PROTOCOL

TITLE: **A PHASE III, MULTICENTER, RANDOMIZED, STUDY OF ATEZOLIZUMAB VERSUS PLACEBO ADMINISTERED IN COMBINATION WITH PACLITAXEL, CARBOPLATIN, AND BEVACIZUMAB TO PATIENTS WITH NEWLY-DIAGNOSED STAGE III OR STAGE IV OVARIAN, FALLOPIAN TUBE, OR PRIMARY PERITONEAL CANCER**

PROTOCOL NUMBER: Roche YO39523
GOG–3015
ENGOT–ov39

VERSION NUMBER: 8

EUDRACT NUMBER: 2016-003472-52

IND NUMBER: 130,637

NCT NUMBER: 03038100

TEST PRODUCT: Atezolizumab (RO5541267)

MEDICAL MONITOR: [redacted], M.D., M.S.

SPONSOR: F. Hoffmann-La Roche Ltd

APPROVAL DATE: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
22-Nov-2021 06:57:16	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
8	See electronic date stamp on title page
7	24 February 2021
6	29 January 2020
5	3 November 2018
4	22 May 2018
3	6 October 2017
2	15 March 2017
1	12 September 2016

PROTOCOL AMENDMENT, VERSION 8:
RATIONALE

Protocol YO39523 has been amended to implement changes to align with Atezolizumab Investigator's Brochure. The changes to the protocol, along with a rationale for each change, are summarized below:

- Benefit-risk assessment and guidance on concomitant administration of COVID-19 vaccines with atezolizumab has been added (Sections 1.3, 4.4.1).
- Language has been added to clarify that the Sponsor may close the study if futility is observed (Section 3.2).
- The responsibilities of the Principal Investigator and the role of the Medical Monitor in determining patient eligibility during study conduct have been clarified (Sections 4.1.2, 4.2.3, 5.1.5, Appendix 7, Appendix 9).
- For clarity, language has been modified regarding a one-time pulse dose of systemic immunosuppressant medication in the exclusion criteria (Section 4.1.2).
- The medical term "primary biliary cirrhosis" has been replaced by the term "primary biliary cholangitis" to align with the updated preferred term in MedDRA (Appendix 7).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 18 (Appendix 9).

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

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PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED STUDY OF ATEZOLIZUMAB VERSUS PLACEBO ADMINISTERED IN COMBINATION WITH PACLITAXEL, CARBOPLATIN, AND BEVACIZUMAB FOR PATIENTS WITH NEWLY-DIAGNOSED STAGE III OR STAGE IV 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 this form to the Sponsor or designee. Contact details will be provided to the Investigator prior to study start.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED STUDY OF ATEZOLIZUMAB VERSUS PLACEBO ADMINISTERED IN COMBINATION WITH PACLITAXEL, CARBOPLATIN, AND BEVACIZUMAB FOR PATIENTS WITH NEWLY-DIAGNOSED STAGE III OR STAGE IV OVARIAN, FALLOPIAN TUBE, OR PRIMARY PERITONEAL CANCER**
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VERSION NUMBER:	8
EUDRACT NUMBER:	2016-003472-52
IND NUMBER:	130,637
NCT NUMBER	03038100
TEST PRODUCT:	Atezolizumab (RO5541267)
PHASE:	Phase III
INDICATION:	Ovarian cancer, fallopian tube cancer, primary peritoneal cancer, and cancers of extra-uterine Müllerian origin
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy and safety of atezolizumab administered with paclitaxel+carboplatin+bevacizumab compared with placebo+paclitaxel+carboplatin+bevacizumab in patients with newly diagnosed, untreated ovarian, fallopian tube, and/or primary peritoneal cancer. Specific objectives and corresponding endpoints for the study are outlined below.

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of atezolizumab versus placebo in combination with paclitaxel + carboplatin + bevacizumab among all patients and in those patients with PD-L1–positive tumors	• Investigator-assessed PFS, defined as the time from randomization to the occurrence of disease progression, as determined by the investigator from tumor assessments per RECIST v1.1, or death from any cause during the study, whichever occurs first • OS, defined as the time from randomization to death from any cause

Secondary Efficacy Objectives	Corresponding Endpoints
Among patients with measurable residual disease in the primary surgery group:	
• To evaluate the efficacy of atezolizumab versus placebo in combination with paclitaxel + carboplatin + bevacizumab	• OR, defined as either a CR or PR as determined by the investigator with the use of RECIST v1.1 for patients with measurable residual disease after primary surgery
• To evaluate the duration of efficacy observed with atezolizumab versus placebo in combination with paclitaxel + carboplatin + bevacizumab	• DOR, defined as the time interval from first occurrence of a CR or PR to the time of disease progression, as determined by the investigator with the use of RECIST v1.1, or death from any cause, whichever comes first for patients with measurable residual disease after primary surgery
• *To evaluate PROs of function and HRQoL associated with atezolizumab versus placebo in combination with paclitaxel + carboplatin + bevacizumab, as measured by the functional andGHS/QoL scales of the EORTC QLQ-C30*	• *Clinically-meaningful improvement, remaining stable, or deterioration in patient-reported function and HRQoL, defined as a ≥ 10-point increase, changes within 10 points, and a ≥ 10-point decrease, respectively, from the baseline score on each of the functional (physical, role, emotional, and social) and GHS/QoL scales of the EORTC QLQ-C30*
Among the patients in the neoadjuvant group:	
• To determine the impact of atezolizumab versus placebo in combination with paclitaxel+carboplatin+bevacizumab on patient-reported abdominal symptoms of OC, 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 on the EORTC QLQ-OV28 abdominal/GI symptom scale (items 31 and 32)
• To evaluate PROs of *function and* HRQoL associated with atezolizumab versus placebo in combination with paclitaxel + carboplatin + bevacizumab, as measured by the functional and *GHS/*QoL scales of the EORTC QLQ-C30	• 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 *GHS*/QoL scales of the EORTC QLQ-C30
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety and tolerability of atezolizumab versus placebo in combination with paclitaxel + carboplatin + bevacizumab	• Occurrence and severity of adverse events, with severity determined in accordance to NCI CTCAE v4.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the pharmacokinetics of atezolizumab when administered in combination with paclitaxel + carboplatin + bevacizumab	• Minimum and maximum serum concentration of atezolizumab

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Objectives	Corresponding Endpoints
• Among neoadjuvant patients only: To evaluate PCR status and its association with clinical outcomes after administration of atezolizumab versus placebo in combination with paclitaxel + carboplatin + bevacizumab	• Among patients who undergo neoadjuvant therapy prior to interval surgery, PCR status is defined as the clinical amount and histologic characteristics of residual disease assessed at the time of interval cytoreductive surgery
• To evaluate the efficacy of atezolizumab versus placebo administered in combination with paclitaxel + carboplatin + bevacizumab	• The OS rate at 3 years after randomization
• To evaluate PROs of disease and/or treatment-related symptoms associated with atezolizumab versus placebo administered in combination with paclitaxel + carboplatin + bevacizumab, as measured by the EORTC QLQ-C30 and QLQ-OV28	• Mean and mean changes from the baseline score in disease and/or treatment-related symptoms by cycle 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 patients may experience in association with the addition of atezolizumab to paclitaxel + carboplatin + bevacizumab compared with placebo + paclitaxel + carboplatin + bevacizumab, as measured by a single item (from GP5: "I am bothered by side effects of treatment") from the physical wellbeing subscale of the FACT-G Quality of Life instrument	• Proportion of patients reporting each response option at each assessment timepoint by treatment arm for item GP5 from the FACT-G
• 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
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response from patients who were administered atezolizumab	• The incidence of ADAs against atezolizumab during treatment with atezolizumab administered in combination with paclitaxel + carboplatin + bevacizumab relative to the incidence of ADAs at the baseline
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the potential effects of ADAs	• The relationship between ADA status and pharmacokinetics, safety, and efficacy

Table 1 Objectives and Corresponding Endpoints (cont.)

Exploratory Biomarker Objective	Corresponding Endpoint
• To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status and/or patient response to study treatment	• Association of tumor immune-mediated or disease type−related exploratory biomarkers (in archival and/or freshly obtained tumor tissues and plasma, whole blood, or serum) with disease status and/or response to administration of atezolizumab+paclitaxel+carboplatin+bevacizumab; biomarkers may include but are not limited to: CD8 as assessed with the use of IHC Breast cancer susceptibility gene (*BRCA*) status, homologous recombination deficiency, and microsatellite instability as assessed with the use of DNA NGS • Molecular subtyping of ovarian cancer, as assessed by RNA profile • Association of cell-free tumor DNA with tumor burden and treatment response
• To identify biomarkers that are associated with resistance to atezolizumab administered in combination with carboplatin and/or paclitaxel and/or bevacizumab activity, or can increase the knowledge and understanding of disease biology	• The relationship between biomarkers in blood and tumor tissue between pretreatment and post-progression samples collected at the time of disease progression. These biomarkers may include but are not limited to: • Acquired mutations assessed with the use of DNA NGS Changes in the tumor immune microenvironment and biology as assessed by RNA profile and IHC

ADA = anti-drug antibody; CR = complete response; DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; FACT-G = Functional Assessment of Cancer Therapy-General; GI = gastrointestinal; $GHS = global\ health\ status;$ HRQoL = health-related quality of life; IHC = immunohistochemistry; PCR = pathologic and clinical response; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NGS = next-generation sequencing; OC = ovarian cancer; OR = objective response; OS = overall survival; PFS = progression-free survival; PR = partial response; PRO =patient-report outcome; 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, global, double-blind, two-arm, randomized study designed to evaluate the efficacy and safety of atezolizumab administered with paclitaxel + carboplatin + bevacizumab compared with placebo + paclitaxel + carboplatin + bevacizumab in patients with Stage III or Stage IV ovarian, fallopian tube, or primary peritoneal cancer with macroscopic residual disease postoperatively (i.e., after primary tumor reductive surgery) or who will undergo neoadjuvant therapy followed by interval surgery. Approximately 1300 patients will be randomized. Patients will be randomized in a 1:1 ratio to one of the two treatment arms.

Eligible patients after primary tumor reductive surgery must be randomized within 42 days of primary surgery postoperatively and commence concurrent treatment with paclitaxel (175 mg/m^2), carboplatin (area under the concentration−time curve at 6 [AUC 6]), and atezolizumab or placebo (1200 mg) on Cycle 1, Day 1. All treatments will be administered

intravenously, and each cycle will be 21 days long. Bevacizumab (15 mg/kg) will be added to paclitaxel, carboplatin, and atezolizumab treatment starting with Cycle 2. After 6 cycles of concurrent chemotherapy+ bevacizumab (5 cycles) + atezolizumab or placebo, patients will continue on maintenance bevacizumab + atezolizumab or bevacizumab +placebo treatment for a total (concurrent + maintenance phases) of 22 cycles of atezolizumab or placebo and 21 cycles of bevacizumab. No additional cycles of maintenance anti-cancer therapy are permitted beyond 22 cycles of therapy in the front-line setting. Study treatment will be discontinued at the time of disease progression, unacceptable toxicity, patient or physician decision to discontinue, death, or study termination by the Sponsor.

Eligible patients in the neoadjuvant therapy group will be randomized prior to the initiation of study treatment. Patients in the neoadjuvant group will commence concurrent treatment with paclitaxel (175 mg/m^2), carboplatin (AUC 6), bevacizumab (15 mg/kg), and atezolizumab or placebo (1200 mg) on Cycle 1, Day 1. All treatments will be administered intravenously, and each cycle will be 21 days long. Cycles 3 and 4 will consist of concurrent paclitaxel (175 mg/m2), carboplatin (AUC 6), and atezolizumab or placebo (1200 mg) with bevacizumab omitted peri-operatively. Interval surgery will occur after Cycle 3 as soon as deemed clinically appropriate, but within a maximum of 6 weeks after receiving Cycle 3. Within 6 weeks after interval surgery, patients will resume concurrent chemotherapy+bevacizumab + atezolizumab or placebo for three more cycles (total of 6 cycles), however bevacizumab treatment will resume at Cycle 5 (i.e., bevacizumab is omitted for Cycle 4). Upon completion of concurrent therapy, patients will commence maintenance treatment with bevacizumab + atezolizumab or bevacizumab+placebo for a total of 22 cycles of atezolizumab or placebo, and 20 cycles of bevacizumab. No additional cycles of maintenance anti-cancer therapy are permitted beyond 22 cycles of therapy in the front-line setting.

After the completion of maintenance therapy (i.e., bevacizumab + atezolizumab or placebo), patients will have an end-of-treatment assessment within 30 days of the last dose of study treatment and then enter the post-treatment follow-up period. The expected study treatment duration for an individual patient is approximately 66 weeks for patients randomized after primary surgery and 70 weeks for patients randomized prior to neoadjuvant therapy.

Progression-free survival (PFS) will be ascertained by the investigator in accordance with radiographic criteria from RECIST v1.1 at fixed intervals. All primary imaging data used for tumor assessment will also be collected by the Sponsor to enable a centralized Independent Review Committee audit of a prespecified subset of PFS data. Overall survival (OS) will be determined by the investigator. Tumor assessments will continue until confirmed disease progression or 5 years after the completion of all study treatment, whichever occurs first. Safety and toxicity assessments will be conducted at each treatment cycle administration.

Patients will undergo a mandatory tumor biopsy sample collection, if clinically feasible, at the time of first evidence of radiographic disease progression according to RECIST v1.1. Cytology from ascites, pleural effusion, and fine needle aspiration (FNA) is not adequate. These samples will be retrospectively analyzed to evaluate and/or characterize pseudoprogression caused by immune cells (ICs) from true progression. In addition, tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab will be analyzed.

Option for additional enrollment in China

Study YO39523 will be enrolling patients globally. Should the Study be opened in mainland China, the Sponsor is targeting a total enrollment of approximately 150 patients. A China extension phase may be initiated if patients enrolled in the global enrollment phase is significantly less than the target. Thus, the China subpopulation will include patients enrolled at sites in China during both the global enrollment phase and the China extension phase. Patients from the China extension phase will be randomized in a 1:1 ratio to the two treatment arms. The patients enrolled in the China extension phase will undergo the same schedule of assessments and will receive paclitaxel, carboplatin, bevacizumab, and atezolizumab or placebo as in the global study. Analyses based on the China subpopulation will be reported separately from the global study.

Number of Patients

Approximately 1300 patients with Stage III or Stage IV ovarian, fallopian tube, or primary peritoneal cancer (i.e., cancers of extra-uterine Müllerian origin) with macroscopic residual disease postoperatively (i.e., after primary tumor reductive surgery) or who will undergo

neoadjuvant therapy followed by interval surgery are expected to be randomized in this study. The enrollment of patients in the neoadjuvant setting will be capped at approximately 20%.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF)
- Age ≥ 18 years
- Able to comply with the study protocol, in the investigator's judgment
- Receive a histologic diagnosis of EOC, peritoneal primary carcinoma, or fallopian tube cancer fulfilling the following criteria:

  All epithelial tumors of extra-uterine Müllerian origin by histology (FNA, cytology and/or cell block are not sufficient)

  For patients who will undergo primary tumor reductive surgery: International Federation of Gynecological Oncologists (FIGO) Stage III with gross (macroscopic or palpable) residual disease or Stage IV

    Measurable disease on postoperative imaging studies is not required for eligibility

    FIGO stage is assessed following the completion of initial abdominopelvic surgery that provides the appropriate tissue for histologic evaluation and diagnosis and can be used for exploratory biomarker studies.

