screening
- A positive test result for HIV
- Severe infections within 4 weeks prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Current or recent (within 10 days prior to randomization) use of aspirin ($>$ 325 mg/day) or other non-steroidal anti-inflammatory agents known to inhibit platelet function
- Serious non-healing wounds, ulcers, or bone fractures

  This includes history of abdominal fistula, GI perforation, or intra-abdominal abscess within 28 days prior to randomization. Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection are eligible but require weekly wound examinations.
- Active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorder, coagulopathy, or tumor involving major vessels
- History or evidence upon physical examination of CNS disease, including primary brain tumor, seizures not controlled with standard medical therapy, any brain metastases, or history of cerebrovascular accident (CVA; stroke), transient ischemic attack (TIA), or subarachnoid hemorrhage within 6 months of the first date of treatment on this study
- History of hypertensive crisis or hypertensive encephalopathy
- Patients with clinically significant cardiovascular disease; this includes the following:
  - Uncontrolled hypertension, defined as systolic $\geq$ 150 mmHg or diastolic $>$ 90 mmHg
  - Myocardial infarction or unstable angina $<$ 6 months prior to randomization
  - New York Heart Association (NYHA) Class II or greater congestive heart failure (CHF)
  - Serious cardiac arrhythmia requiring medication (This does not include asymptomatic, atrial fibrillation with controlled ventricular rate.)
  - NCI CTCAE Grade $\geq$2 peripheral vascular disease (at least brief [$<$ 24 hours] episodes of ischemia managed non-surgically and without permanent deficit)
  - History of CVA within 6 months prior to randomization
- Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies

- Have known sensitivity to any component of paclitaxel
- Patients scheduled to undergo an invasive procedure as defined below:

  Major surgical procedure within 28 days prior to the first date of bevacizumab/placebo therapy (Cycle 2) or anticipated during the course of the study. This includes, but is not limited to, abdominal surgery prior to disease progression, such as colostomy or enterostomy reversal, interval or secondary cytoreductive surgery, or second-look surgery.

  Core biopsy or other minor surgical procedures performed within 7 days prior to the anticipated first dose of bevacizumab/placebo therapy, with the following exception:

  The interval of time between placement of a central vascular access device (CVAD) (e.g., Port-A-Cath®) and the first dose of bevacizumab for a patient must be no shorter than 2 days with a well-healed incision
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 6 months after the last dose of bevacizumab, paclitaxel, or carboplatin, whichever is later

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to randomization.
- Patients with clinical symptoms or signs of GI obstruction and who require parenteral hydration and/or nutrition
- Evidence of any other disease, neurologic or metabolic dysfunction, physical examination finding, or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of any of the study drugs, puts the patient at higher risk for treatment-related complications, or may affect the interpretation of study results
- Requirement for treatment with any medicinal product that contraindicates the use of any of the study drugs, may interfere with the planned treatment, affects patient compliance, or puts the patient at high risk for treatment-related complications
- History or evidence of thrombotic disorders within the last 6 months prior to randomization

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Randomization will be performed centrally using an interactive voice/Web response system (IxRS) that uses stratified block randomization. After screening, patients who meet all eligibility criteria will be randomly assigned in a 1:1 ratio to one of two treatment groups: bevacizumab or placebo.

Randomization to treatment allocation will also be stratified by:

- FIGO stage and debulking status (Stage III optimally debulked vs. Stage III suboptimally debulked vs. Stage IV) and
- ECOG Performance Status (0 vs. 1 or 2)

Stratification factors will ensure balance of these strong prognostic factors across treatment arms and facilitate unbiased estimate of treatment effect in subgroups based on disease severity and performance status.

The study is to be conducted in a double-blind manner to minimize potential bias.

If unblinding is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event).

As per health authority reporting requirements, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator and patient will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are bevacizumab and matching placebo.

All eligible patients will receive a total of six cycles of carboplatin/paclitaxel (given Q3W) with either bevacizumab or placebo. Bevacizumab/placebo must be initiated at Cycle 2, after completion of the six cycles of carboplatin/paclitaxel bevacizumab or placebo will be given as a single agent for a maximum of 16 cycles unless unacceptable toxicity or RECIST-defined disease progression occurs.

If bevacizumab/placebo treatment is discontinued “prematurely” because of unacceptable toxicity or patient refusal, chemotherapy may continue for a maximum of six cycles. Likewise, if any component of chemotherapy is discontinued prematurely because of toxicity, bevacizumab/placebo and the second component of chemotherapy treatment can continue.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Bevacizumab and Placebo

Study drug packaging will be overseen by the Roche clinical trial supplies department and will bear a label with the identification required by local law, the protocol number, the drug identification, and the dosage.

Bevacizumab/placebo will be provided as single-use, 400-mg and 100-mg vials containing a 25-mg/mL concentrate for solution for IV infusion. Bevacizumab is provided in colorless glass vials with a butyl rubber stopper with aluminum seal and plastic flip-off disk.

Upon the receipt of bevacizumab, vials are to be refrigerated at 2°C to 8°C (36°F to 46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Vials should be kept in their outer carton because of light sensitivity.

VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 patient may not be used for any other patient. Vials should not be used after the retest date shown on the pack.

Chemical and physical in-use stability has been demonstrated for 48 hours at 22°C to 30°C in 0.9% sodium chloride (NaCl) solution. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would normally be no longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Incompatibilities

No incompatibilities between bevacizumab and polyvinyl chloride or polyolefin bags have been observed. Concentration-dependent changes in the ion-exchange chromatography profile were observed when bevacizumab was diluted with dextrose solutions (5%). Therefore, bevacizumab should not be administered or mixed with dextrose or glucose solutions.

Stability

Bevacizumab should not be used after the retest date shown on the pack.

The labeling of bevacizumab/placebo will be in accordance with all local legal requirements and will be conducted according to Good Manufacturing Practice. As a minimum, labels will include the following information:

- Bevacizumab/placebo 400 mg or 100 mg
- FOR CLINICAL STUDY USE ONLY
- F. Hoffmann–La Roche Ltd
- Investigator _____
- Protocol YO40268
- Patient No. _____
- RO4876646/placebo
- Store at 2°C – 8°C
- Expiry date _____

For further details, see Bevacizumab Investigator's Brochure.

4.3.1.2 Chemotherapy (Carboplatin and Paclitaxel)

Sites will obtain and utilize commercially available carboplatin and paclitaxel. For information on the formulation and handling of carboplatin and paclitaxel, see the pharmacy manual and local prescribing information.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Any overdose or incorrect administration of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded on the Adverse Event eCRF.

4.3.2.1 Timing and Sequence of Treatment Administration

The timing of treatment administration is shown in Appendix 1 and Table 2. All of the study treatments are administered intravenously. The sequence of administration is as follows for all treatment arms:

Table 2 Treatment Regimens and Order of Administration

Drug [a]	Dose and Route of Administration	Infusion Period
Cycle 1		
Paclitaxel	175 mg/m^2 IV	• 3 hours [b]
Carboplatin	AUC 6 mg/mL/min IV [b]	• Over approximately 30 minutes [c]
Cycles 2–6 (concurrent treatment)		
Paclitaxel	175 mg/m^2 IV	• 3 hours [b]
Carboplatin	AUC 6 mg/mL/min IV [b]	• Over approximately 30 minutes [c]
Bevacizumab or placebo	15 mg/kg IV	• 90 (±15) minutes for the first dose • 60 (±10) minutes for the second dose, depending on patient tolerability of the first dose • 30 (±10) minutes for subsequent doses, depending on patient tolerability of the second dose
Cycles 7–22 (maintenance treatment)		
Bevacizumab or placebo	15 mg/kg IV	If the previous infusion of bevacizumab or placebo is well tolerated by the patient, then the infusion period may be reduced to 30 (±10) minutes for subsequent doses.

AUC = area under the concentration–time curve.

Note: Treatments should be administered in the order listed for each cycle.

[a] Institutional desensitization protocols may be implemented, if clinically indicated.

[b] Exceptions to the paclitaxel infusion time of 3 hours will be allowed for sites that have an institutional policy for infusion of paclitaxel more quickly (over 90 minutes) or more slowly (up to 4 hours for the first infusion).

[c] Per institutional standard, carboplatin should be administered immediately after the completion of the paclitaxel administration.

If scheduled dosing is precluded because of a holiday and/or weekend, then dosing may be postponed to the soonest following date, with subsequent dosing continuing on a 21-day schedule. If treatment was postponed for fewer than 3 days, the patient can resume the original schedule.

4.3.2.2 Bevacizumab and Placebo

Bevacizumab will be administered at a dose of 15 mg/kg on Day 1 of each 21-day cycle. The initial dose of bevacizumab will be calculated on the basis of a patient's weight at screening and will remain the same throughout the study unless the patient's weight changes by $>10\%$ from the baseline body weight, in which case the bevacizumab dose should be modified. Body weight will be re-baselined at the time of dose change, and dose modifications should occur if the patient's weight changes $>10\%$ from the new baseline.

The calculated total dose of bevacizumab/placebo must be diluted in a total volume of 100 mL of 0.9% NaCl solution, United States Pharmacopoeia (USP). In the event that a total dose exceeding 1000 mg is administered, dilute the calculated dose of bevacizumab/placebo with a sufficient amount of 0.9% NaCl solution to keep the final concentration at 1.4–16.5 mg/mL. Keep 100 mL as the minimal volume to administer and limit the infusion volume as much as possible. No incompatibilities between bevacizumab/placebo and polyvinylchloride or polyolefin bags have been observed. Bevacizumab/placebo should not be administered or mixed with dextrose solutions.

Discard any unused portion left in a vial, as the product contains no preservatives. The sterile, single-use vials contain no antibacterial preservatives. Therefore, vials should be discarded 8 hours after initial entry. Once diluted in 0.9% NaCl, solutions of bevacizumab/placebo must be administered within 8 hours.

