Official 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

NCT Number: NCT03635489

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STATISTICAL ANALYSIS PLAN

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
STUDY DRUG:	Bevacizumab (RO4876646)
VERSION NUMBER:	1
IND NUMBER:	113807
SPONSOR:	F. Hoffmann-La Roche Ltd
PLAN PREPARED BY:	[redacted] Ph.D.
DATE FINAL:	See electronic date stamp below

STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
04-Dec-2020 09:09:24	Company Signatory	[redacted]

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1. BACKGROUND

This Statistical Analysis Plan (SAP) describes the planned analyses and statistical methods of Study YO40268 (BevFLOC).

The analyses outlined in this SAP will supersede those specified in the protocol.

Please refer to Section 1 of the Study Protocol for more details about bevacizumab and the study rationale of Study YO40268.

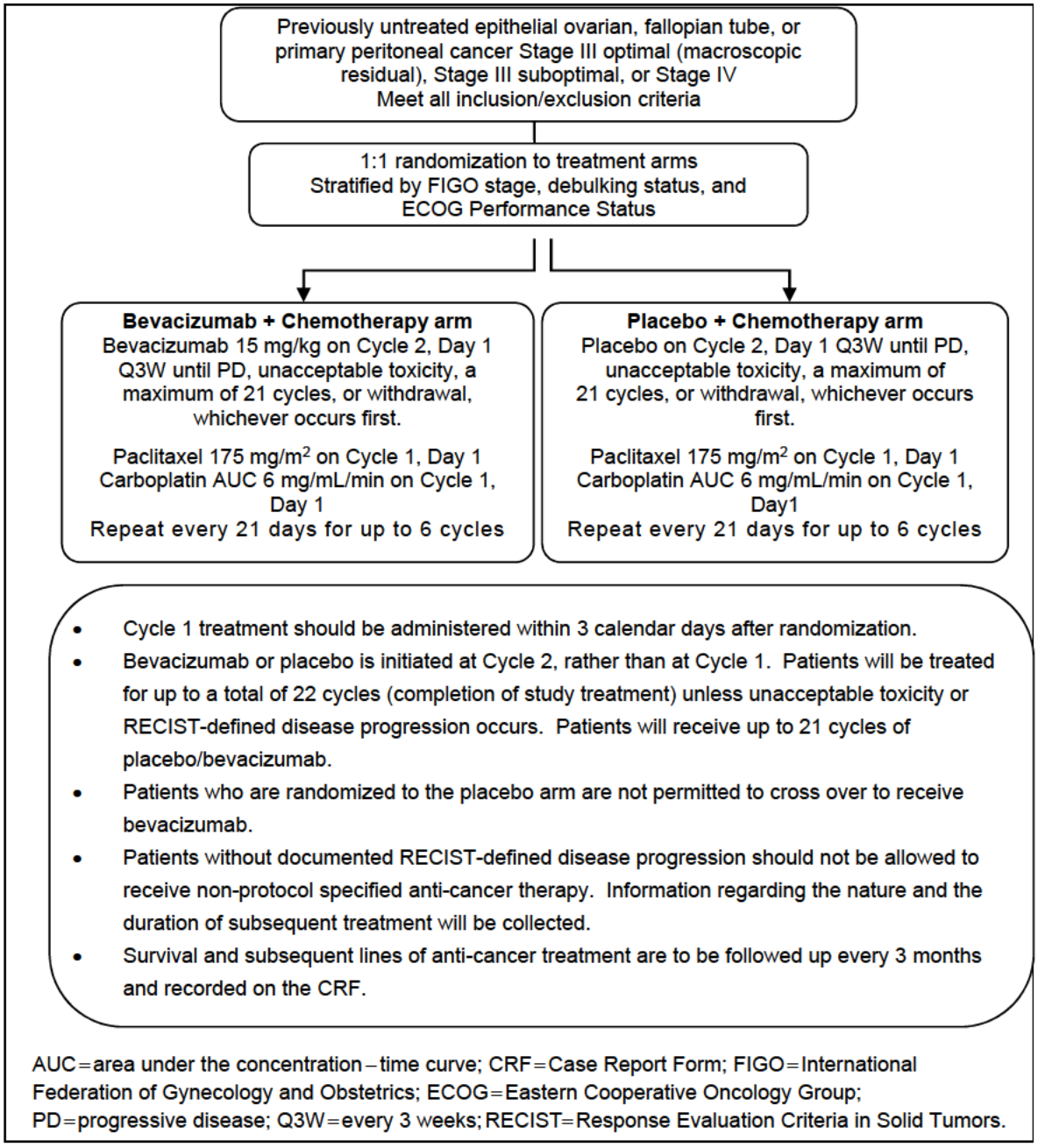
2. STUDY DESIGN

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 International Federation of Gynecology and Obstetrics (FIGO) Stage III with any gross (macroscopic or palpable) residual disease or FIGO Stage IV epithelial ovarian, fallopian tube, or primary peritoneal cancer.
100 patients are randomized.

More details about the study design could be found in Appendix 1, Protocol Synopsis.

Figure 1 illustrates the study design.

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.

2.1 STUDY OBJECTIVES

Study objectives and corresponding endpoints for the study are outlined below (Table 1).

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
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.”)

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
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; EQ-5D-5L = EuroQol 5 Dimension, 5-Level Questionnaire, FACT-G = Functional Assessment of Cancer Therapy–General; 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; ORR = objective response rate; 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.

2.2 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedules of Assessments in Appendix 2.

2.3 OUTCOME MEASURES

See the Protocol Synopsis in Appendix 1 for a description of the primary outcome measures.

2.4 DETERMINATION OF SAMPLE SIZE

The primary efficacy results will be bridged with those of the pivotal Study GOG218.

A total of approximate 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 progression free survival (PFS) will be performed when approximately 56 PFS events have occurred in the intent to treat (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)

- Enrolment 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 will be made.

3. STUDY CONDUCT

3.1 RANDOMIZATION

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 randomized in a 1:1 ratio to one of two treatment groups: bevacizumab or placebo.