    Primary tumor reductive surgery must be within 42 days of randomization.

  For patients who will undergo neoadjuvant treatment and interval surgery: Patients who receive neoadjuvant treatment must also plan to undergo interval surgery after Cycle 3. Mandatory biopsy tissue samples (e.g., core needle or surgically obtained; FNA or cell-block from ascites and/or pleural effusion are inadequate) will be used to confirm histologically that the tumor is of extra-uterine Müllerian origin and to perform exploratory biomarker studies.

    Patients who receive neoadjuvant therapy will include those patients who are not deemed surgically resectable to a state of no gross residual disease due to the extent and/or distribution of disease (e.g., unresectable miliary pattern of peritoneal carcinomatosis, significant diaphragmatic disease, significant involvement of the root of the mesentery, diffuse tumor in the omentum up to the greater curvature of the stomach, extensive miliary carcinomatosis at the root of the mesentery, tumor infiltration of the stomach, surface lesions on the liver).

- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
- Life expectancy > 12 weeks
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to randomization:

  ANC ≥ 1500 cells/μL (without granulocyte colony stimulating factor support)

  Lymphocyte count ≥ 500/μL

  Platelet count ≥ 100,000/μL without transfusion

  Hemoglobin ≥ 9.0 g/dL

    Patients may be transfused to meet this criterion.

  Serum creatinine ≤ 1.5 × institutional upper limit of normal (ULN)

  Serum bilirubin ≤ 1.5 × ULN

    Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled in the study.

  AST, ALT, and alkaline phosphatase (ALP) ≤ 2.5 × ULN, with the following exceptions:

    Patients with documented liver metastases: AST and/or ALT ≤ 5 × ULN

    Patients with documented liver or bone metastases: ALP ≤ 5 × ULN.

  For patients who do not receive therapeutic anticoagulation: INR or aPTT ≤ 1.5 × ULN

- For patients who receive therapeutic anticoagulation: stable anticoagulant regimen
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening

  The HBV DNA test will be performed only for patients who have a positive total HBcAb test.
- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

  A positive HCV RNA test is sufficient to diagnose active HCV infection in the absence of an HCV antibody test.
- 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 5 months after administration of the last dose of atezolizumab and 6 months after the last dose of bevacizumab, paclitaxel, or carboplatin, whichever is later

  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 but are not limited to bilateral tubal ligation and/or occlusion, male sterilization, and intrauterine devices.

  In countries with country-specific health authority mandates, contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation/occlusion, male partner sterilization, established and proper use of estrogen-progestin combination hormonal contraceptives that inhibit ovulation, and intrauterine devices/systems.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study 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, that include the completion of PRO questionnaires
- Availability of a representative formalin-fixed, paraffin-embedded (FFPE) tumor specimen (screening baseline tissue) in paraffin blocks (preferred) or at least 20 unstained slides.

  Patients with fewer than 20 unstained slides available at baseline may be eligible upon discussion with the medical monitor.

  Tumor tissue should be of good quality based on total and viable tumor content and must be evaluated for PD-L1 expression prior to enrollment. Patients whose tumor tissue is not evaluable for PD-L1 expression are not eligible for enrollment in the study.

  If multiple screening baseline tumor specimens are submitted, patients may be eligible if at least one specimen is evaluable for PD-L1. For the purpose of stratification, the PD-L1 score of the patient will be the maximum PD-L1 score among the samples.

    Acceptable samples include tissue obtained from surgery or core needle biopsies (minimum three cores per paraffin block).

    A paraffin block for FFPE tumor specimens is preferred.

    FNA or cell pellets from ascites or pleural effusion are not acceptable.

    Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is not acceptable.
- For patient enrolled in the extended China enrollment phase: residents in Mainland China, residents in Hong Kong and Taiwan of Chinese ancestry and enrolled at sites recognized by China's National Products Administration (NMPA).

Exclusion Criteria

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

- Received a current diagnosis of borderline epithelial ovarian tumor (formerly tumors of low malignant potential)
- Have recurrent invasive epithelial ovarian, fallopian tube, or primary peritoneal cancer that was treated only with surgery (e.g., patients with Stage IA or Stage IB epithelial ovarian or fallopian tube cancers)

  Patients who received a prior diagnosis of a borderline tumor that was surgically resected and who subsequently developed an unrelated, new invasive epithelial ovarian, fallopian tube, or primary peritoneal cancer are eligible for enrollment, if they have never received prior chemotherapy for any ovarian tumor.
- Have non-epithelial ovarian tumors (e.g., germ cell tumors, sex cord stromal tumors)
- Received prior radiotherapy to any portion of the abdominal cavity or pelvis

  Prior focal radiation for localized cancer of the breast, head and neck, or skin is permitted, if it was completed > 5 years prior to initiation of study treatment, and the patient remains free of recurrent or metastatic disease.
- Received prior chemotherapy for any abdominal or pelvic tumor that include NACT for ovarian, primary peritoneal or fallopian tube cancer

  Patients may have received prior chemotherapy for localized breast cancer, if it was completed > 5 years prior to initiation of study treatment, and the patient remains free of recurrent or metastatic disease.
- Received any biological and/or targeted therapy (including but not limited to vaccines, antibodies, tyrosine kinase inhibitors) or hormonal therapy for management and/or treatment of epithelial ovarian or peritoneal primary cancer
- Have synchronous primary endometrial cancer
- Have a prior history of primary endometrial cancer, except for the following:

  A prior diagnosis of endometrial cancer is allowed if all of the following conditions are met:

  Stage IA cancer

  Superficial myometrial invasion, without lymphovascular invasion

  Grade < 3 or not poorly differentiated subtypes, and this includes papillary serous, clear cell or other FIGO Grade 3 lesions
- With the exception of non-melanoma skin cancer and other specific malignancies as noted above, other invasive malignancies within the last 5 years or previous cancer treatment that contraindicates this protocol therapy (e.g., previous chemotherapy treatment for breast cancer completed > 5 years ago is permitted as per above).
- Are pregnant, lactating, or intend to become pregnant during the study
- Have a history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Have a known hypersensitivity or allergy to biopharmaceutical agents produced in Chinese hamster ovary cells or any component of the atezolizumab and/or bevacizumab formulations
- Have an active or history of autoimmune disease or immune deficiency that includes but is not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, or multiple sclerosis (see protocol for a more comprehensive list of autoimmune diseases).
- Exceptions include the following:

  Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone are eligible.

Patients with controlled Type 1 diabetes mellitus on a stable dose of insulin regimen are eligible.

Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are eligible for enrollment in the study provided that they meet all of the following conditions:

Rash must cover less than 10% of body surface area

Disease is well controlled at baseline and requires only low potency topical steroids

No acute exacerbations of underlying condition within the previous 12 months (i.e., does not require psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high-potency or oral steroids)

- Have a history of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis based on a screening chest computed tomography (CT) scan, with the following exceptions

  A history of radiation pneumonitis in the localized radiation field (fibrosis) is permitted. Patient must still meet all other radiotherapy exclusions listed above.
- Have a positive test result for HIV
- Have active tuberculosis
- Have severe infections within 4 weeks prior to initiation of study treatment, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Have received therapeutic oral or IV antibiotic medication within 2 weeks prior to initiation of study treatment, with the following exceptions:

  Patients who receive prophylactic antibiotic medication (e.g., urinary tract infection prophylaxis, prior to dental procedure) are eligible for enrollment.
- Have significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to initiation of study treatment, unstable arrhythmias, or unstable angina

  Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction $<$ 50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.
- Undergo major surgical procedure within 28 days prior to first bevacizumab dose, or anticipation of the need for a major surgical procedure during the course of the study except patients who receive NACT and will need interval surgery. This may include but is not limited to laparotomy. All incisions should be fully healed, as assessed clinically, prior to starting bevacizumab.

  Consult with the Medical Monitor prior to patient entry for any questions related to the classification of surgical procedures.
- Are administered treatment with a live attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during the course of the study or within 5 months after the last dose of atezolizumab
- Current treatment with anti-viral therapy for HBV
- Have prior allogeneic bone marrow transplantation or solid organ transplant
- Have any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results
- Have any approved or investigational anti-cancer therapy, including chemotherapy or hormonal therapy, with the following exceptions:

  Hormone-replacement therapy or oral contraceptives are allowed.
- Current or recent (within 10 days of initiation of study treatment) use of aspirin ($>$ 325 mg/day) or clopidogrel $>$ 75 mg/day)

- Are administered treatment with any other investigational agent or participation in another clinical study with anti-cancer therapeutic intent
- Have prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti–PD-1, anti–PD-L1, or anti-cytotoxic T-lymphocyte-associated protein 4 therapeutic antibodies
- Have treatment with systemic immunostimulatory agents (including but not limited to interferons [IFNs], interleukin [IL]-2) within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment
- Have treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [TNF] agents) within 2 weeks prior to initiation of study treatment, with the following exceptions:

  Patients who have received acute, low-dose, systemic immunosuppressant medications *or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy)* are eligible for enrollment in the study.

  The use of corticosteroids for chronic obstructive pulmonary disease and asthma, mineralocorticoids (e.g., fludrocortisone), *or* low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.
- Have inadequately-controlled hypertension (defined as systolic blood pressure $>$ 150 mmHg and/or diastolic blood pressure $>$ 100 mmHg)

  Anti-hypertensive therapy to achieve these parameters is allowed.
- Have prior history of hypertensive crisis or hypertensive encephalopathy
- Have significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to initiation of study treatment
- Have a history of Grade $\geq$ 2 hemoptysis ($\geq$ 2.5 mL of bright red blood per episode) within 1 month prior to screening
- Have evidence of active bleeding, bleeding diathesis, coagulopathy, tumor that involves major vessels (in the absence of therapeutic anticoagulation)
- Have a history or evidence upon physical examination of any CNS disease, including primary brain tumor, CNS metastases, seizures not controlled with standard medical therapy, any brain metastases, or history of cerebrovascular accident (stroke), transient ischemic attack or subarachnoid hemorrhage within 6 months of the first date of treatment on this study.
- History of leptomeningeal disease
- History of Grade $\geq$ 4 venous thromboembolism
- Have current use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes that has not been stable prior to initiation of study treatment, with the following exceptions:

  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 receiving a stable dose of anticoagulants prior to initiation of study treatment.

  Prophylactic anticoagulation for the patency of venous access devices is allowed, provided the activity of the agent results in an INR $<$ 1.5 $\times$ ULN and aPTT is within normal limits prior to initiation of study treatment.

  Deep venous thrombosis prophylaxis with low-molecular-weight heparin is permitted.
- Have core biopsy or other minor surgical procedures within 7 days prior to the first dose of bevacizumab

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

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.

- Have a history of abdominal fistula or gastrointestinal perforation within 6 months prior to initiation of study treatment, with the following exceptions:

  Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection are eligible but require weekly wound examinations.
- Have clinical signs of gastrointestinal obstruction that require routine parenteral hydration, parenteral nutrition, or tube feeding
- Have evidence of abdominal free air not explained by paracentesis or recent surgical procedure
- Have serious, non-healing wound, active ulcer, or untreated bone fracture
- Have proteinuria, as demonstrated by urine dipstick or $>$ 1.0 of protein in a urine protein-to-creatinine ratio and/or 24-hour urine collection

  All patients with $\geq 2+$ protein on dipstick urinalysis at baseline must undergo a urine protein-to-creatinine ratio and/or 24-hour urine collection and demonstrate $\leq$ 1.0 of protein.
- Have known sensitivity to any component of bevacizumab
- Have known sensitivity to any component of paclitaxel
- Have Grade $\geq$ 2 peripheral neuropathy as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0)
- Have known history of severe allergic reactions to platinum-containing compounds
- Have known history of severe hypersensitivity reactions to products that contain Cremophor® EL (e.g., cyclosporine for injection concentrate and teniposide for injection concentrate)

End of Study

The end of the study is expected to be *approximately 55 months after the first patient is enrolled,* when the approximate preplanned numbers of deaths among the PD-L1–positive patients and the intent-to-treat (ITT) population have been observed. *Deaths will be monitored throughout the course of the study. The sponsor has the right to close the study at any time if futility is observed (e.g., based on the predicted probability of success at the subsequent analysis). The study timelines may be updated as needed.*

Length of Study

The length of study is approximately 55 months from enrollment of the first patient to the "end of study" as described above

Investigational Medicinal Products

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

Atezolizumab

Atezolizumab will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

Placebo

The placebo will be supplied by the Sponsor and will be identical in appearance to atezolizumab and comprise the same excipients but without atezolizumab drug product.

Non-Investigational Medicinal Products

Bevacizumab will be supplied by the Sponsor. Paclitaxel and carboplatin will be used in commercially available formulations. Bevacizumab will be considered an IMP by local regulations in some countries.

Statistical Methods

Primary Analysis

The primary analysis populations for efficacy are the ITT population, defined as all patients randomized in the study, and the PD-L1–positive subgroup, defined as the patients in the ITT population whose PD-L1 status is IC1/2/3 at the time of randomization. Patients will be grouped in accordance with the treatment assigned at randomization.

The primary analysis population for safety is the Safety Population, defined as all randomized patients who receive at least one dose of the study medication. Patients will be grouped in accordance with the treatment they actually receive, and all patients who received any dose of atezolizumab will be included in the atezolizumab treatment arm for analysis.

If the China extension phase is initiated, data from this phase will not be included in the primary analysis of the main study. A separate analysis will be performed for the China subgroup, where data from the China extension phase and from the patients in the global enrollment phase from China will be combined and summarized (refer to the protocol and the statistical analysis plan [SAP] for further details). All analyses discussed in this section will be restricted to the patients recruited in the global study only, unless noted.

Determination of Sample Size

Approximately 1300 patients will be randomized in the global study in a 1:1 ratio to the two treatment arms.

There are two co-primary efficacy endpoints: investigator-assessed PFS and OS. The overall Type I error rate will be controlled at a two-sided level of 0.05 to test PFS and OS in the PD-L1–positive subgroup and the ITT population. PFS in both the ITT and PD-L1–positive subgroup will be tested in parallel at the same significance level of 0.002 (two-sided). To test OS in both these specified populations, a hierarchical testing approach will be applied. The alpha allocated to OS will be used first to test OS in the PD-L1–positive subgroup. If the significance is reached, the same alpha as used for the PD-L1–positive subgroup OS testing will be passed to OS in the ITT. Note that the OS testing sequence of the populations may be inverted. The OS test in the PD-L1–positive subgroup is initially assigned with an alpha level of 0.046 and the actual alpha level will be determined by the results of the PFS tests. If the PFS test in either the ITT or PD-L1–positive population reaches significance, its assigned alpha of 0.002 will be additively passed to OS.

- The alpha level for OS will be 0.046 if neither of the PFS tests (in the ITT and PD-L1–positive subgroup) reaches significance.
- The alpha level for OS will be 0.048 if only one PFS test (in either the ITT or the PD-L1–positive subgroup) reaches significance.
- The alpha level for OS will be 0.05 if both the PFS tests (in the ITT and the PD-L1–positive subgroup) reach significance.

The sample size of the study is determined by the number of patient deaths required to demonstrate efficacy in terms of OS in the PD-L1–positive subgroup and the ITT population. To detect an improvement in OS with the use of a log-rank test at a two-sided significance level of 0.046, approximately 311 deaths in the PD-L1–positive subgroup will be required to achieve 81% power with a target hazard ratio (HR) of 0.72, and approximately 534 deaths in the ITT population to achieve 80% power with a target HR of 0.78.