Bevacizumab/placebo should be administered as a continuous IV infusion with use of a rate-regulating device. Do not administer as an IV push or bolus.

The initial dose of bevacizumab/placebo will be delivered over 90 (± 15) minutes. If the first infusion is tolerated without any infusion-related adverse events (i.e., fever and/or chills), the second infusion may be delivered over 60 (± 10) minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. Bevacizumab/placebo infusions may be slowed or interrupted for patients who experience infusion-related symptoms. If infusion-related symptoms occur, patients should be treated in accordance with the best medical practice, and patients will be monitored until adequate resolution of signs and symptoms.

To ensure complete delivery of bevacizumab/placebo, the IV infusion line must be flushed with 0.9% NaCl. The two recommended methods for flushing the bevacizumab/placebo IV infusion line are as follows:

- When the bevacizumab/placebo infusion has been completed, add an additional 50 mL of 0.9% NaCl for injection to the bevacizumab/placebo infusion bag. Continue the infusion until a volume equal to that of the volume contained in the infusion line has been administered.

- Replace the empty bevacizumab/placebo infusion bag with a 50 mL bag of 0.9% NaCl for injection and infuse a volume equal to the volume contained in the infusion line.

Note: The additional volume used to flush the IV infusion line is not included in the recommended infusion times.

When extravasation of bevacizumab/placebo occurs during an infusion, it is recommended that the following action be taken:

- Discontinue the bevacizumab/placebo infusion.
- Treat the extravasation according to institutional guidelines for extravasation of a non-caustic agent.
- If a significant volume of bevacizumab/placebo remains in the infusion bag, restart the infusion at a more proximal site ipsilaterally or on the contralateral limb.
- Continue to observe the patient, document observations, and administer further treatment as required.

In the event of a suspected anaphylactic reaction during study drug infusion:

- Stop the study drug infusion.
- Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
- Maintain an adequate airway.
- Administer antihistamines, epinephrine, or other medications as required.
- Continue to observe the patient and document observations.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.4.2.

4.3.2.3 Carboplatin and Paclitaxel

The dose of carboplatin for this regimen is AUC 6 mg/mL/min in combination with paclitaxel 175 mg/m^2 on Day 1 for a maximum of six cycles.

Investigators should follow their institution's administration guidelines and local prescribing information for carboplatin and paclitaxel, in line with the suggested guidelines in Figure 1 and Section 5.1.4.3.1. If there is a significant difference between the protocol guidelines and institutional standards of care, please call the Medical Monitor. For further details regarding administration, preparation, and storage, refer to local prescribing information for carboplatin and paclitaxel.

In particular, all patients must be premedicated with corticosteroids, antihistamines, and H_2-receptor antagonists before paclitaxel infusions are administered and in accordance with the product information and local institution guidelines.

Carboplatin should be administered by IV infusion, immediately after the completion of paclitaxel administration, over a 30-minute time period to achieve an initial target AUC of 6 mg/mL/min (Calvert formula dosing) with standard anti-emetic medications, per local practice guidelines.

The carboplatin dose of AUC 6 mg/mL/min will be calculated with the use of the Calvert formula (Calvert et al. 1989):

Calvert formula:

$$\text{Total dose (mg)} = (\text{target AUC}) \times (\text{glomerular filtration rate [GFR]} + 25)$$

Note: The GFR used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min.

For the purposes of this protocol, the GFR is considered to be equivalent to the creatinine clearance (CRCL). The CRCL is calculated by institutional guidelines or by the method of Cockcroft and Gault (1976) with the use of the following formula:

$$\text{CRCL} = \frac{(140 - \text{age}) \times (\text{wt})}{72 \times \text{Scr}} \quad (\times 0.85)$$

Where: CRCL = creatinine clearance in mL/min
age = patient's age in years
wt = patient's weight in kg
Scr = serum creatinine in mg/dL

Note: For patients with an abnormally low serum creatinine level, estimate GFR with the use of a minimum creatinine level of 0.7 mg/dL or cap the estimated GFR at 125 mL/min.

If a patient's GFR is estimated on the basis of serum creatinine measurements by the isotope dilution mass spectroscopy method, the FDA recommends that physicians consider a cap on the dose of carboplatin for desired exposure to avoid potential toxicity due to overdosing. On the basis of the Calvert formula described in the carboplatin label, the maximum doses can be calculated as follows:

$$\text{Maximum carboplatin dose (mg)} = \text{target AUC (mg} \bullet \text{min/mL)} \times (\text{GFR} + 25 \text{ mL/min})$$

The maximum dose is on the basis of a GFR estimate that is capped at 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

For a target AUC = 6, the maximum dose is $6 \times 150 = 900$ mg
For a target AUC = 5, the maximum dose is $5 \times 150 = 750$ mg
For a target AUC = 4, the maximum dose is $4 \times 150 = 600$ mg

Refer to the FDA communication on carboplatin dosing for more details:

https://ctep.cancer.gov/content/docs/carboplatin_information_letter.pdf

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.4.3.

Special Warnings and Precautions for Carboplatin and Paclitaxel

Any contraindications and special warnings and precautions for the use of carboplatin and paclitaxel should be observed, and any medication(s) or therapy(ies) contraindicated in the local prescribing information of carboplatin and paclitaxel are contraindicated in patients receiving carboplatin and paclitaxel.

4.3.3 Additional Required Medication

4.3.3.1 Prophylactic Measures for Carboplatin

Carboplatin is considered moderately to highly emetogenic. Therefore, appropriate anti-emetic non-steroidal medication (e.g., aprepitant) should be administered prior to the initiation of chemotherapy in accordance with the local practice and standard of care.

4.3.3.2 Premedication for Paclitaxel

All patients should be medicated prior to paclitaxel administration to prevent severe hypersensitivity reactions. Prior to administration of paclitaxel, all patients will receive either according to institutional standard of care or the following premedication:

- Dexamethasone 20 mg orally approximately 12 hours and 6 hours prior to the paclitaxel infusion

  Patients may be treated with dexamethasone 10 mg to 20 mg IV within 1 hour prior to paclitaxel infusion if the patient did not take the oral dexamethasone.
- Diphenhydramine 50 mg IV (or equivalent) 30 minutes to 60 minutes prior to paclitaxel infusion
- Cimetidine 300 mg IV or ranitidine 50 mg IV (or equivalent) 30 minutes to 60 minutes prior to paclitaxel infusion

4.3.4 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (bevacizumab and placebo) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs using the Interactive-voice/Web-response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.5 Continued Access to Bevacizumab

Currently, the Sponsor does not have any plans to provide bevacizumab or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing bevacizumab in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to initiation of study drug to the study completion/ discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients are permitted to use the following therapies during the study:

- Oral contraceptives
- Hormone-replacement therapy
- Anticoagulation

  The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or aPTT is within therapeutic limits (according to the medical standard of the treating institution) and the patient has been on a stable dose of anticoagulants for at least 2 weeks at the start of study treatment. Prophylactic use of anticoagulation at baseline and during study treatment for the maintenance of patency of permanent indwelling central venous access devices is permitted. Prophylactic use of anticoagulation during study treatment for patients at high risk of venous thromboembolism is permitted. Bevacizumab or anticoagulation treatment will be stopped in case of:

  - Any evidence of tumor invading major blood vessels on any computed tomography (CT) scan
  - Any evidence of CNS metastases

  Because of a possible risk of bleeding during treatment with bevacizumab, patients should not take more than 325 mg of aspirin daily (or more than 75 mg of clopidogrel daily) at least until discontinuation of bevacizumab/placebo treatment.

Premedication with antihistamines, antipyretics, and/or analgesics may be administered at the discretion of the investigator.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

Transfusions of blood and blood products, antibiotics, colony-stimulating factors, analgesia anti-emetic medications, etc., may be used according to local practice/institutional guidelines where appropriate.

If placing a CVAD between bevacizumab doses, placement must occur at least 14 days from the prior (i.e., pre-CVAD placement) bevacizumab dose, and at least 7 days from the following (i.e., post-CVAD placement) bevacizumab dose.

4.4.2 Cautionary Therapy

4.4.2.1 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. *Herbal therapies are permitted before screening.* Herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

4.4.3 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority approved or experimental, is prohibited for various time periods prior to initiation of the study treatment, depending on the agent (see Section 4.1.2), and during study treatment until disease progression is documented and the patient has discontinued study treatment, except as outlined below.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited during study treatment.
- Reassessment (second-look surgery) or cytoreductive surgery

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient.

If scheduled study assessments cannot be obtained because of a holiday and/or weekend, these assessments should then be obtained at the soonest following date, provided that the soonest following date is not within the windows of scheduled study assessments.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

Randomization of patients with confirmed eligibility should be performed within 3 days before the first dose of study treatment.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 90 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening should include the measurement of weight and height, and an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, temperature, and systolic and diastolic blood pressure while the patient is in a seated position.

Vital signs should be measured within 60 minutes prior to each study treatment infusion and as clinically indicated. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

4.5.5 Tumor and Response Evaluations

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator using RECIST, Version 1.1 (RECIST v1.1) (see Appendix 2).

An initial CT scan (with oral or IV contrast) or magnetic resonance imaging (MRI) scan of at least the chest, abdomen, and pelvis is required to establish a postsurgical baseline for the extent of residual disease within 28 days prior to randomization (Scan 1). If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen and pelvis should be performed. A CT/MRI scan of the neck and/or head may also be performed if necessary.

Follow-up radiographic assessments of disease should use the same imaging modality and should encompass the same field as in the initial pre-treatment evaluation. This should be repeated following the schedule below regardless of whether or not the patient has measurable disease on the initial CT or MRI scan. All radiographic assessments will be performed according to the time interval (e.g., 9 weeks, 12 weeks, etc.) regardless of the treatment cycle *(for more detail, see* Appendix 1*)*. Imaging assessments should be discontinued if RECIST-defined disease progression is confirmed according to criteria.