Randomization to treatment allocation will be stratified by:

- FIGO stage and debulking status (Stage III optimally debulked vs. Stage III suboptimally debulked vs. Stage IV) and
- Eastern Cooperative Oncology Group Performance Status (ECOG PS) (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.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

Analysis populations are defined as follows:

- The 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. For duration of response (DOR), only patients with an objective response will be included.
- The patient-reported outcomes (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, placebo, 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).

4.2 ANALYSIS OF STUDY CONDUCT

Study enrollment, patient disposition, reasons for discontinuation from the study will be summarized for the ITT population. Reason for treatment discontinuation will be summarized for the safety population.

Protocol deviations, including violations of inclusion/exclusion criteria and major deviations during study conduct will be reported and summarized by treatment arm.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographics, baseline disease characteristics, and ovarian cancer (OC) history will be summarized by treatment arm. Descriptive baseline summaries of continuous data will present the group mean, standard deviation, median, ranges and inter-quartile ranges, as appropriate. Descriptive baseline summaries of discrete data will present the category counts as frequencies and percentages.

Previous and concurrent diseases and medications will be summarized. Subsequent anti-cancer therapy will be summarized.

4.4 EFFICACY ANALYSIS

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

4.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is PFS, which will be assessed by the investigator using Response Evaluation Criteria in Solid Tumors v1.1 (RECIST v1.1). 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 stratification factors used for randomization are FIGO stage and debulking status, and ECOG PS (Section 3.1). The number of patients in each stratum will be examined once recruitment is completed but before unblinding and efficacy analyses are performed. If any strata levels are deemed to be too small with limited number of PFS events, the robust stratified analyses cannot be conducted due to the potential risk of over-stratification (Akazawa et al. 1997). Therefore, judging from their clinical relevance,

the following rule will be applied to decide which stratification factor(s) to be dropped when conducting the analyses.

If the smallest stratum contains less than 5 PFS events, drop ECOG PS. If the smallest stratum still contains less than 5 PFS events after ECOG PS is dropped, further drop FIGO stage and debulking status and use unstratified analyses as the primary analyses.