Interim Analyses

There will be no interim analysis for PFS. The primary analysis of PFS will take place when approximately 601 PFS events in the ITT and 347 PFS events in the PD-L1–positive subgroup have occurred (whichever is later), which is expected at approximately 36 months after the first patient is enrolled in the study. This provides 90% power to detect a PFS improvement of HR = 0.7 in the ITT, and 91% power in the PD-L1–positive subgroup with HR = 0.62, at a two-sided significance level of 0.002.

Two interim analyses of OS will be performed on patients who are in the ITT and PD-L1–positive populations. The timing of the two interim analyses and the final analysis for OS depends on the results from the primary analysis of the co-primary endpoint of PFS.

The calculation of the sample size and estimates of the analysis timelines are based on the following assumptions:

- PFS and OS are exponentially distributed.
- The median duration of PFS in the control arm is 18 months.
- The median duration of OS in the control arm is 43 months.
- The prevalence of PD-L1–positive (IC1/2/3) patients is 60%.
- The two interim and final analyses of OS use the Lan-DeMets alpha spending function to approximate the O'Brien-Fleming boundary.
- The dropout rate is 5% over 12 months for PFS and OS.
- The recruitment of 1300 patients will take place over 25 months

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
1LOC	first-line ovarian cancer
ADA	anti-drug antibody, previously known as anti-therapeutic antibody (ATA)
AUC	area under the concentration–time curve
CA	cancer antigen
COVID-19	Coronavirus disease 2019
CrCl	creatinine clearance
CT	computed tomography
ctDNA	circulating tumor DNA
CTL	cytotoxic T lymphocyte
C_{trough}	trough concentration
CVAD	central vascular access device
DOR	duration of response
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EOC	epithelial ovarian cancer
EORTC	European Organisation for Research and Treatment of Cancer
FACT-G	Functional Assessment of Cancer Therapy-General
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FIGO	International Federation of Gynecological Oncologists
FNA	fine needle aspiration
GFR	glomerular filtration rate
GI	gastrointestinal
GOG	Gynecologic Oncology Group
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio
HRQoL	health-related quality of life
IC	immune cell

Abbreviation	Definition
ICF	Informed Consent Form
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICON	International Collaborative Ovarian Neoplasm
IDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IFN	interferon
IHC	immunohistochemistry
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IRR	infusion-related reactions
ITT	intent-to-treat
IWRS	interactive Web-based response system
MID	minimally important difference
MRI	magnetic resonance imaging
NACT	neoadjuvant chemotherapy
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NSCLC	non–small cell lung cancer
OC	ovarian cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PCR	pathologic and clinical response
PFS	progression-free survival
PK	pharmacokinetic
PRO	patient-reported outcome
PVC	polyvinyl chloride
Q3W	every 3 weeks
QLQ-OV28	Quality of Life Questionnaire Ovarian Cancer Module 28
R	resection margin
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation	Definition
RBR	Research Biosample Repository
SAP	statistical analysis plan
SARS CoV 2	*severe acute respiratory syndrome coronavirus 2*
SCORPION	Surgical Complications Related to Primary or Interval Debulking in Ovarian Neoplasm (study)
SMT	Study Management Team
TNF	tumor necrosis factor
TNFi	tumor necrosis factor alpha inhibitors
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
WGS	whole genome sequencing

1. BACKGROUND

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

Ovarian, fallopian tube, and primary peritoneal cancers remain leading causes of cancer-related mortality among women worldwide. Globally, epithelial ovarian cancer (EOC) affects 238,719 women annually and results in 140,200 cancer-related deaths, with an annual incidence of 65,584 (42,749 deaths) in Europe (Ferlay et al. 2013) and 22,280 (14,240 deaths) in the United States (Siegel et al. 2016). Epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer comprise of tumors of extra-uterine Müllerian origin, share common clinical and biological behavior, and are typically grouped together in treatment paradigms and clinical investigations, as will be done in this current study.

The diagnosis of ovarian cancer (OC) in 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 advanced-stage, disseminated disease upon initial diagnosis, making 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 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 identified the initiation of chemotherapy within 42 days following primary cytoreductive surgery as a quality indicator for improving ovarian cancer care (SGO 2017). In addition, due to the clinical benefit of adding the anti-vascular endothelial growth factor (VEGF) molecule bevacizumab to carboplatin and/or paclitaxel, the standard of care for patients who are newly-diagnosed with OC in an advanced stage in the European Union and other countries is now carboplatin and paclitaxel with bevacizumab. 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 OC who are treatment naive, demonstrated improvement in PFS (Burger et al. 2011, Perren et al. 2011). Study GOG218 combined the standard dose of bevacizumab (15 mg/kg every 3 weeks [Q3W]) with carboplatin and paclitaxel followed by bevacizumab monotherapy for 16 cycles, and showed a significant improvement in the Response Evaluation Criteria in Solid Tumors (RECIST)-determined PFS (i.e., excludes the cancer antigen [CA] 125 elevations and non-protocol therapies), with a reduction of 35.5% in the risk of a PFS event 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 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 within 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 (q21days), an analysis of patients administered carboplatin and paclitaxel (q21days) 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 further supports the treatment benefit of the inclusion of bevacizumab in 1LOC treatment (Chan et al. 2016). Study GOG218 and Study ICON7 led to the regulatory approval, in both the European Union and the United States, of bevacizumab combined with carboplatin and paclitaxel for the treatment of women with previously-untreated OC in an advanced stage. The evidence to date from Study GOG262 continues to support this regimen as the best treatment standard for 1LOC.

Although maximizing surgical effort remains the cornerstone of 1LOC treatment, two seminal studies that evaluate the neoadjuvant approach against the traditional primary surgery, followed by adjuvant chemotherapy approach, demonstrated similar PFS and OS durations between the two approaches. (Vergote et al. 2010; Kehoe 2016). In addition to comparable survival metrics, both studies showed that the neoadjuvant approach was associated with markedly superior rates of optimal surgical tumor reduction (73% vs. 41%, $p=0.0001$) and rates of achieving resection margin (R) 0 status (39% vs. 17%, $p=0.0001$), both strong prognostic factors for OC survival. Furthermore, rates of postoperative complications, death, hemorrhage, and infection were less among

those who underwent neoadjuvant therapy prior to interval surgery (Vergote et al. 2010; Kehoe 2016). More recently, supportive data from the Surgical Complications Related to Primary or Interval Debulking in Ovarian Neoplasm (SCORPION) study confirmed these data and provided additional evidence that demonstrated that patients with higher tumor load experienced statistically and clinically better emotional and cognitive functioning, and less nausea and/or vomiting, dyspnea, insomnia, and hair loss when treated with neoadjuvant therapy before interval surgery versus those patients who underwent primary tumor reduction surgery followed by chemotherapy (Fagotti et al. 2016). Bevacizumab has also been successfully employed into the neoadjuvant setting where it was incorporated upfront in >80% of the study population of Study GOG262 (Chan et al. 2016) as well as in the final year of the SCORPION study when bevacizumab received Italian health authority approval for this indication (Fagotti et al. 2016). In both studies, no new clinical or safety findings were cited with the use of bevacizumab in the neoadjuvant setting.

Although the strategy of neoadjuvant therapy followed by interval tumor reductive surgery treatment provides early clinical insight into the patient's response to systemic therapy, no comprehensive set of pathologic parameters has been established to correlate histopathological and clinical responses in patients with OC. Clinical parameters such as peritoneal carcinomatosis, bowel and/or stomach infiltration, liver metastases, and diaphragmatic, mesenteric, and/or omental disease, have been utilized in laparoscopic scoring systems to predict optimal cytoreduction, itself a favorable prognosticator in OC (Fagotti et al. 2011; Gomez-Hidalgo et al. 2015). On the other hand, postneoadjuvant therapy histopathologic parameters such as fibrosis, necrosis, residual tumor percentage, and inflammation have been studied in association with survival and clinical outcome in ovarian cancer (Samrao et al. 2012). Therefore, studying the associations between clinicopathologic parameters and clinical outcome in the neoadjuvant cohort of this study will further refine how therapeutic efficacy might be identified earlier for patients with OC.

Although surgery remains firmly fixed as a cornerstone of treatment for patients with OC, patient characteristics (e.g., performance status, comorbidities) coupled with the likelihood of technically achieving surgical R0 status make neoadjuvant therapy an attractive option for certain patients with newly-diagnosed OC in an advanced stage. Furthermore, the inclusion of patients undergoing neoadjuvant treatment into a prospective clinical study that investigates novel therapies scientifically offers a unique opportunity to advance our understanding of OC biology and response to treatments by systematically studying changes in tumor tissue over the course of treatment.

The current armamentarium of surgery, cytotoxic chemotherapy, and bevacizumab comprise key effective current treatment options for patients with OC, and serve as a foundation upon which this proposed study seeks to improve.

1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized immunoglobulin G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc-receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved *in several countries around the world* (as a single agent and/or in combination) for the treatment of locally advanced or metastatic urothelial carcinoma, non–small cell lung cancer (NSCLC) , small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

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

Clinical Activity in Patients with Ovarian Cancer: Single Agent Activity

In the PCD4989g basket study (GO27831), 9 patients with OC were evaluable for response (Liu et al. 2019). Efficacy results from these 9 patients showed the following:

- An objective response rate (ORR): 2 of 9 patients (22.2%) with a confirmed response and 1 of 9 patients (22.2%) with a best OR of complete response
- The duration of response for the two confirmed responders was 8.11 and 30.6*months (where "*" denotes a censored value).
- The 1-year OS rate was 44.4% (4 patients; 95% CI: 11.98 to 76.91).

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The PD-L1 pathway is an important checkpoint within the immune response to temporarily dampen immune responses in states of prolonged antigen stimulation, such as chronic infection or cancer. PD-L1 is a cell-surface protein that downregulates immune responses through binding to its two receptors, PD-1 and B7.1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and its expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7.1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7.1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells, and

reduced cytotoxic T lymphocyte (CTL)-mediated cancer cell killing (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interrupting the PD-L1 pathway and generating a population of CTLs that can infiltrate tumors and specifically recognize and kill cancer cells represents an attractive strategy to restore tumor-specific T-cell immunity and produce an effective anti-tumor immune response. Emerging data highlight the importance of therapeutically targeting the PD-L1/PD-1 axis. Indeed, encouraging clinical data with anti–PD-L1/anti–PD-1 agents have consistently demonstrated significant survival benefits in patients with multiple advanced malignancies when T-cell responses against cancer are enhanced (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

Among patients with advanced malignancies (e.g., melanoma, renal cell carcinoma (RCC), lung cancer, head and neck squamous cell cancer) who had progressed or relapsed after standard-of-care therapies, therapeutically reinvigorating their immune system by targeting the PD-L1/PD-1 axis resulted in deep, sustained clinical benefit. Refer to the Atezolizumab Investigator's Brochure for detailed efficacy results. In addition to therapeutic effects on these tumor sites, targeting the PD-L1/PD-1 axis has also demonstrated activity in patients with OC. The single-agent activity that was observed in patients with OC who were given different strategies to target the PD-L1/PD-1 axis support the immune system’s irrefutable role in patients with OC (Hamanishi et al, 2015; Disis et al., 2015). However, the modest responses observed leave room for improvement.

Critical events along the cancer-immunity cycle include the release of cancer cell antigens, efficient trafficking of cytotoxic T cells into the tumors, and eliciting and augmenting tumor-specific cell kill (Chen and Mellman 2013). Cytotoxic agents are known to trigger a native immune response by inducing immunogenic cell death and neoantigen release (Obeid et al. 2007; van den Boorn and Hartmann 2013).

Another key phase in the cancer immunity cycle hinges on effective infiltration of T cells into the tumor (Chen and Mellman 2013). VEGF inhibits efficient T cell infiltration (Chen and Mellman 2013); therefore, blocking VEGF may increase intratumoral T-cell recruitment. This hypothesis bore out of the highly VEGF-driven RCC. Here, the combination of bevacizumab + atezolizumab resulted in both quantifiably more CD8+ tumor-infiltrating lymphocytes within the tumors and augmented tumor reduction (Sznol et al. 2015). Analyses of longitudinal gene expression in tumors that are pretreatment, post-bevacizumab, and post-bevacizumab + atezolizumab showed significant decreases of angiogenesis genes and increases of Th1 signaling genes. Importantly, these signatures of these Th1 signaling genes were delinked from the decrease in the angiogenesis-related genes, which indicates that bevacizumab alone resulted in some modulation of the tumor-immune microenvironment (Wallin et al. 2016). Bevacizumab has also been shown to normalize tumor-associated vasculature (Tolaney et al. 2015), thus promoting T cell infiltration and immune-mediated tumor cell

kill. The importance of VEGF in EOC is well-studied (Jackson et al. 2015), and evidenced by the marked therapeutic activity seen with anti-VEGF agents, notably bevacizumab (Miyake et al. 2013; Yang et al. 2015). Study YO39523 employs the current understanding of the role of VEGF in OC proliferation, metastasis, and, now, immune evasion (Motz et al. 2014). This current study explores if clinical outcomes improve beyond the enhanced benefit already conferred by VEGF-targeting with bevacizumab (Burger et al. 2011; Perren et al., 2011). Recent clinical observations, as highlighted above, substantiating the scientific rationale of combining anti-VEGF agents (e.g., bevacizumab) with immune checkpoint inhibitors, including the aforementioned report by Sznol and colleagues (2015), make bevacizumab plus atezolizumab particularly attractive. In VEGF-driven tumors such as RCC and OC, bevacizumab has been shown to normalize the disorganized tumor associated vasculature. This, in turn, promotes T cell infiltration and thus immune-mediated tumor cell kill. Thus, harnessing the translational and clinical observations of this well-tolerated, two-pronged approach holds particularly great therapeutic promise for improving clinical outcomes for patients with ovarian cancer.

This notable efficacy of bevacizumab in patients with OC, coupled with the strong scientific rationale to combine VEGF-targeting with PD-L1 inhibition, warrant the addition of bevacizumab to atezolizumab to capitalize on these complementary therapeutic mechanisms.

Atezolizumab has been generally well tolerated in patients who were administered the treatment. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent include rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, and myasthenia gravis have been observed (refer to Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with $supportive$ treatment or interruption of atezolizumab treatment. Certainly adding a novel agent into a treatment regimen must be fairly evaluated for possible risks of the entire treatment regimen. Approximately 8,000 patients in clinical trials and 5,000 patients in post-marketing have been exposed to atezolizumab to date, either as a single agent or in combination therapies. A pivotal Phase III study (NCT 02366143) is being conducted by the Sponsor in the frontline lung cancer setting using the same regimen as in this study (paclitaxel + carboplatin + bevacizumab + atezolizumab). This study is monitored by an independent Data Monitoring Committee (iDMC). With >300 patients treated to date, the iDMC recommendations have been to continue the study with no changes to the study for safety reasons.

The safety profile of a combination regimen containing atezolizumab appears to be consistent with the known risks specific to the single molecules making up the combination treatment. Immune-mediated risks were manageable with treatment (usually steroids) or interruption of atezolizumab therapy. Chemotherapy- and bevacizumab-related risks were manageable as per standard of care.

This study will enroll patients with newly-diagnosed, previously-untreated advanced stage EOC, fallopian tube cancer, and primary peritoneal cancer (i.e., tumors of extra-uterine Müllerian origin). Despite the administration of an active treatment regimen with carboplatin, paclitaxel and bevacizumab, the disease prognosis remains relatively poor and thus highlights the need to develop novel therapeutic studies for these patients.