- Scans 2 and 3: Every 9 weeks (± 5 days) from the date of randomization during the concurrent treatment phase
- Scans 4, 5, 6, and 7: Every 12 weeks (± 5 days) in the maintenance phase (the first scan in the maintenance phase is performed 12 weeks after the last scan during the concurrent treatment phase)
- After the completion of all protocol therapy, every 3 months (± 14 days) for 2 years, then every 6 months (± 14 days) for 3 years.

  CT scans or MRIs after 5 years of survival follow-up may be performed as clinically indicated.

- During or after completion of all study treatment, as clinically indicated at any time for clinical suspicion of progressive disease (PD)

Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

All laboratory sample collection and testing will be scheduled as indicated in Appendix 1. Additional assessments may be performed as clinically indicated. Normal ranges for the local laboratory parameters must be supplied to the study Sponsors before the study starts. It is recommended that the same units and normal ranges be used throughout the study; the investigator should notify the Sponsor of any updated reference range.

The total volume of blood loss for laboratory assessments will be approximately 20 mL per cycle of therapy.

Baseline laboratory assessments are performed within 14 days prior to initiating study treatment, except urinalysis, which should be performed within 7 days prior to study treatment initiation. Any abnormalities that are discovered during patient assessment should be further investigated where clinically indicated to ensure that patients are fit to be included in the study and to receive study medication.

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells)
- Chemistry panel (serum): sodium, potassium, glucose, blood urea nitrogen (BUN) creatinine, albumin, bilirubin, AST, ALT, and ALP will be collected at baseline and subsequent visits as indicated in Appendix 1.
- Coagulation: INR and aPTT should be assessed at baseline, during the study visit, and when clinically indicated or for monitoring patients who have to receive anticoagulants such as coumarin derivates or heparins (according to local standard).
- HIV serology

  All patients will be tested for HIV infection prior to inclusion into the study, and HIV-positive patients will be excluded from the clinical study.
- HBV serology: HBsAg, hepatitis B surface antibody, total HBcAb

  If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed at screening. HBV DNA must be negative (i.e., undetectable) prior to randomization.

- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must be performed to determine if the patient has an active HCV infection.

- Pregnancy test

  All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed as clinically indicated at subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries, fallopian tubes, and/or uterus).

- Urinalysis, including pH, specific gravity, glucose, protein, ketones, blood and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) is required at baseline and all subsequent visits, followed by 24-hour urine collection in the event of proteinuria $\geq 2+$.
- Serum CA125

4.5.7 Electrocardiograms

A 12-lead ECG is required at screening and as clinically indicated. ECGs should be obtained on the same machine whenever possible.

Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

4.5.8 Patient-Reported Outcomes

To more fully characterize the clinical profile of bevacizumab, PRO data will be obtained through the use of the following instruments: EORTC QLQ-C30 and its ovarian cancer module EORTC QLQ-OV28; FACT-G single item GP5; and EQ-5D-5L.

The PRO questionnaires, official Chinese versions in booklet format with a cover page, will be provided to sites to be distributed by the investigator staff and completed on paper by the patient in their entirety at the investigational site. To ensure instrument validity and that data standards meet health authority requirements, questionnaires must be completed by the patient at the start of the clinic visit before discussion of the patient's health state, laboratory results, or health record; before administration of study

treatment; and/or prior to the performance of any other study assessments that could bias patient's responses. If the patient is unable to complete the measure on her own, interviewer assessment is allowed but may only be conducted by a member of the clinic staff who reads the questionnaire items to the patient verbatim; no interpretation, rephrasing, or rewording of the questions is allowed during interview-assisted completion.

Study personnel should review all questionnaires for completeness before the patient leaves the investigational site, and the hard copy originals of the questionnaires must be maintained as part of the patient's medical record at the site for source data verification. These originals should have the study patient number and date and time of completion at the top of each page as well as the respondent's initials and date of completion at the bottom of each page in compliance with good clinical practice. Sites will enter patient responses to the PRO questionnaires into the electronic data capture (EDC) system.

All patients will complete the questionnaires, beginning with the EORTC QLQ-C30, followed by the QLQ-OV28, FACT-G single item GP5, and then the EQ-5D-5L at timepoints corresponding with in-clinic visits, both while receiving study treatment and during the survival follow-up period. Refer to Appendix 1 for the frequency and timing of PRO assessments.

4.5.8.1 EORTC QLQ-C30 and EORTC QLQ-OV28

The EORTC QLQ-C30 and its ovarian cancer module EORTC QLQ-OV28 are validated, reliable self-reported measures (Aaronson et al. 1993; Cull et al. 2001; Greimel et al. 2003) (see Appendix 4, and Appendix 5, respectively). The EORTC QLQ-C30 consists of 30 questions that assess five aspects of patient functions (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), global health and/or QoL, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales.

The EORTC QLQ-OV28 consists of 28 items that includes a multi-item scale that assesses abdominal and/or gastrointestinal symptoms, peripheral neuropathy, other chemotherapy side effects, hormonal symptoms, body image, attitudes toward disease and/or treatment, and sexuality of patients with local or advanced ovarian cancer who receive treatment by surgery with or without chemotherapy. The EORTC QLQ-C30 and the QLQ-OV28 module take approximately 20 minutes to complete.

4.5.8.2 FACT-G Single Item GP5

The FACT-G, Version 4 (see Appendix 6), is a validated and reliable 27-item questionnaire comprised of four subscales that measure physical (7 items), social and family (7 items), emotional (6 items) and functional wellbeing (7 items) and is considered appropriate for use with patients with any form of cancer (Cella et al. 1993; Webster et al. 1999). In this study, the single item GP5 ("I am bothered by side effects of treatment") from the Physical Well-Being Subscale of the FACT-G has been selected for individual item analysis to document the level of bothersomeness of symptoms on patient's lives. Patients will assess how true the statement "I am bothered by side effects of treatment" has been for them in the previous 7 days on a five-point scale (0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; 4, very much). The single item GP5 from the FACT-G takes less than a minute to complete.

4.5.8.3 EuroQol 5 Dimension, 5 Level

The EQ-5D-5L is a validated, self-reported health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013) (see Appendix 7). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain and discomfort, and anxiety and depression, as well as a visual analogue scale that measures health state. Published weighting systems allow for the creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete and will be utilized in this study to inform pharmacoeconomic evaluations, and, as such, EQ-5D-5L data will not be included in the CSR.

4.5.9 Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be assessed with the use of the ECOG Performance Scale as previously described (Pignata et al. 2014).

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment or the attributable portion of the study treatment regimen (bevacizumab, placebo, paclitaxel, and/or carboplatin) if they experience any of the following:

- Intolerable toxicity related to study treatment that includes the development of an immune-related adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any adverse event that requires study treatment discontinuation per the guidelines in Section 5.1
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient

- Use of an anti-cancer therapy not required per protocol
- Symptomatic deterioration attributed to disease progression
- Confirmed disease progression per investigator assessment according to RECIST v1.1
- Pregnancy

For patients that have urgent/emergency surgery, bevacizumab/placebo treatment should be interrupted. If the patient has healed well and has had no complications after surgery, bevacizumab/placebo treatment can be restarted based on the investigator's judgment. If in doubt, the investigator should contact and discuss with the Medical Monitor.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment discontinuation visit ≤30 days after the last dose of study drug (see Appendix 1 for additional details). The visit during which response assessment shows progressive disease may be used as the treatment discontinuation visit.

After discontinuation of all study treatments, physical examination, CA-125 assessments, and tumor response data, as well as information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits according to the schedule of activities (see Appendix 1), unless the patient withdraws consent specifically for follow-up and/or surveillance or the Sponsor terminates the study. If a patient requests to be withdrawn from follow-up and/or surveillance, this request must be documented in the source documents and signed by the investigator. If the patient withdraws consent from the study that includes follow-up and/or surveillance, the study staff may nevertheless use a public information source (e.g., county records) to obtain only information about survival status.

4.6.2 Patient Discontinuation from Study

Patients will return to the clinic for a study discontinuation visit within 30 days after the last dose of the study treatment is administered.

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure

- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonization (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety profile of bevacizumab plus carboplatin and paclitaxel has been well documented in several clinical trials that included patients with NSCLC and OC. The anticipated important safety risks for bevacizumab are outlined below. Please refer to the Bevacizumab Investigator's Brochure for a complete summary of safety information.

Measures will be taken to ensure the safety of patients who participate in this study, which includes the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of bevacizumab will be performed in a

monitored setting in which there is immediate access to trained personnel and adequate equipment and medication to manage potentially serious reactions. All adverse events will be reported as described in Sections 5.2–5.6.

5.1.1 Risks Associated with Bevacizumab

The most common side effects associated with bevacizumab include GI perforations, surgery and wound-healing complications, hemorrhage (severe or fatal hemorrhage that includes hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, pulmonary hemorrhage, epistaxis, and vaginal bleeding), non-gastrointestinal fistula formation, arterial thromboembolic events (includes cerebral infarction, TIAs, myocardial infarction, angina), and hypertension.

For additional details regarding the safety profile of bevacizumab, refer to the Bevacizumab Investigator's Brochure.

5.1.2 Risks Associated with Paclitaxel

Paclitaxel is known to cause myelosuppression, alopecia, peripheral neuropathy, myalgia, arthralgia, nausea, and vomiting. Less commonly reported adverse events are hypersensitivity reactions, infections, bleeding, diarrhea, mucositis, liver function test elevations, injection-site reactions, and cardiovascular effects such as hypotension, bradycardia, hypertension, arrhythmias, other ECG abnormalities, syncope, and venous thrombosis.

For more details with regard to the safety profile of paclitaxel, refer to the prescribing information for paclitaxel.