The following analyses will be performed for PFS endpoint:

- The HR will be estimated using a stratified Cox regression model. 95% confidence interval (CI) for the HR will be provided. Unstratified HR and its 95% CI will also be provided.
- Kaplan-Meier methodology will be used to estimate median PFS for each treatment arm and to construct survival curves for each treatment arm. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS for each treatment arm (Brookmeyer and Crowley 1982).
- The stratified log-rank test will also be performed.

4.4.2 Secondary Efficacy Endpoints

4.4.2.1 Overall Survival

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 + 1 day.

The methodologies detailed for the PFS analysis will be used for the OS analysis in the ITT population, except that only unstratified analysis will be provided due to the lower number of OS events anticipated.

4.4.2.2 Objective Response Rate (ORR)

An objective response (OR) is defined as either a complete response (CR) or partial response (PR) as determined by the investigator according to RECIST v1.1. The analysis for ORR will include patients in the ITT population with measurable disease at baseline. 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. A confirmation after the first occurrence of an objective response is not required in the analysis. 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.

4.4.2.3 Duration of Response

DOR will be assessed in patients who had an objective response as determined by the investigator according to RECIST v1.1. DOR is defined as the time from the first occurrence of a documented objective response (unconfirmed CR or PR) 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. If no tumor assessments were performed after the date of the first occurrence of the objective response (unconfirmed CR or PR), patient will be censored at the date of the first occurrence of the objective response + 1 day.

DOR is based on a non-randomized subset of patients (specifically, patients who achieved an objective response). Comparisons between treatment arms will be made for descriptive purposes. The methodologies detailed for the PFS analysis will be used for the DOR analysis except that the analysis will not be stratified.

4.4.2.4 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 European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Ovarian Cancer Module 28 (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.

Pre-specified subgroup analysis will also be performed in patients with ascites at baseline (who typically have significantly impaired health-related quality of life [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).

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 $\geq$10-point increase from the baseline score on each of the functional (physical, role, emotional, and social) and global health status/QoL scales of the EORTC QLQ-C30, will be summarized at each post-baseline timepoint by treatment arm as specified above.

All EORTC QLQ-OV28 and QLQ-C30 data will be scored according to the EORTC scoring manual (Fayers et al. 2001b). PRO completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm. For the PRO disease-symptom improvement, patient function and HRQoL endpoints, patients without a baseline assessment visit or at least one post-baseline assessment visit for the calculated scale of interest will be considered non-responders and will not be included in the analysis.

4.4.3 Exploratory Efficacy Endpoints

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

Summary statistics (mean and 95% CI, 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).

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.

4.4.3.2 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 Functional Assessment of

Cancer Therapy–General (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.

4.4.3.3 Health Economic Data: EQ-5D-5L

Health economic data from the EuroQol 5 Dimension, 5-Level Questionnaire (EQ-5D-5L) measure will be used in pharmacoeconomic analyses only and not presented in the Clinical Study Report.

4.4.4 Sensitivity Analyses

Statistical methodologies that are analogous to those methodologies used in the primary analysis of PFS as specified in Section 4.4.1 will be applied for sensitivity analyses.

4.4.4.1 Impact of Missing Scheduled Tumor Assessments on Primary PFS Analysis

If a patient missed two or more consecutive assessments scheduled immediately prior to the date of disease progression per RECIST v1.1 or death in any treatment arm, the following two sensitivity analyses may be performed:

- Patients who missed two or more consecutive assessments scheduled immediately prior to the date of disease progression per RECIST v1.1 or death will be censored at the last tumor assessment prior to the first missed visit.
- Patients who missed two or more consecutive assessments scheduled immediately prior to the date of disease progression per RECIST v1.1 or death will be counted as having progressed on the date of the first of these missing assessments.

4.4.4.2 Impact of Non−Protocol-Specified anti-Cancer Therapy on Primary PFS Analysis

Patients who received non−protocol-specified anti-cancer therapy before a PFS event will be censored at the last tumor assessment date before they received non−protocol-specified anti-cancer therapy in PFS analyses that may be performed for the comparisons between treatment arms.