The combination of atezolizumab with the standard-of-care backbone is hypothesized and expected to result in effective anti-tumor immunity with a favorable therapeutic index, and thus deliver enhanced clinical benefit to these patients. On the basis of the promising efficacy data to date coupled with the *manageable* risk and tolerability of atezolizumab combination regimens, this study in patients with advanced-stage, poor-prognosis ovarian cancer carries a favorable benefit-risk assessment.

The benefit-risk ratio for atezolizumab when administered in combination with paclitaxel, carboplatin, and bevacizumab is expected to be acceptable in this setting, as per individual health authorities assessments.

1.3.1 COVID-19 Benefit-Risk Assessment

In the setting of the Coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from COVID-19. However, it is unclear whether or how systemic cancer therapies such as chemotherapy, targeted therapy, or immunotherapy impact the incidence or severity of COVID-19.

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from COVID-19 is altered by cancer immunotherapy.

Severe COVID-19 appears to be associated with a cytokine-release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon-γ (Merad and Martin 2020). While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops *severe* acute *respiratory syndrome coronavirus 2 (*SARS-CoV-2*)* infection while receiving atezolizumab. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from COVID-19.

There may be potential synergy or overlap in clinical and radiologic features for immune-mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for *SARS-CoV-2*–related interstitial pneumonia. Thus, investigators should use

their clinical judgment when evaluating and managing patients with pulmonary symptoms.

There are limited data concerning the possible interactions between cancer immunotherapy treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune modifying therapies may positively or negatively impact the efficacy and safety of COVID-19 vaccination (Society for Immunotherapy for Cancer [SITC] 2020).

Per recommendations of the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving atezolizumab treatment, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving atezolizumab treatment to receive COVID-19 vaccination include the following: the risk of SARS CoV 2 infection and potential benefit from the vaccine, the general condition of the patient and potential complications associated with SARS CoV 2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

The SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID 19 vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID 19 vaccine is considered a concomitant medication and should be documented as such (see Section 4.4.1).

Neutropenia and lymphopenia associated with chemotherapy may increase the risk for developing an infection in patients receiving atezolizumab in combination with chemotherapy.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of atezolizumab administered with paclitaxel + carboplatin + bevacizumab compared with placebo + paclitaxel + carboplatin + bevacizumab in patients with newly diagnosed, untreated ovarian, fallopian tube, and/or primary peritoneal cancer. Specific objectives and corresponding endpoints for the study are outlined below in Table 1.

Table 1 Objectives and Corresponding Endpoints

Primary Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of atezolizumab versus placebo in combination with paclitaxel + carboplatin + bevacizumab among all patients and in those patients with PD-L1–positive tumors	• Investigator-assessed PFS, defined as the time from randomization to the occurrence of disease progression, as determined by the investigator from tumor assessments per RECIST v1.1, or death from any cause during the study, whichever occurs first • OS, defined as the time from randomization to death from any cause
Secondary Efficacy Objectives	**Corresponding Endpoints**
Among patients with measurable residual disease in the primary surgery group:	
• To evaluate the efficacy of atezolizumab versus placebo in combination with paclitaxel + carboplatin + bevacizumab	• OR, defined as either a CR or PR as determined by the investigator with the use of RECIST v1.1 for patients with measurable residual disease after primary surgery
• To evaluate the duration of efficacy observed with atezolizumab versus placebo in combination with paclitaxel + carboplatin + bevacizumab	• DOR, defined as the time interval from first occurrence of a CR or PR to the time of disease progression, as determined by the investigator with the use of RECIST v1.1, or death from any cause, whichever comes first for patients with measurable residual disease after primary surgery
• *To evaluate PROs of function and HRQoL associated with atezolizumab versus placebo in combination with paclitaxel + carboplatin + bevacizumab, as measured by the functional and GHS/QoL scales of the EORTC QLQ-C30*	• *Clinically-meaningful improvement, remaining stable, or deterioration in patient-reported function and HRQoL, defined as a ≥ 10-point increase, changes within 10 points, and a ≥ 10-point decrease, respectively, from the baseline score on each of the functional (physical, role, emotional, and social) and GHS/QoL scales of the EORTC QLQ-C30*
Among the patients in the neoadjuvant group:	
• To determine the impact of atezolizumab versus placebo in combination with paclitaxel + carboplatin + bevacizumab on patient-reported abdominal symptoms of OC, 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 on the EORTC QLQ-OV28 abdominal/GI symptom scale (items 31 and 32)
• To evaluate PROs of *function and* HRQoL associated with atezolizumab versus placebo in combination with paclitaxel + carboplatin + bevacizumab, as measured by the functional and *GHS/*QoL scales of the EORTC QLQ-C30	• 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 *GHS*/QoL scales of the EORTC QLQ-C30

Table 1 Objectives and Corresponding Endpoints (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety and tolerability of atezolizumab versus placebo in combination with paclitaxel + carboplatin + bevacizumab	• Occurrence and severity of adverse events, with severity determined in accordance to NCI CTCAE v4.0 • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the pharmacokinetics of atezolizumab when administered in combination with paclitaxel + carboplatin + bevacizumab	• Minimum and maximum serum concentration of atezolizumab
Exploratory Objectives	**Corresponding Endpoints**
• Among neoadjuvant patients only: To evaluate PCR status and its association with clinical outcomes after administration of atezolizumab versus placebo in combination with paclitaxel + carboplatin + bevacizumab	• Among patients who undergo neoadjuvant therapy prior to interval surgery, PCR status is defined as the clinical amount and histologic characteristics of residual disease assessed at the time of interval cytoreductive surgery
• To evaluate the efficacy of atezolizumab versus placebo administered in combination with paclitaxel + carboplatin + bevacizumab	• The OS rate at 3 years after randomization
• To evaluate PROs of disease and/or treatment-related symptoms associated with atezolizumab versus placebo administered in combination with paclitaxel + carboplatin + bevacizumab, as measured by the EORTC QLQ-C30 and QLQ-OV28	• Mean and mean changes from the baseline score in disease and/or treatment-related symptoms by cycle 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 patients may experience in association with the addition of atezolizumab to paclitaxel + carboplatin + bevacizumab compared with placebo + paclitaxel + carboplatin + bevacizumab, as measured by a single item (from GP5: "I am bothered by side effects of treatment") from the physical wellbeing subscale of the FACT-G Quality of Life instrument	• Proportion of patients reporting each response option at each assessment timepoint by treatment arm for item GP5 from the FACT-G
• 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

Table 1 Objectives and Corresponding Endpoints (cont.)

Immunogenicity Objective	Corresponding Endpoint
• To evaluate the immune response from patients who were administered atezolizumab	• The incidence of ADAs against atezolizumab during treatment with atezolizumab administered in combination with paclitaxel + carboplatin + bevacizumab relative to the incidence of ADAs at the baseline
Exploratory Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the potential effects of ADAs	• The relationship between ADA status and pharmacokinetics, safety, and efficacy
Exploratory Biomarker Objectives	**Corresponding Endpoint**
• To assess predictive, prognostic, and pharmacodynamic exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status and/or patient response to study treatment	• Association of tumor immune-mediated or disease type−related exploratory biomarkers (in archival and/or freshly obtained tumor tissues and plasma, whole blood, or serum) with disease status and/or response to administration of atezolizumab + paclitaxel + carboplatin + bevacizumab; biomarkers may include but are not limited to: CD8 as assessed with the use of IHC Breast cancer susceptibility gene (*BRCA*) status, homologous recombination deficiency, and microsatellite instability as assessed with the use of DNA NGS • Molecular subtyping of ovarian cancer, as assessed by RNA profile • Association of cell-free tumor DNA with tumor burden and treatment response
• To identify biomarkers that are associated with resistance to atezolizumab administered in combination with carboplatin and/or paclitaxel and/or bevacizumab activity, or can increase the knowledge and understanding of disease biology	• The relationship between biomarkers in blood and tumor tissue between pretreatment and post-progression samples collected at the time of disease progression. These biomarkers may include but are not limited to: Acquired mutations assessed with the use of DNA NGS Changes in the tumor immune microenvironment and biology as assessed by RNA profile and IHC

ADA = anti-drug antibody; CR = complete response; DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; FACT-G = Functional Assessment of Cancer Therapy-General; GI = gastrointestinal; *GHS = global health status;* HRQoL = health-related quality of life; IHC = immunohistochemistry; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NGS = next-generation sequencing; OC = ovarian cancer; OR = objective response; OS = overall survival; PCR = pathologic and clinical response; PFS = progression-free survival; PR = partial response; PRO = patient-report outcome; 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, global, double-blind, two-arm, randomized study designed to evaluate the efficacy and safety of atezolizumab administered with paclitaxel + carboplatin + bevacizumab compared with placebo + paclitaxel + carboplatin + bevacizumab in patients with Stage III or Stage IV ovarian, fallopian tube, or primary peritoneal cancer with macroscopic residual disease postoperatively (i.e., after primary tumor reductive surgery) or who will undergo neoadjuvant therapy followed by interval surgery. Approximately 1300 patients will be randomized. Patients will be randomized in a 1:1 ratio to one of the two treatment arms.

Eligible patients after primary tumor reductive surgery (see Figure 1) must be randomized within 42 days of primary surgery postoperatively and commence concurrent treatment with paclitaxel (175 mg/m^2), carboplatin (area under the concentration–time curve at 6 [AUC 6]), and atezolizumab or placebo (1200 mg) on Cycle 1, Day 1. All treatments will be administered intravenously, and each cycle will be 21 days long. Bevacizumab (15 mg/kg) will be added to paclitaxel, carboplatin, and atezolizumab treatment starting with Cycle 2. After 6 cycles of concurrent chemotherapy+ bevacizumab (5 cycles) + atezolizumab or placebo, patients will continue on maintenance bevacizumab + atezolizumab or bevacizumab + placebo treatment for a total (concurrent + maintenance phases) of 22 cycles of atezolizumab or placebo and 21 cycles of bevacizumab. No additional cycles of maintenance anti-cancer therapy are permitted beyond 22 cycles of therapy in the front-line setting. Study treatment will be discontinued at the time of disease progression, unacceptable toxicity, patient or physician decision to discontinue, death, or study termination by the Sponsor.

Eligible patients in the neoadjuvant therapy group (see Figure 2) will be randomized prior to the initiation of study treatment. Patients in the neoadjuvant group will commence concurrent treatment with paclitaxel (175 mg/m^2), carboplatin (AUC 6), bevacizumab (15 mg/kg), and atezolizumab or placebo (1200 mg) on Cycle 1, Day 1. All treatments will be administered intravenously, and each cycle will be 21 days long. Cycles 3 and 4 will consist of concurrent paclitaxel (175 mg/m^2), carboplatin (AUC 6), and atezolizumab or placebo (1200 mg) with bevacizumab omitted peri-operatively. Interval surgery will occur after Cycle 3 as soon as deemed clinically appropriate, but within a maximum of 6 weeks after receiving Cycle 3. Within 6 weeks after interval surgery, patients will resume concurrent chemotherapy + bevacizumab + atezolizumab or placebo for three more cycles (total of six cycles), however bevacizumab treatment will resume at Cycle 5 (i.e., bevacizumab is omitted for Cycle 4). Upon completion of concurrent therapy, patients will commence maintenance treatment with bevacizumab + atezolizumab or bevacizumab + placebo for a total of 22 cycles of atezolizumab or placebo, and 20 cycles of bevacizumab. No additional cycles of

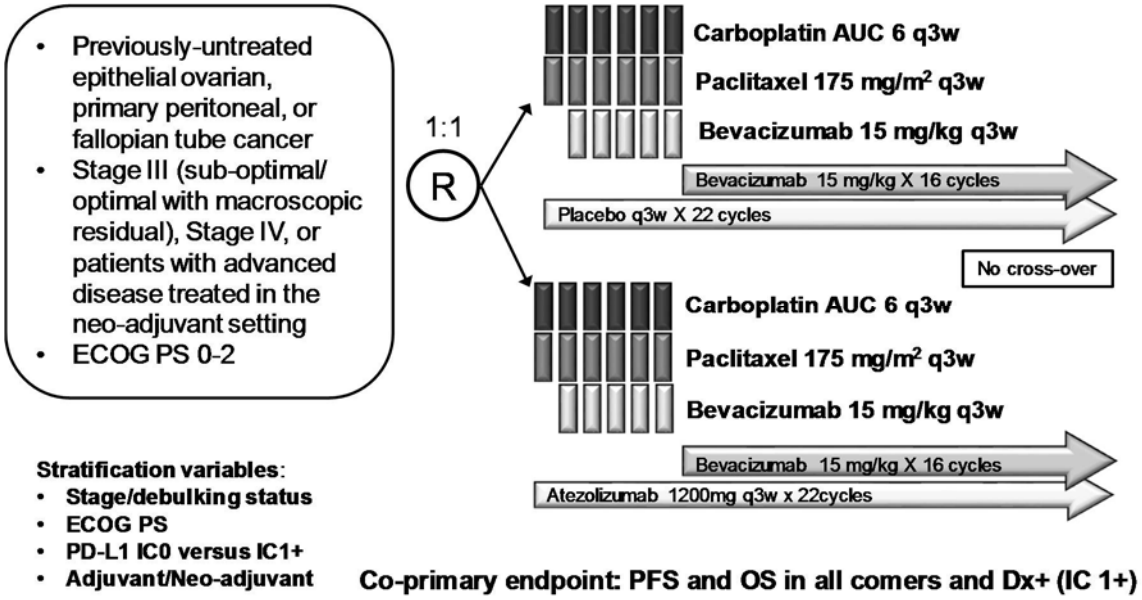
maintenance anti-cancer therapy are permitted beyond 22 cycles of therapy in the front-line setting.

After the completion of maintenance therapy (i.e., bevacizumab + atezolizumab or placebo), patients will have an end-of-treatment assessment within 30 days of the last dose of study treatment and then enter the post-treatment follow-up period.
The expected study treatment duration for an individual patient is approximately 66 weeks for patients randomized after primary surgery and 70 weeks for patients randomized prior to neoadjuvant therapy.

Progression-free survival will be ascertained by the investigator in accordance with radiographic criteria from RECIST v1.1 at fixed intervals. All primary imaging data used for tumor assessment will also be collected by the Sponsor to enable a centralized Independent Review Committee audit of a prespecified subset of PFS data. Overall survival will be determined by the investigator. Tumor assessments will continue until confirmed disease progression or 5 years after the completion of all study treatment, whichever occurs first. Safety and toxicity assessments will be conducted at each treatment cycle administration.

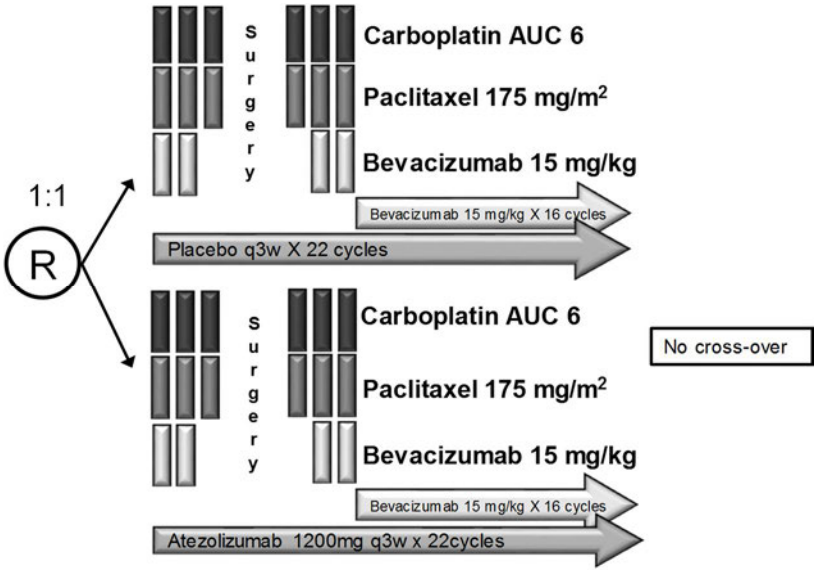
Figure 1 and Figure 2 illustrate the study design. A schedule of assessments is provided in Appendix 1 for patients who undergo primary surgery and in Appendix 2 for patients who undergo neoadjuvant chemotherapy or interval surgery, and a schedule of PK, ADA, and biomarker sampling is in Appendix 3.