5.1.3 Risks Associated with Carboplatin

Carboplatin is known to cause bone marrow suppression, which includes myelosuppression, anemia, and thrombocytopenia. Carboplatin-based chemotherapy is considered to be moderately emetogenic.

For more details with regard to the safety profile of carboplatin, refer to the prescribing information for carboplatin.

5.1.4 Management of Patients Who Experience Specific Adverse Events

5.1.4.1 Dose Modifications, Interruptions, and Delays

In order to maintain dose-intensity and cumulative dose-delivery in this study, reasonable efforts will be made to minimize dose reduction and treatment delays as specified. Any patient whose treatment is delayed must be evaluated on a weekly basis until adequate hematologic and non-hematologic parameters have been met. No dose escalation is planned for this study.

Carboplatin and paclitaxel and bevacizumab/placebo must be given on the same day; hence delays in carboplatin and paclitaxel should result in delay of bevacizumab/placebo as well, until they can all be given safely. Alternatively, if it is not safe to proceed with bevacizumab/placebo, bevacizumab/placebo should be held and omitted, and treatment with carboplatin and paclitaxel should proceed. There is no delay plan in the bevacizumab/placebo-only treatment phase. When it is not safe to proceed with bevacizumab/placebo, bevacizumab/placebo should be omitted. The option to re-start bevacizumab/placebo in the next cycle will depend on the patient's situation and the investigator's judgment. In the event that bevacizumab/placebo is omitted for more than two consecutive administrations (6 weeks), restarting bevacizumab/placebo treatment must be discussed with the Medical Monitor.

5.1.4.2 Management of Adverse Events Related to Bevacizumab/Placebo

Dose reductions of bevacizumab/placebo for adverse events are not allowed. Criteria for treatment modifications and guidelines for the management of toxicities are summarized in Table 3. If adverse events occur that necessitate withholding bevacizumab/placebo from patients, the dose will remain unchanged once treatment resumes.

Table 3 Bevacizumab Dose Management for Adverse Events

Event	Action to Be Taken
Hypertension	
Grade 1 (prehypertension [systolic BP 120–139 mm Hg or diastolic BP 80–89 mm Hg])	No bevacizumab dose modifications. *Consider increased BP monitoring; start anti-hypertensive medication if appropriate.*
Grade 2 *(Stage 1 hypertension [systolic BP 140–159 mm Hg or diastolic BP 90–99 mm Hg]; medical intervention indicated; recurrent or persistent [≥24 hrs]; symptomatic increase by >20 mm Hg [diastolic] or to >140/90 mm Hg if previously WNL; monotherapy indicated)*	Withhold bevacizumab. Start antihypertensive therapy. Once blood pressure is <150/100 mmHg, patient may continue bevacizumab therapy.
Grade 3 *(Stage 2 hypertension [systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg]; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated)*	More than one antihypertensive drug or more intensive therapy than previously required: If not controlled to 150/100 mmHg with medication, discontinue bevacizumab
Grade 4 *(life-threatening consequences [e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis]; urgent intervention indicated)*	Discontinue bevacizumab
Hemorrhage	
Grade 1 or Grade 2 (non–pulmonary-related or non–CNS-related event)	No bevacizumab modifications

Table 3 Bevacizumab Dose Management for Adverse Events (cont.)

Event	Action to Be Taken
Hemorrhage (cont.)	
Grade 3 (non-pulmonary or non-brain or non-spinal cord hemorrhage)	Withhold bevacizumab until all of the following criteria are met: • The bleeding has resolved, and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. Patients who experience a repeat Grade 3 hemorrhagic event will be discontinued from bevacizumab.
Grade 4 (non-pulmonary or non-brain or non-spinal cord hemorrhage)	Discontinue bevacizumab
Grade 1 (pulmonary or brain or spinal cord hemorrhage)	Withhold bevacizumab until all of the following criteria are met: • The bleeding has resolved, and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.
Grade 2, Grade 3, or Grade 4 (pulmonary or brain or spinal cord hemorrhage)	Discontinue bevacizumab

Table 3 Bevacizumab Dose Management for Adverse Events (cont.)

Venous thromboembolic event	
Grade 1 or 2	No bevacizumab modifications
Grade 3 or asymptomatic Grade 4	If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be withheld until the full-dose anticoagulation period is over If the planned duration of full-dose anticoagulation is > 2 weeks, bevacizumab may be resumed after 2 weeks of full-dose anticoagulation if all of the following criteria are met: • The patient must have an in-range INR (between 2 and 3) if on warfarin, low molecular weight heparin, or other anticoagulant dosing must be stable prior to re-initiation of the study treatment. • The patient must not have had a Grade 3 or Grade 4 hemorrhagic event while on anticoagulation.
Symptomatic Grade 4	Discontinue bevacizumab
Arterial thromboembolic event (new onset, deteriorating, or unstable angina, myocardial infarction, TIA, cerebrovascular accident, and any other arterial thromboembolic event)	
Any grade	Discontinue bevacizumab
Congestive heart failure (left ventricular systolic dysfunction)	
Grade 1 or Grade 2	No bevacizumab modifications
Grade 3	*Discontinue bevacizumab*
Grade 4	Discontinue bevacizumab
Proteinuria [a]	
Grade 1 *(1+ proteinuria; urinary protein <1.0 g/24 hrs)*	No bevacizumab modifications
Grade 2 *(2+ proteinuria; urinary protein 1.0–3.4 g/24hrs)*	For 2+ dipstick, may administer bevacizumab and obtain 24-hr urine prior to next dose. For 3+ dipstick, obtain 24-hour urine prior to administration of bevacizumab, withhold bevacizumab for proteinuria > 2 g/24 hr and resume when proteinuria is ≤ 2 g/24 hr. [a]
Grade 3 (*urinary protein ≥ 3.5 g/24 hrs)*	Withhold bevacizumab. Resume when proteinuria is ≤ 2 g/24 hr. [a]
Nephrotic syndrome	Discontinue bevacizumab

Table 3 Bevacizumab Dose Management for Adverse Events (cont.)

Gastrointestinal perforation	
Any grade	Discontinue bevacizumab
Fistula	
Any grade tracheoesophageal fistula	Discontinue bevacizumab
Grade 4 fistula (other than tracheoesophageal)	Discontinue bevacizumab
Bowel obstruction	
Grade 1	Continue patient in the study for partial obstruction that does not require medical intervention.
Grade ≥2	*Withhold and resume at investigator/Medical Monitor discretion after complete resolution. Restart no sooner than 28 days after surgical intervention and complete resolution of post-surgical wound at investigator/Medical Monitor discretion.*
Wound dehiscence	
Any grade (requires medical or surgical therapy)	Discontinue bevacizumab
Reversible posterior leukoencephalopathy	
Any grade (confirmed by magnetic resonance imaging)	Discontinue bevacizumab

[a] All proteinuria values are from 24-hour urine collection. *Institutional protocols are acceptable.*

Temporary suspension of bevacizumab/placebo must occur if a patient experiences a serious adverse event or a Grade 3 or Grade 4 adverse event as assessed by the investigator to be related to bevacizumab/placebo. If the event resolves to Grade ≤1, bevacizumab/placebo may be reinitiated at the same dose level. If bevacizumab/placebo is delayed due to toxicity for >42 days beyond when the next dose should have been given, restarting bevacizumab/placebo treatment must be discussed with Medical Monitor.

The appropriate interval between the last dose of bevacizumab/placebo and major surgery is unknown. Because bevacizumab has a half-life of approximately 21 days, elective surgery should be delayed whenever possible, but if necessary, bevacizumab/placebo should be withheld for ≥28 days prior to the procedure. Emergency surgery should be performed as appropriate without delay after a careful benefit-risk assessment. Reinitiation of bevacizumab after surgery should not occur for ≥28 days, and until wounds have fully healed. Reinitiation of bevacizumab after surgery requires documented approval from the Medical Monitor.

Infusion of bevacizumab/placebo should be interrupted in patients who develop dyspnea or clinically significant hypotension. Patients who experience an NCI CTCAE Grade 3 or Grade 4 allergic reaction and/or hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade level) will be discontinued from bevacizumab/placebo treatment. If possible, a sample for ADA assessment will be collected at the time of discontinuation.

Bevacizumab/placebo infusion should be slowed to ≤50% or interrupted for patients who experience any infusion-associated symptoms not specified above. If the infusion is interrupted, it may be resumed at ≤50% of the rate prior to the reaction after the patient's symptoms have adequately resolved, and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.

For guidelines on the dosing of other study drugs when bevacizumab/placebo is withheld, see Table 4.

5.1.4.3 Management of Adverse Events Related to Carboplatin/Paclitaxel

The dose for this regimen is carboplatin AUC 6 mg/mL/min with paclitaxel 175 mg/m^2 on Day 1 for a maximum of six cycles.

Investigators should follow their institution's administration guidelines for carboplatin and paclitaxel and local prescribing information for carboplatin and paclitaxel. For further details of administration, preparation, and storage, refer to the pharmacy manual and local prescribing information for carboplatin and paclitaxel. Carboplatin-based chemotherapy is considered to be highly emetogenic, and the appropriate anti-emetic prophylaxis should be administered.

5.1.4.3.1 Carboplatin and Paclitaxel Dose Modifications

Dose levels of carboplatin and paclitaxel are shown in Table 4.

Table 4 Dose Levels of Chemotherapy

Drug	Starting Dose Level	Dose Level 1	Dose Level 2
Carboplatin	AUC 6 mg/mL/min	AUC 5 mg/mL/min	AUC 4 mg/mL/min
Paclitaxel	175 mg/m^2	135 mg/m^2	110 mg/m^2

AUC = area under the concentration–time curve.

5.1.4.3.2 Hematologic Toxicity

Treatment decisions will be based on the ANC rather than total WBC. ANC must be ≥1,500/mm^3 and platelet count must be ≥10,0000/mm^3 on Day1 of each cycle.