4.4.4.3 Impact of Demographics, Baseline Characteristics and Ovarian Cancer History on Primary PFS Analysis

In order to further evaluate if the baseline variables exert any potential confounding effect on the estimation of PFS HR, adjusted PFS HR will be estimated by fitting multivariate Cox regression models including important baseline variables, i.e., age, FIGO stage and debulking status, ECOG PS and histological grade. Other demographics or baseline characteristics might also be included if clinically relevant.

4.4.5 Subgroup Analyses

To assess the consistency of the study PFS results, results in subgroups will be examined. The following subgroups will be considered:

- Demographics
- Baseline prognostic characteristics (e.g., FIGO stage and debulking status, ECOG PS etc.)

Summaries of PFS, including unstratified HRs estimated from Cox proportional hazards models, will be displayed for each level of the categorical variables in a forest plot (Lewis and Clarke 2001). Kaplan-Meier estimates of median PFS will be produced separately for each level of the categorical variables for the comparisons between treatment arms.

4.5 SAFETY ANALYSES

All safety analyses will be performed on the safety population, i.e., all patients who receive any dose of study medication (see Section 4.1).

Safety will be assessed through study treatment exposures, summaries of adverse events (AEs), changes in laboratory test results and changes in vital signs, and will be presented by treatment arm. Non-overlapping visit windows will be assigned to post-baseline assessments.

4.5.1 Exposure of Study Medication

Study drug exposure, including but not limited to treatment duration, number of cycles, dose intensity, and total cumulative dose will be summarized for each treatment arm with descriptive statistics. The number of missed doses will also be displayed.

4.5.2 Adverse Events

Verbatim description of AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). Adverse events, occurring on or after the first dose of study treatment will be summarized by mapped term, appropriate thesaurus level, and NCI CTCAE grade regardless of relationship to study drug, as assessed by the investigator. For each patient, if multiple incidences of the same AEs occur, the maximum severity reported will be used in the summaries.

Summary tables including but not limited to the following will be provided:

- AEs
- Serious Adverse Events (SAEs)
- AEs leading to study treatment discontinuation
- AEs leading to dose reduction or interruption

- Treatment-related AEs
- Severe adverse events (Grade ≥ 3)
- AEs leading to death
- AEs by highest NCI CTCAE Grade
- Sponsor-defined AESI

Multiple occurrences of the same event will be counted once at the maximum severity. All listings of AEs will include all AEs with onset on or after the first study drug treatment up to the data cutoff date.

All deaths and causes of death will be summarized by treatment arm as well.

4.5.3 Laboratory Data

Laboratory data will be classified according to NCI CTCAE v4.0 and will be summarized descriptively over time including change from baseline. Highest NCI CTCAE grade post-baseline will also be reported and shift tables from baseline to worst value during the study post-baseline will be presented.

A Hy's law analysis will be provided. The potential Hy's law quadrant is defined as the occurrence of either of the following:

- Treatment-emergent ALT or AST $> 3 \times$ upper limit of normal (ULN) (or baseline value if baseline value was above the ULN) in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin).
- Treatment-emergent ALT or AST $> 3 \times$ ULN (or baseline value if baseline value was above the ULN) in combination with clinical jaundice.

4.5.4 Vital Signs and ECOG Performance Status

Vital signs outside normal limits among subjects without abnormality at baseline will be summarized in the safety population. Change of ECOG PS from baseline to worst value will be summarized in the ITT population.

4.6 MISSING DATA

The handling of missing data is summarized in Section 4.4 for each endpoint.

4.7 INTERIM ANALYSIS

There will be no planned interim analysis for PFS.

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Appendix 1
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
VERSION NUMBER:	3
EUDRACT NUMBER:	To be determined
IND NUMBER:	113807
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 ≥ 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 ≥ 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.

Appendix 2
Schedule of Assessments

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						

Appendix 2
Schedule of Assessments (cont.)

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
Radiographic disease assessment	x [b, n]			x [d, o]		x [d, o]	x [p]	x [o]
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 2
Schedule of Assessments (cont.)

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 2
Schedule of Assessments (cont.)

[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.

[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.