Figure 1 Study Schema for Patients in the Primary Tumor-Reductive Surgery Group



AUC = area under the concentration–time curve; Dx = diagnosis; ECOG PS = Eastern Cooperative Oncology Group performance status; IC = immune cell; OS = overall survival; PFS = progression-free survival; q3w = every 3 weeks.

Figure 2 Study Schema for Patients in the Neoadjuvant Chemotherapy Group



AUC = area under the concentration–time curve; q3w = every 3 weeks.

Patients will undergo a mandatory tumor biopsy sample collection, if clinically feasible, at the time of first evidence of radiographic disease progression according to RECIST v1.1. Cytology from ascites, pleural effusion, and fine needle aspiration (FNA) is not adequate. These samples will be retrospectively analyzed to evaluate and/or characterize pseudoprogression caused by immune cells (ICs) from true progression. In addition, tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab will be analyzed.

Option for additional enrollment in China: Study YO39523 will be enrolling patients globally. Should the Study be opened in mainland China, the Sponsor is targeting a total enrollment of approximately 150 patients. A China extension phase may be initiated if patients enrolled in the global enrollment phase is significantly less than the target. Thus, the China subpopulation will include patients enrolled at sites in China during both the global enrollment phase and the China extension phase. Patients from the China extension phase will be randomized in a 1:1 ratio to the two treatment arms. The patients enrolled in the China extension phase will undergo the same schedule of assessments and will receive paclitaxel, carboplatin, bevacizumab, and atezolizumab or placebo as in the global study. Analyses based on the China subpopulation will be reported separately from the global study.

3.1.2 Independent Data Monitoring Committee

An iDMC will evaluate safety data during the study. Unblinded safety data will be reviewed by the iDMC on a periodic basis, approximately every 6 months from the time the first patient is enrolled until after the primary PFS analysis. In addition, the iDMC will review safety data when 12 patients have been enrolled into each treatment arm and have been administered treatment for at least two cycles. The safety data will include demographic data, adverse events, serious adverse events, adverse events leading to treatment discontinuation, adverse events leading to death, all deaths, and relevant laboratory test result data. The iDMC will not review efficacy data. The iDMC and the Sponsor may request an interim iDMC meeting prior to the pre-specified 6-month interval, if needed.

All data summaries and analyses by treatment arm for iDMC review will be prepared by an external independent Data Coordinating Center (iDCC). Following the data review, the iDMC will provide a recommendation as to whether the study may continue, whether study modifications and/or amendment(s) to the protocol should be implemented, or whether the study should be terminated. The final decision will rest with the Sponsor.

Members of the iDMC will be external to the Sponsor and follow a separate iDMC Charter that outlines their roles and responsibilities, and a detailed monitoring plan. After the primary PFS analysis, the iDMC will be dissolved, and the responsibility will be taken by the internal Study Management Team (SMT). The SMT will review the data on serious adverse events and deaths at least once every 3 months until the last patient has completed the study treatment regimen.

Any outcomes from these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the Institutional Review Boards (IRBs) and/or Ethics Committees (ECs).

3.2 END OF STUDY AND LENGTH OF STUDY

The primary PFS analysis will be performed when approximately 601 PFS events in the intent-to-treat (ITT) population or approximately 347 PFS events among the PD-L1–positive subpopulation have occurred, whichever occurs last.

The end of the study is expected to be approximately 55 months after the first patient is enrolled, when the approximate preplanned numbers of deaths among the PD-L1–positive patients and the ITT population have been observed (see Appendix 4). Deaths will be monitored throughout the course of the study. *The sponsor has the right to close the study at any time if futility is observed (e.g., based on the predicted probability of success at the subsequent analysis). The* study timelines may be updated as needed.

Treatment will continue until disease progression, unacceptable toxicity, completion of the study treatment (i.e., 22 cycles of atezolizumab or placebo), patient or physician

decision to discontinue, or death. Tumor response data collection will continue if the 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 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, 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 Atezolizumab Dose and Schedule

The atezolizumab fixed dose of 1200 mg Q3W was selected on the basis of both nonclinical studies and available clinical data from Study PCD4989g, as described below.

The target exposure for atezolizumab was projected on the basis of clinical and nonclinical parameters, including nonclinical tissue distribution data in tumor-bearing mice, target-receptor occupancy in the tumor, and observed atezolizumab interim pharmacokinetics in humans. The target trough concentration (C_{trough}) was projected to be 6 μg/mL on the basis of several assumptions that include: 1) 95% tumor-receptor saturation is needed for efficacy, and 2) the tumor interstitial concentration–to-plasma ratio is 0.30 on the basis of tissue distribution data in tumor-bearing mice.

In Study PCD4989g, the first-in-human study in patients with advanced solid tumors and hematologic malignancies, 30 patients were treated with atezolizumab at doses that ranged from 0.01 mg/kg to 20 mg/kg Q3W administered during the dose-escalation stage and 247 patients were treated with atezolizumab at doses of 10, 15, or 20 mg/kg Q3W during the dose-expansion stage. Anti-tumor activity has been observed across doses that ranged from 1 mg/kg to 20 mg/kg. There was no evidence of dose-dependent toxicity in Study PCD4989g. The maximum tolerated dose of atezolizumab was not reached, and no dose-limiting toxicities were observed. Anti-drug antibodies (ADAs) to atezolizumab were associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg), but patients treated with doses of 10, 15, and 20 mg/kg maintained the expected C_{trough} despite the detection of ADAs. To date, no relationship has been observed between the development of measurable ADAs and safety or efficacy. After review of available pharmacokinetic (PK) and ADA data for a range of doses, 15 mg/kg Q3W was identified as the lowest atezolizumab dosing regimen to maintain C_{trough} at $\geq$6 μg/mL and further safeguard against interpatient variability and potential ADAs to lead to subtherapeutic levels of atezolizumab.

Simulations do not suggest any clinically-meaningful differences in exposure following a fixed dose compared with a body weight–adjusted dose (Bai et al. 2012). Therefore, patients in this study will be treated Q3W at a fixed dose of 1200 mg.

Refer to Atezolizumab Investigator's Brochure for details regarding nonclinical and clinical pharmacology of Atezolizumab.

3.3.2 Rationale for Patient Population

This study will enroll patients with newly-diagnosed Stage III or Stage IV ovarian, fallopian tube, or primary peritoneal cancer (i.e., cancers of extra-uterine Müllerian origin) who have macroscopic residual disease postoperatively (i.e., after primary tumor reductive surgery) or who will undergo neoadjuvant therapy followed by planned interval surgery. 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 their 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 survival rates at 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 highly effective cytotoxic agents coupled with potent anti-angiogenic 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 justify their inclusion into this study.

In addition to those patients with advanced stage, postoperative residual disease, this study also includes patients who are deemed not surgically resectable to a state of no gross residual disease, and thus *are* in need of neoadjuvant therapy first. These patients are also at extreme high risk for a poor clinical outcome and in need of new, more effective treatments.

Although cytoreductive surgery constitutes the mainstay of treatment for EOC, an increase in data indicates that delivery of neoadjuvant therapy followed by interval surgery in certain patients, instead of performing surgery followed by chemotherapy, will likely provide equivalent clinical efficacy with more favorable perioperative morbidity and health-related quality of life (HRQoL) for some patients with EOC (Vergote et al. 2010; Kehoe 2016, Fagotti et al. 2016). Indeed, two prospective randomized Phase III studies demonstrated equivalent survival rates among patients with advanced stage EOC who received either neoadjuvant therapy followed by interval surgery or primary tumor reduction surgery (Vergote et al. 2010; Kehoe 2016). These data likely explain the increase in the use of neoadjuvant chemotherapy (NACT) in the United States

(Hinchclilff et al. 2016). In fact, in a 2009 survey for clinician members of the Society of Gynecologic Oncology, approximately 90% of respondents reported the use of NACT in 11%–25% of patients with 1LOC (Dewdney et al. 2010). At the Memorial Sloan Kettering Cancer Center alone, the rate for NACT increased significantly ($p = 0.037$) from 22% (56 of 256 patients) from 2008–2010, to 30% (98 of 330 patients) from 2010 until mid-2013 (Mueller et al. 2016). The clinical emphasis on achieving complete surgical resection, along with fewer perioperative morbidities, collectively account for the increase in uptake of NACT for patients with newly-diagnosed OC, and highlight the need to include patients with OC who were treated with the use of a NACT paradigm into this study.

A 20% cap on patients in the NACT cohort is proposed for this Phase III study to ensure that (1) the mix of patients in this study approximates global clinical practice patterns, and (2) the patient population does not become so heterogeneous so as to unduly bias or obscure the efficacy imparted by this immunotherapy based regimen.

3.3.3 Rationale for Control Group

To minimize the bias between the control and experimental patient groups, this study will administer a placebo to patients in the control group and ensure that patients, physician, and the Sponsor remain blinded to the treatment that is assigned to each group. Paclitaxel, carboplatin, bevacizumab, and placebo treatment followed by bevacizumab and/or placebo treatment is the comparator regimen for this patient population because paclitaxel, carboplatin, and bevacizumab constitute the standard-of-care regimen for this patient population with advanced OC.

The cytotoxic doublet of carboplatin and paclitaxel represents the cytotoxic agents typically used for patients with newly-diagnosed, previously untreated EOC (McGuire et al. 1996; Ozols et al. 2003; Vergote et al. 2010). Attempts to add another cytotoxic agent to this platinum doublet added toxicity without improving clinical outcomes (Bookman et al. 2009). However, the anti-VEGF molecule, bevacizumab, became the first targeted biological agent to demonstrate prolonged and profound PFS improvements when added to carboplatin and/or paclitaxel and then administered as maintenance therapy, especially among patients with postoperative gross residual disease (ICON7 and Study GOG218; Burger et al. 2011; Perren et al. 2011). Study ICON7 showed that the addition of bevacizumab to chemotherapy led to a reduction of 13% in the risk of a PFS event (hazard ratio [HR]: 0.87; 95% CI: 0.77 to 0.99, $p=0.04$), and an improvement by 2.4 months (Perren et al. 2011). Similarly, Study GOG0218, which also combined bevacizumab with chemotherapy, resulted in a reduction of approximately 35% in the risk of a PFS event (HR: 0.645; 95% CI: 0.551 to 0.756, $p < 0.001$) when censored for CA-125 progression, corresponding to a $>$6-month improvement in RECIST-defined PFS (from 12.0 months to 18.0 months; Burger et al. 2011). This improvement in clinical efficacy led to the approval of bevacizumab to be administered in combination with carboplatin and

paclitaxel followed by treatment of single-agent bevacizumab in patients with 1LOC in Europe and other countries globally, and incorporation into European treatment guidelines (Ledermann et al. 2013).

Of additional clinical interest within the ICON7 study (Oza et al. 2015) was the more pronounced benefit conferred by bevacizumab in patients with tumor characteristics that placed them at a high risk for recurrence and death (i.e., postoperative macroscopic residual and Stage IV disease). Bevacizumab plus carboplatin and paclitaxel for these patients resulted in a reduction of 27% in the risk of a PFS event (HR: 0.73; 95% CI: 0.61 to 0.88, $p < 0.0001$), which corresponded to an improvement in median PFS from 10.5 months to 16.0 months. There was also a reduction of 22% in the risk of death, which corresponded to an improvement in median OS from 30.2 months to 39.7 months (Oza et al. 2015).

Recent clinical observations that support the scientific rationale for the combination of anti-VEGF agents (e.g., bevacizumab) with immune checkpoint inhibitors make bevacizumab + atezolizumab particularly attractive. Sznol and colleagues (2015) reported the first combinatorial clinical data demonstrating pronounced therapeutic benefit when bevacizumab was combined with atezolizumab in patients with metastatic RCC. In VEGF-driven tumors, bevacizumab has been shown to normalize the tumor-associated vasculature, and this, in turn, promotes T cell infiltration. The administration of bevacizumab in combination with atezolizumab further increases the immune infiltration and tumor growth control. Harnessing the translational and clinical observations of this well tolerated, 2-pronged approach against both VEGF and PD-L1 holds particularly great therapeutic promise for patients with OC.

3.3.4 Rationale for Progression-Free Survival and Overall Survival as Co-Primary Endpoints

In this study, the co-primary efficacy endpoints will be investigator-assessed PFS and OS. This study will test the hypothesis that treatment with atezolizumab added to paclitaxel, carboplatin, and bevacizumab will prolong PFS and OS compared with treatment with placebo plus paclitaxel, carboplatin, and bevacizumab.

The use of co-primary endpoints of PFS and OS is based on the complexity and dynamic nature of treatment for patients with OC, and the clinical observations and lessons learned from other cancer immunotherapy studies. Wolchok and colleagues (2009) described the unique clinical trajectory of patients' tumors when treated with immunomodulators and suggest short-term radiographic assessments may not capture the true efficacy of cancer immunomodulators. This is further exemplified by the superior and prolonged OS benefit conferred by atezolizumab, despite comparable PFS rates with docetaxel, as demonstrated in the randomized Phase II NSCLC Study GO28753 (POPLAR) (Fehrenbacher et al. 2016). The prolongation of OS in diseases such as recurrent NSCLC reflects the durable biological effects of cancer immunotherapies, such as atezolizumab.

Because tumor response to treatment is dynamic, and the progressive decrease in tumor size alleviates disease burden and demonstrates clinical benefit, PFS remains an important, clinically-meaningful metric to demonstrate the efficacy of anti-cancer regimens for patients with OC. Furthermore, PFS is not subject to potential confounding by post-progression treatments (including anti–PD-L1/PD-1 therapies) that may obscure OS improvements. PFS benefit has been shown consistently across several prospective and retrospective studies of patients with OC who were administered a combination of chemotherapy and bevacizumab, thus reinforcing the importance of this clinical endpoint (Burger et al. 2011, Perren et al. 2011; Aghajanian et al. 2012; Eskander et al. 2014; Coleman et al. 2015).

In acknowledgment of the clinical significance of both PFS and OS, the primary endpoints for this study will be both PFS and OS. This study has been designed to detect a substantial magnitude of benefit in the ITT population with a target HR of 0.70 for PFS and 0.78 for OS.