5.1.4.3.2.1 Dose Modification

Initial occurrence of dose-limiting toxicity neutropenia (DLT ANC) or dose-limiting toxicity thrombocytopenia (DLT PLT) will be handled according to Table 5.

DLT ANC is defined by the occurrence of febrile neutropenia or prolonged Grade 4 neutropenia persisting for 7 days. There will be no modifications for uncomplicated Grade 4 neutropenia lasting less than 7 days. Febrile neutropenia is defined according to the NCI CTCAE as fever with or without clinically or microbiologically documented infection with ANC $<1000/mm^3$ and fever $\geq 38.5°C$. DLT PLT is defined by any occurrence of Grade 4 thrombocytopenia ($<25,000/mm^3$) or bleeding associated with Grade 3 thrombocytopenia (25,000 to $<50,000/mm^3$). There will be no modifications for uncomplicated Grade 3 thrombocytopenia.

Table 5 Modification Instructions for DLT Hematologic Toxicity

DLT ANC	DLT PLT	First Occurrence	Second Occurrence
Yes	No	Reduce carboplatin to AUC 5 mg/mL/min (and paclitaxel to 135 mg/m2)	Add G-CSF and maintain all current drug doses
Yes	Yes	Reduce carboplatin to AUC 5 mg/mL/min (and paclitaxel to 135 mg/m2)	Add G-CSF and decrease carboplatin to AUC 4 mg/mL/min (and paclitaxel to 110 mg/m2)
No	Yes	Reduce carboplatin to AUC 5 mg/mL/min (and paclitaxel to 135 mg/m2)	Decrease carboplatin to AUC 4 mg/mL/min (and paclitaxel to 110 mg/m2)

AUC = area under the curve; DLT ANC = dose-limiting neutropenia; DLT PLT = dose-limiting thrombocytopenia; G-CSF = granulocyte colony-stimulating factor.

All dose reduction for the first episode of DLT ANC and DLT PLT are permanent. If a second episode of DLT ANC and DLT PLT requiring dose reduction occurs, the doses of carboplatin will be reduced to AUC 4 mg/mL/min. For patients who require a third dose reduction, chemotherapy should be immediately discontinued.

5.1.4.3.2.2 Treatment Delay

Treatment should be delayed if either of the following occurs within 24 hours prior to scheduled therapy: ANC is $\leq 1500/mm^3$ (or $<1000/mm^3$ if the patient is receiving or is planned to receive G-CSF) or the platelet count is $\leq 10,0000/mm^3$.

Full blood counts (including differential WBC counts) should be repeated at least weekly until hematological recovery has occurred. If hematological recovery occurs within 7 days, no dose modification is mandated. If hematological recovery occurs in 7 to 21 days, for an abnormal ANC, G-CSF should be added with the next cycle; for patients with platelet count decrease, carboplatin should be decreased one AUC unit.

However, if the ANC and platelet counts have not recovered in 3 weeks, the patient's chemotherapy should be discontinued.

Investigators should be vigilant and alert to early and overt signs of myelosuppression/infection/febrile neutropenia so that these complications can be promptly and appropriately managed.

Patients should be made aware of these signs and encouraged to seek medical attention at the earliest opportunity.

No dose reductions will be made for anemia. Patients should be supported per the treating physician's institution's guidelines.

5.1.4.3.3 Hepatic Toxicity (Paclitaxel)

The Day 1 value should be used to determine the dose (see Table 6).

Table 6 Paclitaxel Dose Level for Different Hepatic Values

AST		Bilirubin	Paclitaxel Dose to Give
$\leq 5 \times$ ULN	And	WNL	175 mg/m^2
$> 5 \times$ ULN	Or	$>$ ULN $- 1.5 \times$ ULN	135 mg/m^2
		$> 1.5 \times$ ULN	0

AST = aspartate aminotransferase; ULN = upper limit of normal; WNL = within normal limit.

If paclitaxel is withheld because of hepatic toxicity, carboplatin should also be withheld and administered when paclitaxel is resumed. If paclitaxel is withheld, hepatic values must recover within 3 weeks, or the patient's paclitaxel treatment should be discontinued. No dose reductions for carboplatin should be made for hepatic toxicity.

The investigator should make all efforts to exclude malignant disease progression as a cause of liver enzyme derangement. All study medication should be discontinued if the disease under investigation has progressed.

5.1.4.3.4 Cardiovascular Toxicity (Paclitaxel)

Cardiac rhythm disturbances have occurred infrequently in patients in clinical trials with paclitaxel treatment; however, most patients were asymptomatic, and cardiac monitoring is not required. Transient asymptomatic bradycardia has been noted in as many as 29% of patients. More significant atrioventricular block has rarely been noted. Cardiac events should be managed as follows:

- **Asymptomatic bradycardia:** Report as an adverse event.
- **Symptomatic arrhythmia during infusion:** Stop paclitaxel infusion and manage arrhythmia according to standard practice. Paclitaxel treatment will be discontinued. Report as an adverse event.

- **Chest pain and/or symptomatic hypotension (<90/60/mmHg or requires fluid replacement):** Stop paclitaxel infusion. Perform an ECG. Give IV diphenhydramine and dexamethasone if hypersensitivity is considered. Also consider epinephrine or bronchodilators if chest pain is not thought to be cardiac in origin. Report as an adverse event. Paclitaxel treatment will be discontinued, and cardiovascular support should be given as appropriate. If appropriate, the advice of a cardiologist should also be sought.

5.1.4.3.5 Neurologic Toxicity (Paclitaxel)

Severe peripheral neuropathy requires reduction of one dose level in paclitaxel and delay in all subsequent study treatment for a maximum of 3 weeks until recovery to Grade 1. If peripheral neuropathy does not recover to Grade 1 by a maximum delay of 3 weeks from the time therapy is scheduled, the patient's chemotherapy should be discontinued.

5.1.4.3.6 Allergic Reaction/Hypersensitivity (Paclitaxel)

CAUTION: Patients who had a mild to moderate hypersensitivity reaction have been successfully rechallenged, but the administration of prophylactic medication (see below) and intensive monitoring of vital signs is recommended.

In general, the occurrence of a hypersensitivity reaction to paclitaxel, carboplatin, or bevacizumab/placebo is not considered a DLT. Patients may be retreated at full doses after administration of medication to prevent hypersensitivity reactions, and adjustments in infusion rates should be made. However, if despite these safety measures, repeat attempt at infusion of the inciting drug results in a recurrent hypersensitivity reaction, the inciting drug should be discontinued for the remainder of the study. In the event of any Grade 3 or 4 allergic or infusional reaction to bevacizumab / placebo, bevacizumab/placebo will be permanently discontinued. Allergic reaction/hypersensitivity events should be managed as follows:

- **Mild symptoms:** Complete paclitaxel infusion. Supervise at bedside.
- **Moderate symptoms:** Stop paclitaxel infusion. Give IV diphenhydramine 25 to 50 mg and IV dexamethasone 10 mg. Resume paclitaxel infusion, after recovery of symptoms, at a low rate, 20 mL/hr for 15 minutes, and then 40 mL/hr for 15 minutes, then if no further symptoms, at full-dose rate until infusion is complete. Report as an adverse event. If symptoms recur, stop paclitaxel infusion. Paclitaxel treatment should be discontinued.
- **Severe life-threatening symptoms:** Stop paclitaxel infusion. Give IV diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. Report as an adverse event. Paclitaxel treatment should be discontinued.

5.1.4.3.7 Other Toxicities

There will be no dose modifications for alopecia, nausea, constipation, or diarrhea. It is recommended that routine medical measures be employed to manage nausea, constipation, and diarrhea.

Potential modifications for other non-hematologic toxicities with an impact on organ function of Grade ≥2 require discussion with the Medical Monitor or his or her designee except where noted below.

For any Grade 3 non-hematologic adverse event (except controllable nausea/emesis) considered to be at least possibly related to study treatment, study treatment should be held until symptoms resolve to Grade 1 or better. If a Grade 3 adverse event persists for more than 3 weeks or recurs after resumption of therapy, the patient may be discontinued from study treatment after consulting with the Medical Monitor or his or her designee.

For any Grade 4 non-hematologic adverse event (except controllable nausea or emesis), the patient may be discontinued from study treatment after consulting with the Medical Monitor or his or her designee.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline

- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Grade ≥3 hypertension
- Grade ≥3 proteinuria
- Any grade GI perforation, abscess, or GI fistulae
- Grade ≥2 non–GI-related fistula or abscess
- Tracheoesophageal fistula
- Grade ≥3 wound-healing complication
- Hemorrhage

  Any grade CNS bleeding

  Grade ≥ 2 hemoptysis

  Other Grade ≥ 3 hemorrhagic event
- Any grade arterial thromboembolic event
- Grade ≥3 venous thromboembolic event
- Any grade posterior reversible encephalopathy syndrome
- Grade ≥3 congestive heart failure

These events may or may not be serious adverse events, and they may or may not be considered related to study medication. Regardless of relationship or severity, these events will be followed for 6 months after the last study treatment or until resolution.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After the initiation of the study treatment, all adverse events will be reported until 30 days after the last dose of the study treatment is administered or until the initiation of a new anti-cancer therapy, whichever occurs first. Serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of the study treatment was administered or until the initiation of a new anti-cancer therapy, whichever occurs first.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 7 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 7 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration *(see also Table 8):*

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

Table 8 Causal Attribution Guidance

Is the adverse event suspected to be caused by study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	*There is a plausible temporal relationship between the onset of the adverse event and administration of study treatment, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to study treatment; and/or the adverse event abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon re-challenge.*
NO	*An adverse event will be considered related, unless it fulfills the criteria specified below.* *Evidence exists that the adverse event has an etiology other than study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment).*

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of ovarian, fallopian tube, or primary peritoneal cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An independent monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical

concept on the Adverse Event eCRF. Generally, one such event should be reported only. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Ovarian, Fallopian Tube, or Primary Peritoneal Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration, insertion of access device for study drug administration or the performance of an efficacy measurement for the study)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

  The patient has not experienced an adverse event.

- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

The highest dose of bevacizumab tested in human patients (20 mg/kg of body weight every 2 weeks administered by IV infusion) was associated with severe migraine in several patients.

Carboplatin was administered in Phase I studies at a dosage of up to 1600 mg/m^2 by IV per course. At this dosage, life-threatening hematological side effects with granulocytopenia, thrombocytopenia, and anemia were observed in the study patients. See the Carboplatin Package Insert for more details.

There is no known antidote for paclitaxel overdose. Treatment should be directed at the primary anticipated toxicities, which consist of bone marrow suppression. See Paclitaxel Package Insert for more details.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and Institutional Review Board (IRB)/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor/Roche Medical Responsible: [redacted] M.D., Ph.D. (Primary)

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

Medical Monitor/Roche Medical Responsible: [redacted], *M.D., M.S.* (Secondary)

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all

calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of study treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur $>$90 days after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 6 months after the last dose of bevacizumab, paclitaxel, or carboplatin, whichever is later. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 90 days after the last dose of any study treatment), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study drug, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Bevacizumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Analysis populations are defined as follows:

- The intent-to-treat (ITT) population is defined as all randomized patients regardless of whether the assigned study treatment was received. For efficacy analyses, patients will be analyzed according to their randomized treatment assignment.
- Objective response rate (ORR) will be analyzed in patients in the ITT population with measurable disease at baseline.
- The duration of response (DOR) evaluable population is defined as patients with an objective response.
- The PRO-evaluable population is defined as patients in the ITT population with a baseline and ≥ 1 post-baseline PRO assessment.
- The safety population is defined as patients who received any amount of any component of the study treatments (bevacizumab, paclitaxel or carboplatin). Patients will be allocated to treatment arms according to the treatment they actually received (i.e., patients randomized to placebo + chemotherapy alone who received at least one full or partial dose of bevacizumab will be included in the bevacizumab + chemotherapy arm for safety).

Baseline measurements are the last available data obtained prior to the patient receiving the first dose of study treatment.

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of this study is to confirm the efficacy and safety of bevacizumab in a population of Chinese women with advanced ovarian, fallopian tube, and primary peritoneal cancers who have not received prior chemotherapy for this disease, and to investigate the consistency in treatment effect between Chinese patients and the patients in global study for the purpose of registration in China. The primary efficacy results will be bridged with those of the pivotal Study GOG218.

A total of approximately 100 patients will be randomized in a 1:1 ratio to either the bevacizumab or placebo arms of the study. The final analysis of the primary endpoint of PFS will be performed when approximately 56 PFS events have occurred in the ITT

population (56% of 100 patients), which will provide an 80% probability of demonstrating consistency with the global study.

The calculation is based on the following assumptions:

- Median PFS is 18.2 months for the bevacizumab arm and 12 months for the placebo arm (hazard ratio [HR]=0.624)
- Enrollment rate is 9.6 patients per month
- 5% yearly dropout rate

On the basis of the above assumptions, the required number of PFS events for the final analysis is projected to occur at approximately 24 months after the first patient is randomized.

The study is not powered to demonstrate statistical significance of treatment benefit on the primary and secondary efficacy endpoints. Because no formal hypothesis testing will be performed, no type I error adjustment for multiple comparisons will be made.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized by treatment arm for the ITT population. Reasons for premature study withdrawal will be summarized. Enrollment and major protocol deviations will be reported and summarized by treatment arm for the ITT population.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race/ethnicity, baseline disease characteristics, etc.) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented by treatment arm for the ITT population.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy endpoints will be analyzed for the ITT population unless specified otherwise, with patients grouped according to their assigned treatment.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is PFS, which will be assessed by the investigator using RECIST v1.1. The study is not fully powered for the primary endpoint; instead consistency with the global pivotal study (GOG218) will be considered for the primary endpoint.

PFS after randomization is defined as the time from randomization to the first documented occurrence of disease progression or death from any cause during the study (whichever occurs first), as determined by the investigator according to

RECIST v1.1. Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment. Data for patients with no post-baseline tumor assessment will be censored at the date of randomization plus 1 day.

The primary endpoint of PFS will be analyzed between treatment and control arms based on the stratified log-rank test. The HR of PFS in the experimental arm compared with the control arm will be estimated using a stratified Cox regression model, and the 95% CI will be provided. The stratification factors will be those used during randomization, as recorded in eCRF. Results from an unstratified analysis will also be presented. Kaplan-Meier methodology will be used to estimate median PFS for each treatment arm, and Kaplan-Meier curves will be constructed to provide visual descriptions of the difference between the treatment and control arms.

The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS and OS for each treatment arm (Brookmeyer and Crowley 1982).

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Overall Survival

OS is defined as the time from randomization to death from any cause. Data for patients who are not reported as having died at the date of analysis will be censored at the date when they were last known to be alive. Data for patients who do not have post-baseline information will be censored at the date of randomization plus 1 day.

The methodologies detailed for the PFS analysis will be used for the OS analysis in the ITT population.

6.4.2.2 Objective Response Rate (ORR)

An objective response is defined as either a CR or PR, as determined by the investigator according to RECIST v1.1. Patients who do not meet these criteria, including patients without any post-baseline tumor assessment, will be considered non-responders.

ORR is defined as the proportion of patients who had an objective response. The analysis population for ORR will be all patients in the ITT population with measurable disease at baseline. An estimate of ORR and its 95% CI will be calculated using the Clopper Pearson method for each treatment arm. CIs for the difference in ORRs between the two treatment arms will be determined using the normal approximation to the binomial distribution.

6.4.2.3 Duration of Response

DOR will be assessed in patients who had an objective response as determined by the investigator by use of RECIST v1.1. DOR is defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause during the study (whichever occurs first), as determined by the investigator according to RECIST v1.1. Patients who have not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date. DOR is based on a non-randomized subset of patients (specifically, patients who achieved an objective response), and formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes. The methodologies detailed for the PFS analysis will be used for the DOR analysis.

6.4.2.4 Patient-Reported Disease Symptoms, Function and Health-Related Quality of Life—EORTC Data

Patient-Reported Abdominal Pain or Bloating—EORTC QLQ-OV28

The primary patient-reported outcomes endpoint of the proportion of patients in each arm who report a clinically meaningful improvement in patient-reported abdominal pain or bloating, defined as a ≥10-point decrease from the baseline score on each of two items from the EORTC QLQ-OV28 abdominal/gastrointestinal symptom scale (Items 31 and 32), will be summarized at each post-baseline timepoint by treatment arm, with its 95% CI, with the use of Clopper Pearson method. The difference in proportions will be provided, with its 95% CI, with the use of the Hauck-Anderson method.

Prespecified subgroup analysis will also be performed in patients with ascites at baseline (who typically have significantly impaired HRQoL) and in patients with sufficient symptoms at baseline to allow detection of a 10-point improvement in a given symptom score.

The definition of improvement in patient-reported abdominal pain or bloating (i.e., a ≥10-point decrease from the baseline score in QLQ-OV28 abdominal symptom items) is based on the standard analysis method for the EORTC QLQ-C30 that deems a score change of 10 points on any item or scale to be clinically meaningful (Osoba et al. 1998; Fayers 2001a; Osoba 2002; Osoba et al. 2005; Brundage et al. 2007; Luckett et al. 2010; Cocks et al. 2011). Although the clinical meaningfulness of a 10-point change was established based on the EORTC QLQ-C30, the disease-specific modules, including the QLQ-OV28, were designed on the same structure using the same rating scale and are, therefore, applicable in this context. Additionally, other OC studies have used the 10-point minimally important difference (MID) threshold for the QLQ-OV28, demonstrating that a change of this magnitude is significant to patients with OC while setting a precedent for its use and supporting its utility in this context (Richter et al. 2012; Brotto et al. 2016; Fagotti et al. 2016).

A sensitivity analysis will be performed to evaluate the robustness of the published standard threshold for meaningful change of 10-points with the use of the raw data for

the abdominal pain and bloating items of the EORTC QLQ-OV28. The proportion of patients in each arm reporting a 1-category decrease on each of the 4-point symptom scales of the EORTC QLQ-OV28 abdominal symptom items (Items 31 and 32) will be summarized at each post-baseline timepoint by treatment arm. All analyses of the abdominal symptoms single item data that involve the 10-point MID will be replicated with this alternate MID threshold.

Patient-Reported Function and HRQoL: EORTC QLQ-C30

For the additional secondary PRO endpoint, the proportion of patients in each arm who report a clinically meaningful improvement in patient-reported function and HRQoL, defined as a ≥10-point increase from the baseline score on each of the functional (physical, role, emotional, and social) and global health status and/or HRQoL scales of the EORTC QLQ-C30, will be summarized at each post-baseline timepoint by treatment arm as specified above.

6.4.3 Exploratory Efficacy Endpoints

6.4.3.1 Patient-Reported Disease and/or Treatment-Related Symptoms—EORTC Data

Summary statistics (mean, standard deviation, median, and range) of absolute scores and mean changes from the baseline will be calculated for all disease and/or treatment-related symptom items and subscales of the EORTC QLQ-C30 and QLQ-OV28 at each assessment timepoint for each arm during the administration of the treatment and the survival follow-up period. The mean (and 95% CI) and median of the absolute scores and the changes from the baseline will be reported for interval and continuous variables. Previously published minimally-important differences will be used to identify meaningful change from the baseline within each treatment group on the disease and/or treatment-related symptoms scales (Osoba et al. 1998; Cocks et al. 2011).