3.3.5 Rationale for Biomarker Assessments

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-1 and anti–PD-L1 therapy (Topalian et al. 2012; Herbst et al. 2014; Borghaei et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016). In the current study, screening baseline tumor specimens will be collected from patients and tested for PD-L1 expression by a central laboratory during the screening period. Patients who participate in the study after primary tumor reductive surgery must provide a tumor specimen from that surgery. Patients who will undergo neoadjuvant therapy followed by interval tumor reduction will need to provide a tumor specimen from a core needle biopsy (i.e., not from FNA or a cell block generated after centrifuging ascites and/or pleural fluid). Only patients with evaluable tumor PD-L1 expression will be enrolled in the study. Randomization will be stratified by PD-L1 expression. In addition to the assessment of PD-L1 status, other exploratory biomarkers, such as potential predictive and prognostic biomarkers related to the clinical benefit of atezolizumab, tumor immunobiology, mechanisms of resistance, or tumor type, may be analyzed.

Patients who undergo neoadjuvant therapy and participate in the biomarker cohort will undergo a mandatory biopsy tissue sample collection at Cycle 1, Day 15 and provide corresponding plasma. This will enable a robust characterization of the temporal effects of systemic treatment with and without atezolizumab on the immune response (e.g., immune cell infiltration) and on circulating biomarkers (e.g., cell free tumor DNA).

Patients will undergo mandatory tumor biopsy sample collection, if deemed clinically feasible by the investigator, at the time of first evidence of radiographic disease progression to evaluate the utility of the biopsy specimen in distinguishing pseudoprogression (caused by ICs) from true progression. In addition, tumor tissue

biomarkers related to resistance, disease progression, and clinical benefit of atezolizumab will be analyzed.

Blood samples will be collected at baseline and during the study to evaluate changes in surrogate biomarkers. Changes in biomarkers such as cytokines associated with T-cell activation, circulating tumor DNA (ctDNA) concentration, and T-cell subpopulations may provide evidence of biologic activity of atezolizumab in humans. Correlations between these biomarkers and safety and efficacy endpoints will be explored to identify blood-based biomarkers that might predict which patients are more likely to benefit from atezolizumab.

Tumor tissue and blood samples collected at baseline and, if deemed clinically feasible by the investigator, tumor tissue collected at the time of disease progression may enable DNA- and RNA-sequencing to identify somatic mutations and characteristics of the tumor-immune microenvironment predictive of response, and associated with progression to a more severe disease state. These newly-identified somatic mutations and tumor microenvironment changes associated with acquired resistance to study treatment can increase the knowledge and understanding of disease biology.

Genomics is increasingly informing researchers' understanding of disease pathobiology. Whole genome sequencing (WGS) provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity to develop new therapeutic approaches. Data will be analyzed in the context of this study but also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in the identification of important pathways, and guide the development of new targeted agents.

3.3.6 Rationale for Patient-Reported Outcome Assessments

Abdominal symptoms (e.g., bloating, increased abdominal size, 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 in the neoadjuvant setting 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 Organisation 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 the neoadjuvant setting (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 key secondary endpoints among patients receiving neoadjuvant therapy to document the impact of atezolizumab 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 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 benefits in the overall patient population and support and inform on the benefit-risk assessment of atezolizumab therapy, a global assessment of the impact of treatment on patients' functioning and HRQoL will be conducted and analyzed with the functional (role, physical, emotional, and social) and global health status and QoL scale scores of the validated, reliable EORTC QLQ-C30 (Aaronson et al. 1993). In addition, to evaluate any treatment burden patients may experience with the addition of atezolizumab, the proportion of patients who select each response option at each assessment timepoint by treatment arm will be reported for single item GP5 ("I am bothered by side effects of treatment") from the physical wellbeing subscale of the validated and reliable Functional Assessment of Cancer Therapy–General (FACT-G) Quality of Life Instrument–Version 4, (Cella et al. 1997; Webster et al. 1999). Patients will also complete the validated EQ-5D-5L (Herdman et al. 2011; Janssen et al. 2013; see Appendix 6) to generate utility scores to inform pharmacoeconomic evaluations. As such, the utility results will not be included in the CSR.

Given the duration of treatment and the potential for long-term treatment impact, all patient-reported outcome (PRO) measures will be assessed while patients are enrolled in the study and after treatment discontinuation as defined in the schedule of assessments (see Appendix 1 and Appendix 2). Patients will complete all PRO questionnaires on paper at the study site.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 1300 patients with Stage III or Stage IV ovarian, fallopian tube, or primary peritoneal cancer (i.e., cancers of extra-uterine Müllerian origin) with macroscopic residual disease postoperatively (i.e., after primary tumor reductive surgery) or who will undergo neoadjuvant therapy followed by interval surgery are expected to be randomized in this study. The enrollment of patients in the neoadjuvant setting will be capped at approximately 20%.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form (ICF)
- Age ≥ 18 years
- Able to comply with the study protocol, in the investigator's judgment
- Receive a histologic diagnosis of EOC, peritoneal primary carcinoma, or fallopian tube cancer fulfilling the following criteria:

  All epithelial tumors of extra-uterine Müllerian origin by histology (FNA, cytology and/or cell block are not sufficient)

  For patients who will undergo primary tumor reductive surgery: International Federation of Gynecological Oncologists (FIGO) Stage III with gross (macroscopic or palpable) residual disease or Stage IV

    Measurable disease on postoperative imaging studies is not required for eligibility.

    FIGO stage is assessed following the completion of initial abdominopelvic surgery that provides the appropriate tissue for histologic evaluation and diagnosis and can be used for exploratory biomarker studies.

    Primary tumor reductive surgery must be within 42 days of randomization.

  For patients who will undergo neoadjuvant treatment and interval surgery: Patients who receive neoadjuvant treatment must also plan to undergo interval surgery after Cycle 3. Mandatory biopsy tissue samples (e.g., core needle or surgically obtained; FNA or cell-block from ascites and/or pleural effusion are inadequate) will be used to confirm histologically that the tumor is of extra-uterine Müllerian origin and to perform exploratory biomarker studies.

    Patients who receive neoadjuvant therapy will include those patients who are not deemed surgically resectable to a state of no gross residual disease due to the extent and/or distribution of disease (e.g., unresectable miliary pattern of peritoneal carcinomatosis, significant diaphragmatic disease, significant involvement of the root of the mesentery, diffuse tumor in the omentum up to the greater curvature of the stomach, extensive miliary carcinomatosis at the root of the mesentery, tumor infiltration of the stomach, surface lesions on the liver).
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2
- Life expectancy > 12 weeks

- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to randomization:

  ANC $\geq$ 1500 cells/μL (without granulocyte colony stimulating factor support)

  Lymphocyte count $\geq$ 500/μL

  Platelet count $\geq$ 100,000/μL without transfusion

  Hemoglobin $\geq$ 9.0 g/dL

  Patients may be transfused to meet this criterion.

  Serum creatinine $\leq 1.5 \times$ institutional upper limit of normal (ULN)

  Serum bilirubin $\leq 1.5 \times$ ULN

  Patients with known Gilbert disease who have serum bilirubin level $\leq 3 \times$ ULN may be enrolled in the study.

  AST, ALT, and 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.

  For patients who do not receive therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN

- For patients who receive therapeutic anticoagulation: stable anticoagulant regimen
- Negative hepatitis B surface antigen (HBsAg) test at screening
- Negative total hepatitis B core antibody (HBcAb) test at screening, or positive total HBcAb test followed by a negative hepatitis B virus (HBV) DNA test at screening

  The HBV DNA test will be performed only for patients who have a positive total HBcAb test.

- Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening

  The HCV RNA test will be performed only for patients who have a positive HCV antibody test.

  A positive HCV RNA test is sufficient to diagnose active HCV infection in the absence of an HCV antibody test.

- 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 5 months after administration of the last dose of atezolizumab and 6 months after the last dose of bevacizumab, paclitaxel, or carboplatin, whichever is later

  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 but are not limited to bilateral tubal ligation and/or occlusion, male sterilization, and intrauterine devices.

In countries with country-specific health authority mandates, contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation/occlusion, male partner sterilization, established and proper use of estrogen-progestin combination hormonal contraceptives that inhibit ovulation, and intrauterine devices/systems.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study 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, that include the completion of PRO questionnaires
- Availability of a representative formalin-fixed, paraffin-embedded (FFPE) tumor specimen (screening baseline tissue) in paraffin blocks (preferred) or at least 20 unstained slides.

  Patients with fewer than 20 unstained slides available at baseline may be eligible upon discussion with the medical monitor.

  Tumor tissue should be of good quality based on total and viable tumor content and must be evaluated for PD-L1 expression prior to enrollment. Patients whose tumor tissue is not evaluable for PD-L1 expression are not eligible for enrollment in the study.

  If multiple screening baseline tumor specimens are submitted, patients may be eligible if at least one specimen is evaluable for PD-L1. For the purpose of stratification, the PD-L1 score of the patient will be the maximum PD-L1 score among the samples.

    Acceptable samples include tissue obtained from surgery or core needle biopsies (minimum three cores per paraffin block).

    A paraffin block for FFPE tumor specimens is preferred.

    FNA or cell pellets from ascites or pleural effusion are not acceptable.

    Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is not acceptable.

- For patient enrolled in the extended China enrollment phase: residents in Mainland China, residents in Hong Kong and Taiwan of Chinese ancestry and enrolled at sites recognized by China's National Products Administration (NMPA).

4.1.2 Exclusion Criteria

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

- Received a current diagnosis of borderline epithelial ovarian tumor (formerly tumors of low malignant potential)
- Have recurrent invasive epithelial ovarian, fallopian tube, or primary peritoneal cancer that was treated only with surgery (e.g., patients with Stage IA or Stage IB epithelial ovarian or fallopian tube cancers)

  Patients who received a prior diagnosis of a borderline tumor that was surgically resected and who subsequently developed an unrelated, new invasive epithelial ovarian, fallopian tube, or primary peritoneal cancer are eligible for enrollment, if they have never received prior chemotherapy for any ovarian tumor.
- Have non-epithelial ovarian tumors (e.g., germ cell tumors, sex cord stromal tumors)
- Received prior radiotherapy to any portion of the abdominal cavity or pelvis

  Prior focal radiation for localized cancer of the breast, head and neck, or skin is permitted, if it was completed >5 years prior to initiation of study treatment, and the patient remains free of recurrent or metastatic disease.
- Received prior chemotherapy for any abdominal or pelvic tumor that include NACT for ovarian, primary peritoneal or fallopian tube cancer

  Patients may have received prior chemotherapy for localized breast cancer, if it was completed >5 years prior to initiation of study treatment, and the patient remains free of recurrent or metastatic disease.
- Received any biological and/or targeted therapy (including but not limited to vaccines, antibodies, tyrosine kinase inhibitors) or hormonal therapy for management and/or treatment of epithelial ovarian or peritoneal primary cancer
- Have synchronous primary endometrial cancer
- Have a prior history of primary endometrial cancer, except for the following:

  A prior diagnosis of endometrial cancer is allowed if all of the following conditions are met:

  Stage IA cancer

  Superficial myometrial invasion, without lymphovascular invasion

  Grade <3 or not poorly differentiated subtypes, and this includes papillary serous, clear cell or other FIGO Grade 3 lesions
- With the exception of non-melanoma skin cancer and other specific malignancies as noted above, other invasive malignancies within the last 5 years or previous cancer treatment that contraindicates this protocol therapy (e.g., previous chemotherapy treatment for breast cancer completed >5 years ago is permitted as per above).
- Are pregnant, lactating, or intend to become pregnant during the study

- Have a history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Have a known hypersensitivity or allergy to biopharmaceutical agents produced in Chinese hamster ovary cells or any component of the atezolizumab and/or bevacizumab formulations
- Have an active or history of autoimmune disease or immune deficiency that includes but is not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 7 for a more comprehensive list of autoimmune diseases).

  Exceptions include the following:

  Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone are eligible.

  Patients with controlled Type 1 diabetes mellitus on a stable dose of insulin regimen are eligible.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are eligible for enrollment in the study provided that they meet all of the following conditions:

  Rash must cover less than 10% of body surface area

  Disease is well controlled at baseline and requires only low potency topical steroids

  No acute exacerbations of underlying condition within the previous 12 months (i.e., does not require psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high-potency or oral steroids)
- Have a history of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis based on a screening chest computed tomography (CT) scan, with the following exceptions

  A history of radiation pneumonitis in the localized radiation field (fibrosis) is permitted. Patient must still meet all other radiotherapy exclusions listed above.
- Have a positive test result for HIV
- Have active tuberculosis
- Have severe infections within 4 weeks prior to initiation of study treatment, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia

- Have received therapeutic oral or IV antibiotic medication within 2 weeks prior to initiation of study treatment, with the following exceptions:

  Patients who receive prophylactic antibiotic medication (e.g., urinary tract infection prophylaxis, prior to dental procedure) are eligible for enrollment.

- Have significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction, or cerebrovascular accident within 3 months prior to initiation of study treatment, unstable arrhythmias, or unstable angina

  Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or left ventricular ejection fraction $<$50% must be on a stable medical regimen that is optimized in the opinion of the treating physician, in consultation with a cardiologist if appropriate.

- Undergo major surgical procedure within 28 days prior to first bevacizumab dose, or anticipation of the need for a major surgical procedure during the course of the study except patients who receive NACT and will need interval surgery. This may include but is not limited to laparotomy. All incisions should be fully healed, as assessed clinically, prior to starting bevacizumab.

  Consult with the Medical Monitor prior to patient entry for any questions related to the classification of surgical procedures.

- Are administered treatment with a live attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during the course of the study or within 5 months after the last dose of atezolizumab
- Current treatment with anti-viral therapy for HBV
- Have prior allogeneic bone marrow transplantation or solid organ transplant
- Have any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results
- Have any approved or investigational anti-cancer therapy, including chemotherapy or hormonal therapy, with the following exceptions:

  Hormone-replacement therapy or oral contraceptives are allowed.

- Current or recent (within 10 days of initiation of study treatment) use of aspirin ($>$ 325 mg/day) or clopidogrel ($>$ 75 mg/day)
- Are administered treatment with any other investigational agent or participation in another clinical study with anti-cancer therapeutic intent
- Have prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti–PD-1, anti–PD-L1, or anti-cytotoxic T-lymphocyte-associated protein 4 therapeutic antibodies
- Have treatment with systemic immunostimulatory agents (including but not limited to interferons [IFNs], interleukin [IL]-2) within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment

- Have treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [TNF] agents) within 2 weeks prior to initiation of study treatment, with the following exceptions:

  Patients who have received acute, low-dose, systemic immunosuppressant medications *or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy)* are eligible for enrollment in the study.

  The use of corticosteroids for chronic obstructive pulmonary disease and asthma, mineralocorticoids (e.g., fludrocortisone), *or* low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

- Have inadequately-controlled hypertension (defined as systolic blood pressure >150 mmHg and/or diastolic blood pressure >100 mmHg)

  Anti-hypertensive therapy to achieve these parameters is allowed.

- Have prior history of hypertensive crisis or hypertensive encephalopathy
- Have significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to initiation of study treatment
- Have a history of Grade ≥ 2 hemoptysis (≥ 2.5 mL of bright red blood per episode) within 1 month prior to screening
- Have evidence of active bleeding, bleeding diathesis, coagulopathy, tumor that involves major vessels (in the absence of therapeutic anticoagulation)
- Have a history or evidence upon physical examination of any CNS disease, including primary brain tumor, CNS metastases, seizures not controlled with standard medical therapy, any brain metastases, or history of cerebrovascular accident (stroke), transient ischemic attack or subarachnoid hemorrhage within 6 months of the first date of treatment on this study.
- History of leptomeningeal disease
- History of Grade ≥ 4 venous thromboembolism
- Have current use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic purposes that has not been stable prior to initiation of study treatment, with the following exceptions:

  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 receiving a stable dose of anticoagulants prior to initiation of study treatment.