The EORTC QLQ-C30 and QLQ-OV28 data will be scored according to the EORTC scoring manual (Fayers et al. 2001b). In the event of incomplete data, if the scale has more than 50% of the constituent items completed, a pro-rated score will be computed that is consistent with the scoring manual and the validation papers of the measure. For subscales with less than 50% of the items completed, the subscale will be considered missing. PRO completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm.

6.4.3.2 FACT-G, Single Item GP5 Data

A descriptive analysis of absolute scores and the proportion of patients who selected each response option at each assessment visit by treatment arm will be reported for item GP5 ("I am bothered by side effects of treatment") from the FACT-G physical well-being subscale. Item GP5 from Version 4 of the FACT-G questionnaire will be scored according to the FACIT scoring manual (Cella 1997). PRO completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm.

6.4.3.3 Health Economic Data

Health economic data, as assessed by the EQ-5D-5L, will be evaluated for patients with a baseline assessment and at least one post-baseline EQ-5D-5L assessment. The results from the health economic data analyses will be reported separately from the CSR as they will be used in pharmacoeconomic analyses only.

6.4.4 Handling of Missing Data

For PFS, patients who are alive without a date of disease progression will be analyzed as censored observations on the date of the last tumor assessment. If no post-baseline tumor assessment is available, PFS will be censored at the date of randomization plus 1 day.

For OS, patients who are not reported as having died will be analyzed as censored observations on the date they were last known to be alive. If no post-baseline data are available, OS will be censored at the date of randomization plus 1 day.

For objective response, patients without any post-baseline assessment will be considered non-responders.

For DOR, data for patients who have not progressed and who have not died at the time of analysis will be censored at the time of the last tumor assessment date.

For the PRO disease-symptom improvement, patient function and HRQoL endpoints, patients without a baseline assessment visit or a certain post-baseline assessment visit will be considered non-responders and will not be included in the analysis.

6.5 SAFETY ANALYSES

Safety analyses will be performed on the safety-evaluable population, which is defined as patients who received any amount of any component of the study treatments (bevacizumab, paclitaxel or carboplatin). Patients will be allocated to treatment arms according to the treatment they actually received (i.e., patients randomized to placebo+chemotherapy alone who received at least one full or partial dose of bevacizumab will be included in the bevacizumab+chemotherapy arm for safety).

Drug exposure will be summarized to include treatment duration, number of doses, and dose intensity.

Verbatim description of adverse events will be mapped to MedDRA thesaurus terms and graded according to NCI CTCAE v4.0. All adverse events occurring during or after the first study drug dose will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events, severe adverse events (Grade ≥ 3), adverse events of special interest, and adverse events leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity.

Laboratory data with values outside the normal ranges will be identified. In addition, selected laboratory data will be summarized by treatment arm and grade.

Changes in vital signs will be summarized by treatment arm.

Deaths reported during the study treatment period and those reported during the follow-up period after study treatment completion and discontinuation will be summarized by treatment arm.

6.6 INTERIM ANALYSIS

There will be no planned interim analysis.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Other electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data. eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, paper PRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC – approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures like optional tumor and plasma samples (see Section 4.5.6). The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 16 sites countrywide will participate to enroll approximately 100 patients. Enrollment will occur through an IxRS.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study, and redacted clinical study reports and other summary reports will be provided upon request (see Section 8.4 for more details).

For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective CSR. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Observations and Tests	Pre-Treatment	Chemotherapy (Cycles 1–6) and Bevacizumab/Placebo (Cycles 2–6) [a]			Bevacizumab/ Placebo Only (Cycle 7 through Discontinuation) [a]		Study Completion/Early Termination Visit [a]	Post-Treatment [a]
	Day –28 to –1	Weekly	Every Course	Every Other Course	Every Course	Every Other Course	Within 30 days of the last dose of the study treatment	Every 3 Months for 2 Years, Every 6 Months for 3 Years, Then Annually
Informed consent	x							
History and physical examination	x [b]		x [c, d]			x [c, d]		x
ECOG PS	x		x		x		x	
Vital signs	x [b]	x [e]	x [c]		x [c]			
Hematology [f]	x [g]		x			x	x	
Urinalysis	x [h]		x [i]		x [i]		x	
Serum chemistry [j]	x [g]		x			x	x	
Serum pregnacy test (for women of childbearing potential)	x [g]	As clinically indicated						
PT/INR, aPTT	x [g]		x [k]			x [k]	x [l]	
Audiogram	x [m]							
ECG	x [b]	As clinically indicated						
Radiographic disease assessment	x [b, n]			x [d, o]		x [d, o]	x [p]	x [o]

Appendix 1: Schedule of Activities

Observations and Tests	Pre-Treatment	Chemotherapy (Cycles 1–6) and Bevacizumab/Placebo (Cycles 2–6) [a]			Bevacizumab/ Placebo Only (Cycle 7 through Discontinuation) [a]		Study Completion/Early Termination Visit [a]	Post-Treatment [a]
	Day –28 to –1	Weekly	Every Course	Every Other Course	Every Course	Every Other Course	Within 30 days of the last dose of the study treatment	Every 3 Months for 2 Years, Every 6 Months for 3 Years, Then Annually
HIV, HBV, HCV serology [q]	x							
Serum CA-125 level	x [b, r]		x [c, s]			x [c, s]		x
EORTC QLQ-C30, QLQ-OV28, and EQ-5D-5L [t]				x		x	x	x
FACT-G and the single item GP5 [t]				Starting at Cycle 4		x	x	x
Adverse events [u]	x [g]	x	x		x		x	x
Concomitant medications	x [v]		x		x		x	x
Incision check	x	x [w]						
Bevacizumab/placebo administration			x [x]		x			
Paclitaxel administration			x					
Carboplatin administration			x					

Appendix 1: Schedule of Activities

aPTT = activated partial thromboplastin time; CA-125=cancer antigen 125; CT=computed tomography; ECOG PS = Eastern Cooperative Oncology Group Performance Status; EORTC=European Organization for Research and Treatment of Cancer; EQ-5D-5L = EuroQol 5 Dimension, 5-Level Questionnaire; FACT-G GP5 = Functional Assessment of Cancer Therapy–General; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; INR = International Normalized Ratio; MRI=magnetic resonance imaging; QLQ-OV28=Quality of Life Questionnaire Ovarian Cancer Module 28; QLC-C30 = Quality of Life Questionnaire Core 30; PRO=patient-reported outcome; PT = prothrombin time; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Each cycle is 21 days. Study drug administration occurs on Day 1 (± 3 days) of each cycle. All other events and assessments during the study treatment must occur within 3 days prior to the administration. The end of the study treatment or early discontinuation visit should occur within 30 days after the last dose of the study treatment is administered. The post-treatment follow up visits will occur every 3 months (± 14 days) for the first 2 years after *the end of study treatment or early discontinuation visit,* then every 6 months (± 14 days) for 3 years, and then annually.

[b] Must be performed within 28 days prior to start of study treatment.

[c] Within 1 week before and as close to the beginning of the next applicable course as possible.

[d] Patients who do not experience disease progression, including those who will discontinue study treatment, need to be followed in a consistent fashion to monitor tumor status. Therefore, the schedule of tumor assessment by physical examination, CA-125 monitoring, and imaging should be conducted according to the timeline shown per the study calendar.

[e] Vital signs should be assessed at least weekly during the first cycle of bevacizumab/placebo therapy. During the time between treatments, vital sign assessments may be performed at home by the patient at the investigator's discretion, and the investigator or study nurse are responsible for obtaining the results from the patient.

[f] Hematology should include hemoglobin, hematocrit, platelet count, red blood cell count, and WBC count with differential (neutrophils). Additional hematologic assessments may be performed as clinically indicated or per local practice.

[g] Must be obtained within 14 days prior to start of study treatment.

[h] Within 7 days before treatment.

[i] Does not need to be repeated on Day 1 if tests are performed within 7 days before Day 1 (start of study treatment).

j Serum chemistry includes sodium, potassium, glucose, blood urea nitrogen (BUN), creatinine, albumin, bilirubin, AST, ALT, and ALP.

[k] For patients on prophylactic or therapeutic anticoagulation with warfarin, PT/INR should be monitored before each treatment. Treatment should be withheld for PT INR of > 1.5 on prophylactic warfarin or greater than the therapeutic range if patient is on full-dose warfarin.

[l] When clinically indicated.

[m] For patients with a history of hearing loss; an audiogram should be repeated as clinically indicated.

[n] An initial CT or MRI scan of at least the chest, abdomen, and pelvis is required to establish a postsurgical baseline for the extent of residual disease within 28 days prior to randomization (Scan 1). A CT/MRI scan of the neck and/or head may also be performed if necessary.

Appendix 1: Schedule of Activities

[o] Follow-up radiographic assessment of disease. In the absence of RECIST-defined disease progression, imaging using the same modality and encompassing the same field as in the initial pre-treatment evaluation should be repeated with the following schedule, regardless of whether or not the patient has measurable disease on initial CT or MRI scan and regardless of the treatment cycle:

- Scans 2 and 3: Every 9 weeks (± 5 days) from the date of randomization during the concurrent treatment phase
- Scans 4, 5, 6, and 7: Every 12 weeks (± 5 days) in the maintenance phase (the first scan in the maintenance phase is performed 12 weeks after the last scan during the concurrent treatment phase)
- After the completion of all protocol therapy, every 3 months (± 14 days) for 2 years, then every 6 months (± 14 days) for 3 years. CT scans or MRIs after 5 years of survival follow-up may be done as clinically indicated.
- During or after completion of all study treatment, as clinically indicated at any time for clinical suspicion of progressive disease, including rising serum CA-125 levels, not meeting criteria for disease progression. Imaging assessments as part of this protocol should be discontinued if RECIST-defined disease progression is confirmed according to guidelines.
- *Patients with no RECIST-defined disease progression who are early discontinued from study treatment before Cycle 6 (including Cycle 6), Scans 2 and 3: Every 9 weeks (± 5 days) from the date of randomization; the following tumor assessments should be conducted every 3 months (± 14 days) after the study completion/early termination visit for 2 years, then every 6 months (± 14 days) for 3 years. CT scans or MRIs after 5 years of survival follow-up may be done as clinically indicated.*
- *Patients with no RECIST-defined disease progression who are early discontinued from study treatment after Cycle 6, the following tumor assessments should be conducted every 3 months (± 14 days) after the study completion/early termination visit for 2 years, then every 6 months (± 14 days) for 3 years. CT scans or MRIs after 5 years of survival follow-up may be done as clinically indicated.*

[p] If not performed within 28 days prior to the treatment discontinuation visit.