  Prophylactic anticoagulation for the patency of venous access devices is allowed, provided the activity of the agent results in an INR $<1.5\times$ ULN and aPTT is within normal limits prior to initiation of study treatment.

  Deep venous thrombosis prophylaxis with low-molecular-weight heparin is permitted.

- Have core biopsy or other minor surgical procedures within 7 days prior to the first dose of bevacizumab

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

  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.
- Have a history of abdominal fistula or gastrointestinal perforation within 6 months prior to initiation of study treatment, with the following exceptions:

  Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection are eligible but require weekly wound examinations.
- Have clinical signs of gastrointestinal obstruction that require routine parenteral hydration, parenteral nutrition, or tube feeding
- Have evidence of abdominal free air not explained by paracentesis or recent surgical procedure
- Have serious, non-healing wound, active ulcer, or untreated bone fracture
- Have proteinuria, as demonstrated by urine dipstick or >1.0 of protein in a urine protein-to-creatinine ratio and/or 24-hour urine collection

  All patients with $\geq 2+$ protein on dipstick urinalysis at baseline must undergo a urine protein-to-creatinine ratio and/or 24-hour urine collection and demonstrate ≤ 1.0 of protein.
- Have known sensitivity to any component of bevacizumab
- Have known sensitivity to any component of paclitaxel
- Have Grade ≥ 2 peripheral neuropathy as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0
- Have known history of severe allergic reactions to platinum-containing compounds
- Have known history of severe hypersensitivity reactions to products that contain Cremophor® EL (e.g., cyclosporine for injection concentrate and teniposide for injection concentrate)

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, double-blind study. After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from the interactive Web-based response system (IWRS).

Randomization will occur in a 1:1 ratio with the use of a permuted-block randomization method. The same randomization method and ratio will be implemented for the China extension phase, if applicable.

Patients will be randomized to one of two treatment arms:
atezolizumab + carboplatin + paclitaxel + bevacizumab or
placebo + carboplatin + paclitaxel + bevacizumab. The randomization scheme is designed to ensure that an approximately equal number of patients will be enrolled in each treatment arm within the prognostic categories of the following stratification factors:

- Stage and/or residual disease status (Stage III vs. Stage IV)
- ECOG performance status (0 vs. 1 or 2)
- Tumor PD-L1 status (IC0 vs. IC1/2/3)
- Treatment strategy (adjuvant vs. neoadjuvant)

4.2.2 Blinding the Treatment Assignment

The Sponsor and its agents (with the exception of the IWRS service provider, laboratory personnel who perform PK or biomarker analyses, the external iDCC, and the iDMC members), study site personnel that includes the investigator, and the patient will be blinded to the treatment assignment. After analysis of the first co-primary endpoint, PFS, the Sponsor will be unblinded to the treatment assignment. The study site personnel with the inclusion of the investigator(s), and the patient, will remain blinded to the treatment assignment until the completion of the analysis of the second co-primary endpoint, OS. Unblinding of site personnel and patients to the treatment assignment may be considered if the benefit-risk assessment at the time of the PFS analysis is favorable for unblinding of the data (see Section 4.2.3).

4.2.3 Unblinding the Treatment Assignment

Treatment codes should not be broken except in emergency situations in which knowledge of treatment assignment will affect ongoing treatment of the patient. If emergency unblinding of the treatment code becomes necessary, the investigator will be able to break the treatment code by contacting the IWRS. Investigators are encouraged to consult with the Medical Monitor prior to emergency unblinding of the treatment code. *However, the investigator should inform the Medical Monitor that the treatment code has been broken.* The investigator should document the emergency and treatment unblinding process and provide an explanation for any premature treatment unblinding (e.g., accidental treatment unblinding, treatment unblinding due to serious adverse event). After emergency unblinding occurs, medical- and study-related questions should be directed to the "Post-Unblinding Medical Monitor" (see Section 5.4.1).

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 treatment.
The treatment code will be available to the Sponsor's drug safety group through the IWRS. The patient may continue to receive treatment, and the investigator, patient, and other Sponsor personnel will remain blinded to treatment assignment.

Treatment assignment will be unblinded to the Sponsor prior to the primary analysis of PFS, after all data have been cleaned and verified and the database has been locked.

Treatment assignment will be unblinded to the investigator and patients after all data for the analysis of the co-primary endpoint of OS have been cleaned and verified and the database has been locked. Unblinding of site personnel (i.e., investigator[s], study coordinators, research nurses, etc.) and patients may be considered earlier if the benefit-risk assessment at the time of the PFS analysis is favorable.

Whereas atezolizumab PK and ADA samples must be collected from patients who are assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for atezolizumab in these patients are generally not needed for the safe conduct or proper interpretation of this study. Study personnel who are responsible to perform PK and ADA assays will be unblinded to patients' treatment assignments to identify appropriate samples to be analyzed. Samples from patients assigned to the comparator arm will be analyzed only for atezolizumab concentration if requested (e.g., to evaluate possible error in dosing). Atezolizumab ADA samples collected on Day 1 of Cycle 1 may be analyzed for all patients, whereas subsequent samples from patients who are assigned to the comparator arm will not be analyzed for ADA unless requested.

4.3 STUDY TREATMENT

The product (IMP) for this study is atezolizumab.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab and Placebo

Atezolizumab will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution. For information on the formulation and handling of atezolizumab, refer to the Atezolizumab Investigator's Brochure and Pharmacy Manual.

The placebo will be supplied by the Sponsor and will be identical in appearance to atezolizumab and comprise the same excipients but without atezolizumab drug product. The placebo should be handled, stored, and used in the same manner as atezolizumab.

4.3.1.2 Paclitaxel, Carboplatin, and Bevacizumab

Bevacizumab will be supplied by the Sponsor. Paclitaxel and carboplatin will be used in commercially available formulations. Bevacizumab will be considered an IMP by local regulations in some countries. For information on the formulation, packaging, and

handling of paclitaxel and carboplatin, refer to the local prescribing information for each drug.

4.3.2 Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.5.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Appendix 9 and Appendix 10.

4.3.2.1 Timing and Sequence of Treatment Administration

The timing of treatment administration is shown in Appendix 1 and Appendix 2. All of the study treatments are administered intravenously. The sequence of administration is as follows in Table 2 and Table 3 for all treatment arms:

Table 2 Treatment Regimen and Order of Administration for Patients Who Undergo Primary Surgery

Drug[a]	Dose and Administration Route	Infusion Period
Cycle 1		
Paclitaxel	175 mg/m^2 IV	• 3 hours [b]
Carboplatin	AUC 6 IV [b]	• Over approximately 30 minutes [c]
Atezolizumab or placebo	1200 mg IV	• 60 (±15) minutes for the first dose
Cycles 2–6 (Concurrent Treatment)		
Paclitaxel	175 mg/m^2 IV	• 3 hours [b]
Carboplatin	AUC 6 IV [b]	• Over approximately 30 minutes [c]
Bevacizumab	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
Atezolizumab or Placebo	1200 mg IV	• If the previous infusion of atezolizumab or placebo is well tolerated by the patient, then the infusion period may be reduced to 30 (±10) minutes for subsequent doses.
Cycles 7–22 (Maintenance Treatment)		
Bevacizumab	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
Atezolizumab or Placebo	1200 mg IV	• If the previous infusion of atezolizumab or placebo is well tolerated by the patient, then the infusion period may be reduced to 30 (±10) minutes for subsequent doses.

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.

Table 3 Treatment Regimen and Order of Administration for Patients Who Undergo Neoadjuvant Chemotherapy or Interval Surgery

Drug [a]	Dose and Administration Route	Infusion Period
Cycles 1 and 2 (Concurrent Neoadjuvant Treatment)		
Paclitaxel	175 mg/m^2 IV	• 3 hours [b]
Carboplatin	AUC 6 IV [b]	• Over approximately 30 minutes [c]
Bevacizumab	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
Atezolizumab or Placebo	1200 mg IV	• 60 (±15) minutes for the first dose • If the previous infusion of atezolizumab or placebo is well tolerated by the patient, then the infusion period may be reduced to 30 (±10) minutes for subsequent doses.
Cycle 3 (Concurrent Neoadjuvant Treatment)		
Paclitaxel	175 mg/m^2 IV	• 3 hours [b]
Carboplatin	AUC 6 IV [b]	• Over approximately 30 minutes [c]
Atezolizumab or Placebo	1200 mg IV	• 60 (±15) minutes for the first dose • If the previous infusion of atezolizumab or placebo is well tolerated by the patient, then the infusion period may be reduced to 30 (±10) minutes for subsequent doses.
Surgery		
Cycle 4 (Concurrent Post-Neoadjuvant Treatment)		
Paclitaxel	175 mg/m^2 IV	• 3 hours [b]
Carboplatin	AUC 6 IV [b]	• Over approximately 30 minutes [c]
Atezolizumab or Placebo	1200 mg IV	• 60 (±15) minutes for the first dose • If the previous infusion of atezolizumab or placebo is well tolerated by the patient, then the infusion period may be reduced to 30 (±10) minutes for subsequent doses.

Table 3 Treatment Regimen and Order of Administration for Patients Who Undergo Neoadjuvant Chemotherapy or Interval Surgery (cont.)

Drug [a]	Dose and Administration Route	Infusion Period
Cycles 5 and 6 (Concurrent Post-Neoadjuvant Treatment)		
Paclitaxel	175 mg/m^2 IV	• 3 hours [b]
Carboplatin	AUC 6 IV [b]	• Over approximately 30 minutes [c]
Bevacizumab	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
Atezolizumab or Placebo	1200 mg IV	• 60 (±15) minutes for the first dose • If the previous infusion of atezolizumab or placebo is well tolerated by the patient, then the infusion period may be reduced to 30 (±10) minutes for subsequent doses.
Cycles 7 – 22 (Maintenance Treatment)		
Bevacizumab	15 mg/kg IV	• 90 (±15) minutes for the first dose • 60 (±10) minutes for the second dose depending on tolerability of first dose • 30 (±10) minutes for subsequent doses depending on tolerability of second dose
Atezolizumab or Placebo	1200 mg IV	• If the previous infusion of atezolizumab or placebo is well tolerated by the patient, then the infusion period may be reduced to 30 (±10) minutes for subsequent doses.

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.

4.3.2.2 Atezolizumab and Placebo

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle for 22 cycles total or until disease progression, unacceptable toxicity, patient or physician's decision to discontinue, patient death, or study termination by the Sponsor.

Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to

manage potentially serious reactions. For anaphylaxis precautions, see Appendix 8. Atezolizumab infusions will be administered per the instructions outlined in Table 4.

Table 4 Atezolizumab Infusion Guidelines

First Infusion	Subsequent Infusions
• No premedication is permitted. • Atezolizumab should be infused over 60 (±15) minutes. • If clinically indicated, vital signs should be recorded during the infusion at 15, 30, 45, and 60 minutes (±5 minutes for all timepoints) during the infusion, and at 30 (±10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient experiences an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Atezolizumab should be infused over 30 (±10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (±15) minutes if the patient experiences an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (±10) minutes after the infusion.

Atezolizumab will be delivered in 250 mL 0.9% NaCl IV infusion bags.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Guidelines for medical management of infusion-related reactions (IRRs) are provided in the Appendix 9.

No dose modification of atezolizumab is allowed.

4.3.2.3 Bevacizumab, Paclitaxel, and Carboplatin

Bevacizumab

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 on the basis of the patient's baseline weight. Doses should be verified by the treating physician and remain the same throughout the study unless the patient's weight changes by >10%, provided that this aligns with standard institutional practice patterns.

See Appendix 10 for preparation, administration, and disposal details.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.5 and in the Bevacizumab Investigator's Brochure.

Paclitaxel

Institutions should follow their standard administration regimens for paclitaxel.
In general, paclitaxel will be administered intravenously at a dose of 175 mg/m^2 over a period of 3 hours, followed by carboplatin.

Paclitaxel injections must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL.

Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 μm. Use of filter devices, such as IVEX-2® filters, which incorporate short inlet and outlet PVC-coated tubing, has not resulted in significant leaching of bis(2-ethylhexyl)phthalate.

Sites should follow their institutional standard of care for dose adjustments and/or modifications in the event of patient weight changes and/or adverse events. For paclitaxel infusion, exceptions to the infusion time of 3 hours will be allowed for sites that have an institutional policy of infusing paclitaxel more quickly (over a 90-minute time period) or more slowly (up to 4 hours for the first infusion).

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.6.

Carboplatin

Carboplatin should be administered by IV infusion, immediately after the completion of paclitaxel administration, over a 15- to 30-minute time period to achieve an initial target AUC of 6 mg/mL/min (Calvert formula dosing) with standard anti-emetics per local practice guidelines.

The carboplatin dose of AUC 6 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:

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

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 U.S. Food and Drug Administration (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.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.6.

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 nonsteroidal 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 the 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 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 to 60 minutes prior to paclitaxel infusion
- Cimetidine 300 mg IV or ranitidine 50 mg IV (or equivalent) 30 to 60 minutes prior to paclitaxel infusion

Because the effects of corticosteroids on T-cell proliferation have the potential to ablate early atezolizumab-mediated anti-tumor immune activity, it is recommended that dexamethasone doses be minimized to the extent that is clinically feasible.
For example, if Cycle 1 is tolerated without apparent hypersensitivity reaction, a reduction in dexamethasone premedication dose should be considered for subsequent cycles if permitted by institutional standard of care.

4.3.4 Investigational Medicinal Product Accountability

The IMP required for completion of this study of atezolizumab will be provided by the Sponsor where required by local health authority regulations. The study site (i.e., investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each patient, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that patients are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs, with the use of the IWRS to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only patients enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs either will be disposed of at the study site in accordance with the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied 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.

Refer to the pharmacy manual and/or Atezolizumab Investigator's Brochure for information on IMP handling, including preparation and storage, and accountability.

4.3.5 Post-Study Access to Atezolizumab

Currently, the Sponsor does not have any plans to provide atezolizumab or any other study treatments or interventions to patients who have completed the study.
The Sponsor may evaluate whether to continue to provide atezolizumab 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 includes 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 study treatment from 7 days prior to initiation of the study treatment to the treatment 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 with a failure rate of $<1\%$ per year (See Section 4)
- Hormone-replacement therapy
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled or low-dose corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

- *Vaccinations (such as influenza, COVID-19)*

  Live, attenuated vaccines are not permitted (see Section 4.4.3).

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Section 4.4.3) 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; see Appendix 8).

4.4.2 Cautionary Therapy for Atezolizumab-Treated Patients

4.4.2.1 Corticosteroids, Immunosuppressive Medications, and TNF-Alpha Inhibitors

Systemic corticosteroids, immunosuppressive medications, and TNF-alpha inhibitors (TNFi) may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNFi would be routinely administered, alternatives that include antihistamines should be considered. For example, systemic corticosteroids for chemotherapy-induced nausea and vomiting (treatment or prophylactic) should be avoided and alternatives (e.g., aprepitant, 5-HT3 antagonists, etc.) should be utilized instead. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNFi (e.g., infliximab) may be administered at the discretion of the investigator (see Section 4.4.3).

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to the Atezolizumab Investigator's Brochure for details).