[q] HBsAg, HBsAb, HBcAb, and HCV Ab serology and HIV testing are required at screening. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection.

[r] Baseline pre-chemotherapy value is required. When available, also include pre-surgical value.

[s] PFS will be assessed using RECIST, Version 1.1. CA-125 elevation alone will not be used to define progressive disease. However, CA-125 levels will be collected as described in the schedule of activities to enable further analysis.

Appendix 1: Schedule of Activities

[t] All PRO questionnaires must be completed in their entirety by the patient at the investigational site at the start of the clinic visit before discussion of the patient's health state, laboratory test results, or health records, before the administration of the study treatment, and/or prior to the performance of any other study assessments (e.g., scans) that could bias the patient's responses.

- The EORTC QLQ-C30, QLQ-OV28, and EQ-5D-5L questionnaires must be administered and completed by patients in that order at the following assessment timepoints: baseline, defined as prior to Cycle 1 (± 3 days); prior to Cycle 4 of chemotherapy (± 3 days); prior to Cycle 7 (± 3 days); prior to Cycle 13 (± 3 days); prior to Cycle 22 (± 3 days); at the end of treatment or discontinuation visit within 30 days of the administration of the last dose of study treatment; after the treatment completion visit, every 3 months (± 14 days) for the first year of the survival follow-up period; every 6 months (± 14 days) for the second year of the survival follow-up period; and every year (± 14 days) for the final 3 years of the survival follow-up period.
- The single-item GP5 from the FACT-G questionnaire will be the final PRO measure to be administered and must be completed by patients beginning at the Cycle 4, Day 1 visit; and then at all other assessment timepoints listed above along with the other PRO questionnaires.

[u] All serious adverse events and adverse events of special interest, regardless of their relationship to the study drug, will be reported until 90 days after the last dose of the study drug is administered or the initiation of new anti-cancer therapy, whichever occurs first. All other adverse events, regardless of the relationship to the study drug, will be reported until 30 days after the last dose of the study drug is administered or the initiation of new anti-cancer therapy, whichever occurs first. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment.

[v] Concomitant medications need to be collected 7 days prior to starting study treatment.

[w] Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection are eligible, but require weekly wound examinations until complete closure.

[x] Bevacizumab/placebo is initiated at Cycle 2 rather than at Cycle 1.

Appendix 2
Response Evaluation Criteria in Solid Tumors (RECIST), V 1.1: Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1,[1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below.

a) Measurable Tumor Lesions

Tumor Lesions: Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

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[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

b) Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

c) Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic–blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques, such as CT or MRI, can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable

Appendix 2: Response Evaluation Criteria in Solid Tumors (RECIST), V 1.1: Modified Excerpt from Original Publication

Target Lesions: Specifications by Methods of Measurements

d) Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

e) Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial and $\geq$ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

Chest X-Ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions on a different modality and interpretation of

non-target disease or new lesions, since the same lesion may appear to have a different size using a new modality.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology: The utilization of these techniques for objective tumor evaluation cannot generally be advised.

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

Baseline Documentation of Target and Non-Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is $>$ 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq$ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally

reported as two dimensions in the plane in which the image is obtained (for CT this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq$ 10 mm but $<$ 15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$ 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Response Criteria

f) Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to $<$ 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters

- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.
- Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

g) Special Notes on the Assessment of Target Lesions

Lymph Nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to $<$ 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if complete response (CR) criteria are met, since a normal lymph node is defined as having a short axis of $<$ 10 mm.

Target Lesions That Become Too Small to Measure: During the study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and below measurable limit (BML) should be ticked. (BML is equivalent to a “less than” sign.) (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

<u>To reiterate, however, if the radiologist is able to provide an actual measure, it should be recorded, even if it is below 5 mm, and in that case BML should not be ticked.</u>

Appendix 2: Response Evaluation Criteria in Solid Tumors (RECIST), V 1.1: Modified Excerpt from Original Publication

Lesions That Split or Coalesce on Treatment: When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

h) Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

- Complete response: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level
- All lymph nodes must be non-pathological in size ($<$10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- Progressive disease: Unequivocal progression of existing non-target lesions

  The appearance of one or more new lesions is also considered progression.

i) Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease: In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease: This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that

can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy." If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

j) New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show partial or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

(18)F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly, possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. A negative FDG-PET scan at baseline with a positive[3] FDG-PET scan during the study is a sign of PD based on a new lesion.

2. In the case of no FDG-PET scan at baseline and a positive FDG-PET scan during the study:

   If the positive FDG-PET scan during the study corresponds to a new site of disease confirmed by CT, this will be considered PD.

   If the positive FDG-PET scan during the study is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine whether there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

   If the positive FDG-PET scan during the study corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this will not be considered PD.

Evaluation of Response

k) Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

[3] A “positive” FDG-PET scan lesion means one that is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation-corrected image.

Appendix 2: Response Evaluation Criteria in Solid Tumors (RECIST), V 1.1: Modified Excerpt from Original Publication

Table 1 Timepoint Response: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2 Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

Appendix 2: Response Evaluation Criteria in Solid Tumors (RECIST), V 1.1: Modified Excerpt from Original Publication

l) Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would most likely happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess" except where this is clear evidence of progression, as this equates with the case being not evaluable at that timepoint.

m) Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1 and 2.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Appendix 2: Response Evaluation Criteria in Solid Tumors (RECIST), V 1.1: Modified Excerpt from Original Publication

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 3
CA-125 Response and Progression Evaluation Criteria

CA-125 RESPONSE

Guidelines for using CA-125 response have been developed (Rustin 2004). Patients should have a pretreatment CA-125 of at least twice the upper limit of normal (ULN) in order to be considered for CA-125 response. In those patients, a CA-125 response would be obtained the moment the CA-125 is reduced by 50% and this should be confirmed with a consecutive CA-125 assessment not earlier than 28 days after the previous one, with however the date of the first 50% reduction to be the reference date for the CA-125 response.

CA-125 PROGRESSIVE INCREASE

CA-125 progressive increase will be defined on the basis of a progressive serial elevation of serum CA-125 according to the following criteria:

- Patients with elevated CA-125 levels pre-treatment and normalization of CA-125 must show evidence of CA-125 $\geq 2\times$ the ULN on two occasions at least 1 week apart **or**
- Patients with elevated CA-125 pre-treatment that never normalizes must show evidence of CA-125 $\geq 2\times$ times the nadir value on two occasions at least 1 week apart **or**
- Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 $\geq 2\times$ times the upper normal limit on two occasions at least 1 week apart

Elevated values must be confirmed by two separate measurements obtained at least 1 week apart. A progressive increase in CA-125 levels will be assigned the date of the first measurement that meets the criteria as noted.

Appendix 4
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Appendix 4: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 5
Quality of Life Questionnaire Ovarian Cancer Module 28

EORTC QLQ - OV28

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have abdominal pain?	1	2	3	4
32. Did you have a bloated feeling in your abdomen / stomach?	1	2	3	4
33. Did you have problems with your clothes feeling too tight?	1	2	3	4
34. Did you experience any change in bowel habit as a result of your disease or treatment?	1	2	3	4
35. Were you troubled by passing wind / gas / flatulence?	1	2	3	4
36. Have you felt full too quickly after beginning to eat?	1	2	3	4
37. Have you had indigestion or heartburn?	1	2	3	4
38. Have you lost any hair?	1	2	3	4
39. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
40. Did food and drink taste different from usual?	1	2	3	4
41. Have you had tingling hands or feet?	1	2	3	4
42. Have you had numbness in your fingers or toes?	1	2	3	4
43. Have you felt weak in your arms or legs?	1	2	3	4
44. Did you have aches or pains in your muscles or joints?	1	2	3	4
45. Did you have problems with hearing?	1	2	3	4
46. Did you urinate frequently?	1	2	3	4
47. Have you had skin problems (e.g. itchy, dry)?	1	2	3	4
48. Did you have hot flushes?	1	2	3	4
49. Did you have night sweats?	1	2	3	4

Please go on to next page

Appendix 5: Quality of Life Questionnaire Ovarian Cancer Module 28

During the past week:	Not at All	A Little	Quite a Bit	Very Much
50. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
51. Have you been dissatisfied with your body?	1	2	3	4
52. How much has your disease been a burden to you?	1	2	3	4
53. How much has your treatment been a burden to you?	1	2	3	4
54. Were you worried about your future health?	1	2	3	4

During the past 4 weeks:	Not at All	A Little	Quite a Bit	Very Much
55. To what extent were you interested in sex?	1	2	3	4
56. To what extent were you sexually active?	1	2	3	4
Answer the following two questions only if you were sexually active:				
57. To what extent was sex enjoyable for you?	1	2	3	4
58. Did you have a dry vagina during sexual activity?	1	2	3	4

Appendix 6
Patient Questionnaire FACT-G Single Item GP5

GP5 (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP5	I am bothered by side effects of treatment.....	0	1	2	3	4

Appendix 7
Patient Questionnaire EuroQol 5 Dimension, 5-Level Questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY
- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE
- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*
- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION
- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