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.4.3) 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:

- Concomitant therapy intended for the treatment of cancer (including but not limited to chemo-, hormonal, immune-, radio-, herbal therapy, hyperthermic intraperitoneal chemotherapy [HIPEC], etc.), 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 the study treatment phase until disease progression is documented.
- Anti-cancer treatment prior to disease progression is prohibited for patients who have completed protocol-directed therapy and are in long-term follow-up.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to randomization, during study treatment with atezolizumab, and for 5 months after the last dose of study treatment.
- Systemic immunostimulatory agents (including, but not limited to, IFNs and IL-2) are prohibited within 4 weeks or five half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic corticosteroids may not be administered as a premedication to patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance). Such patients should undergo non-contrast CT scans or magnetic resonance imaging (MRI) scans instead (see Section 4.5.5).

4.5 STUDY ASSESSMENTS

The schedules of assessments to be performed during the study are provided in Appendix 1, Appendix 2, and Appendix 3. All activities must be performed and documented for each patient. 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.

During the treatment period, a time window of ±5 days will apply to all scheduled assessments, unless otherwise specified. All hematologic and serum chemistry assessments required to be performed before dosing in any treatment cycle should be performed within 3 days prior to dosing, unless otherwise specified. Note: Study assessments/cycles may be adjusted slightly to accommodate holidays, vacations, and unforeseen major life events. Documentation to justify this decision should be provided.

4.5.1 Informed Consent Forms and Screening Log

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

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. 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 and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history and use of alcohol and drugs of abuse. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the initiation of the study treatment will 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 and other specified visits, should include 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 post-baseline 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, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

Vital signs should be measured at the beginning of each cycle before the first infusion and as clinically indicated. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of assessments (see Appendix 1 and Appendix 2).

4.5.5 Tumor and Response Evaluations

For patients who have had primary tumor reductive surgery, an initial CT scan or MRI of at least the chest, abdomen, and pelvis is required to establish postsurgical (i.e., primary

cytoreductive surgery) baseline of the extent of residual disease within 28 days (± 5 days) prior to randomization. In the absence of disease progression, imaging that uses the same modality and encompasses the same field as in the initial pre-treatment evaluation should be repeated as follows:

1. Every 9 weeks (±5 days) from the date of randomization during the concurrent treatment phase
2. Every 12 weeks (±5 days) in the maintenance phase (the first scan in the maintenance phase is performed 12 weeks after the last scan in the concurrent treatment phase)
3. Every 3 months (±21 days) from the treatment completion visit for the first 2 years after completion of all protocol therapy
4. Every 6 months (±21 days) for the next 3 years, regardless of whether the patient showed measurable disease on the initial CT or MRI (see Appendix 1 and Appendix 2)
5. After 5 years of survival follow-up, as clinically indicated

For patients who will undergo neoadjuvant therapy followed by interval surgery, an initial CT scan or MRI of at least the chest, abdomen, and pelvis is required at baseline within 28 days (±5 days) prior to randomization. In the absence of disease progression, imaging that uses the same modality and encompasses the same field as in the initial pretreatment evaluation should be repeated as follows:

1. Nine weeks (±5 days) after the date of randomization
2. Within 12 weeks (±5 days) after Cycle 3 (i.e., after interval tumor reductive surgery) and as close as possible (within 14 days ± 5 days) to starting Cycle 4 to establish a post interval tumor reduction surgery baseline (CT scan or MRI of at least the chest, abdomen and pelvis is required)
3. Nine weeks (± 5 days) after the post interval tumor reduction surgery baseline scan
4. Every 12 weeks (±5 days) in the maintenance phase (the first scan in the maintenance phase is performed 12 weeks (± 5 days) after the last scan in the concurrent treatment phase)
5. Every 3 months (± 21 days) from the treatment completion visit for the first 2 years after completion of all protocol therapy
6. Every 6 months (± 21 days) for the next 3 years.
7. After 5 years of survival follow-up, as clinically indicated

Baseline assessments must include CT scans (with oral or IV contrast) or MRI scans of the chest, abdomen, and pelvis. A spiral CT scan of the chest may be obtained but is not a requirement. 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 scan with contrast or MRI scan of the head must be completed at screening to

evaluate CNS metastasis in all patients, if there is any clinical evidence of CNS involvement. An MRI scan of the head is required if clinically indicated to confirm or dispel receipt of the diagnosis of CNS metastases in the event of an equivocal CT scan. Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

If a CT scan for tumor assessment is performed in a positron emission tomography and/or CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans). The change from a CT to an MRI scan due to an allergic reaction to IV contrast is permissible.

Radiographic tumor assessment must be performed at designated fixed time intervals regardless of the cycle of the study treatment. Responses will be assessed by the investigator with the use of RECIST v1.1 (see Appendix 11) for the co-primary endpoint. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

Scans will be submitted to an independent review facility for prospective centralized auditing.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

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

- Hematology: WBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum): sodium, potassium, magnesium, glucose, BUN creatinine, albumin, calcium, total bilirubin, ALP, ALT, AST
- Coagulation: PT/INR, aPTT
- 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, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

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.

- 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.

  A positive HCV RNA test is sufficient to diagnose active HCV infection in the absence of an HCV antibody test.

- Pregnancy test

  All women of childbearing potential will have a urine pregnancy test at screening. For women of childbearing potential in countries with country-specific health authority mandates (e.g., Spain, Norway, Czech Republic, Poland, Germany, and Belgium), urine pregnancy tests will continue to be performed at the following specified visits: on Day 1 of Cycles 2–22, at treatment discontinuation (unless administered within 30 days); and at 3 months and 6 months after treatment discontinuation. If a urine pregnancy test result is positive, it must be confirmed by a serum quantitative human chorionic gonadotropin and pelvic ultrasound (see Appendix 1 and Appendix 2).

  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).

- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted
- Thyroid-function testing (TSH, T3, [or total T3 for sites where free T3 is not performed], T4)
- Serum CA-125

Results from the following tests will not be provided back to the site. The following samples will be sent to one or several central laboratories or to the Sponsor for analysis:

- Serum samples for atezolizumab PK analysis through use of a validated assay
- Serum samples for assessment of ADAs to atezolizumab through use of validated assays
- Residual PK and ADA samples will be retained for further method development, validation and characterization or for testing for bevacizumab PK and ADA if deemed necessary. Samples will be stored for up to 5 years after the final Clinical Study Report has been completed.
- Plasma and whole blood samples for exploratory research on biomarkers
- Screening baseline tumor tissue sample collected at baseline for determination of PD-L1 expression and for exploratory research on biomarkers

A representative FFPE tumor specimen in a paraffin block (preferred) or at least 20 slides that contain unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment. After receipt of the signed ICF, patient retrieval and submission of an screening baseline tumor sample can occur outside the 28-day screening period.

For patients who undergo primary tumor reduction surgery, tumor tissue from that surgery must be submitted. For those patients who undergo neoadjuvant treatment, tumor tissue samples from pre-treatment and at the time of interval cytoreduction are required. Neoadjuvant patients who opt to be in the biomarker cohort are also required to provide tumor tissue during treatment collected on Cycle 1, Day 15. A pretreatment tumor biopsy may also be performed if a patient's screening baseline tissue does not meet PD-L1 eligibility criteria. Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Tumor tissue should be of good quality based on total and viable tumor content. Acceptable samples include those from surgical resections or core needle biopsies (at least three cores [18 gauge minimum]), embedded in a single paraffin block. FNA (i.e., samples that do not preserve histologic tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from ascites and/or pleural effusion, lavage samples, and bone metastases are not acceptable. Remaining tumor tissue after material for biomarker analysis has been collected for enrolled patients will be returned to the site upon request or within 18 months after final closure of the study database, whichever occurs first. Remaining tumor tissue for patients who are not enrolled in the study will be returned to the site no later than 6 weeks after eligibility determination.

- Tumor tissue sample collected during treatment for neoadjuvant patients who were enrolled into the biomarker cohort.

  Tumor biopsy samples should be collected by core needle (18 gauge minimum) biopsy. Three cores should be submitted for evaluation. Radiographic guidance is permitted, if needed (e.g., CT, ultrasound).

- Tumor tissue sample collected at the time of investigator-determined progression, if deemed clinically feasible by the investigator, for exploratory research on biomarkers

  Biopsies should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. Acceptable samples include those from resections or core needle biopsies (1 FFPE block or at least 15 unstained slides from no less than two cores [18 gauge minimum]).

Exploratory biomarker research may include but will not be limited to analysis of ctDNA, genes or gene signatures associated with tumor immunobiology, PD-L1, lymphocytes or cytokines associated with T-cell activation and may involve DNA or RNA extraction, analysis of somatic mutations, and use of WGS or next-generation sequencing (NGS).

NGS will be performed by Foundation Medicine for post-progression samples. If performed by Foundation Medicine, the investigator can obtain results from these analyses in the form of an NGS report, which is available upon request directly from Foundation Medicine. The investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by health authorities. The NGS report is generated for research purposes and is not provided to guide future treatment decisions.

Depending on country-specific regulations, the NGS report may not be available in all countries.

For sampling procedures, storage conditions, and shipment instructions, refer to the laboratory manual.

Unless the patient gives specific consent for leftover samples to be stored for optional exploratory research (see Section 4.5.11), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Plasma and serum samples collected for PK analysis and immunogenicity analysis will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood samples collected for WGS will be stored until they are no longer needed or until they are exhausted.
- Leftover plasma and tumor samples collected for biomarker analysis during the study will be destroyed no later than 15 years after the final Clinical Study Report has been completed.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples.

Data that arise from sample analysis will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law, with the exception of the report from the Foundation Medicine. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

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 should be performed after the patient has rested in a supine position for at least 10 minutes.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be maintained as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.8 Patient-Reported Outcomes

To more fully characterize the clinical profile of atezolizumab, PRO data will be obtained through 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.

Official versions of the PRO questionnaires, translated as appropriate into the local language, along with a booklet cover page, will be provided to sites in PDF format to print and distribute to patients. The PRO questionnaires will be completed on paper in their entirety by the patient 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 and followed by the QLQ-OV28, EQ-5D-5L, and FACT-G single item GP5 at timepoints corresponding with in-clinic visits, both while receiving study treatment and during the survival follow-up period. See Appendix 1 and Appendix 2 for the frequency and timing of PRO assessments.

To generate data supporting the primary clinical efficacy endpoints (PFS, OS) while acknowledging the impact of the global COVID-19 pandemic, patients in the survival follow-up phase who are unable to visit the site in-person due to COVID-19 may complete PRO questionnaires via phone interview by site staff. Instructions for phone administration of PROs will be provided to sites.

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-report measures (Aaronson et al. 1993; Cull et al. 2001; Greimel et al. 2003; see Appendix 5). 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, pain), global health and/or quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, 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 instrument v4 (see Appendix 12) 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. 1997; Webster et al. 1999). In this study, the single item GP5 ("I am bothered by side effects of treatment") from the physical wellbeing subscale of the FACT-G has been selected for individual item analysis to document the level of bother 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). Single item GP5 from the FACT-G instrument takes less than a minute to complete.

4.5.8.3 EQ-5D-5L

The EQ-5D-5L is a validated self-report 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 6). 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).

4.5.10 Mandatory Samples for Whole Genome Sequencing

At participating sites, blood samples will be collected for DNA extraction to enable WGS and identify germline mutations that are predictive of response to study drug, associated with progression to a more severe disease state and/or susceptibility to develop adverse events, or can increase knowledge and understanding of disease biology. The blood samples may be sent to one or more laboratories for analysis.

Collection and submission of WGS samples is contingent upon the review and approval of the exploratory research and the WGS portion of the ICF by each site's IRB or EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS sampling, this section of the protocol will not be applicable at that site.

Genomics increases researchers' understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity to develop new therapeutic approaches. Data will be analyzed in the context of this study but also explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, and guide the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, refer to the laboratory manual.

Blood samples collected for WGS are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC-approved ICF and applicable laws (e.g., health authority requirements).

Patient medical information associated with WGS specimens is confidential and may be disclosed only to third parties as permitted by the ICF or a separate authorization for use and disclosure of personal health information signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses, data derived from WGS specimens will not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.11 Samples for Research Biosample Repository

4.5.11.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens that include body fluids,

solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Tumor tissue, blood, and plasma from RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response that includes drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.11.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage and analysis of RBR samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the ICF by each site's IRB or EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol will not be applicable at that site.

4.5.11.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including but not limited to research on biomarkers related to atezolizumab, diseases, or drug safety:

- Tumor tissue samples from biopsies performed at the investigator's discretion during the study
- Leftover blood, plasma, and tumor tissue samples (except leftover tissue from archival FFPE blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides) that include leftover tissue samples from additional tumor biopsies or medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study
- A whole blood sample for DNA isolation will be collected from patients who have consented to optional RBR sampling at Cycle 1, Day 1 as shown in the schedules of assessments in Appendix 1 and Appendix 2. If, however, the RBR genetic blood sample is not collected during the scheduled visit, it may be collected as soon as possible (after randomization) during the conduct of the clinical study. Collection of whole blood will enable the evaluation of single nucleotide polymorphisms in genes

associated with immune biology that include but are not restricted to the target and pathway associated genes such as PD-L1, PD-1, and B7.1 as well as IL-8, IL-6, and related cytokines. The sample may be processed with the use of techniques such as kinetic polymerase chain reaction and DNA sequencing.

The above samples may be sent to one or more laboratories for analysis of germline mutations or somatic mutations via WGS, NGS, or other genomic analysis methods.

Genomics increases researchers' understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity to develop new therapeutic approaches. Data will be analyzed in the context of this study but also explored in aggregate with data from other studies. The availability of a larger dataset will assist in the identification of important pathways, and guide the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, refer to the laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB and/or EC-approved ICF and applicable laws (e.g., health authority requirements).

4.5.11.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens is confidential and may be disclosed only to third parties as permitted by the ICF (or a separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR specimens, data derived from these analyses will not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and patents that result from the inventions, improvements, and/or know-how that originates from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where otherwise agreed upon.

4.5.11.5 Consent to Participate in the Research Biosample Repository

The ICF will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be informed that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not be requested to provide a separate signature.

The investigator should document whether or not the patient has provided consent to participate and (if applicable) the date(s) of consent, with completion of the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

A separate, specific signature is not required for mandatory RBR blood samples.

4.5.11.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the performance of tests on their specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global_rcr-withdrawal@roche.com

A patient's withdrawal from Study YO39523 does not, in itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from Study YO39523.

4.5.11.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the ICF. Sponsor monitors and auditors will have direct access to appropriate parts of records related to patient participation in the RBR for verification of the data provided to the

Sponsor. The site will permit monitoring, audits, IRB and/or EC review, and health authority inspections through direct access to source data and documents related to the RBR samples.

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 (atezolizumab, placebo, paclitaxel, carboplatin, and/or bevacizumab) if they experience any of the following:

- Intolerable toxicity related to study treatment that includes the development of an immune-mediated 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 and the Atezolizumab Investigator's Brochure
- Any medical condition that may jeopardize the patient's safety if they continue study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Use of another non-protocol anti-cancer therapy
- Pregnancy
- Symptomatic deterioration attributed to disease progression
- Radiographic disease progression per RECIST v1.1

    CA-125 elevations do not constitute disease progression and cannot be used for determining disease progression.

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

Patients will return to the clinic for a treatment discontinuation visit ≤30 days after the last dose of all study treatments. The visit during which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo limited physical examination and CA-125, tumor response, and PRO assessments at the time intervals outlined in the schedules of assessments (see Appendix 1 and Appendix 2). Patients who discontinue study treatment for progressive disease or loss of clinical benefit, regardless of receipt of subsequent anti-cancer therapy, should continue to undergo limited physical examination, CA-125 and PRO assessments at the time intervals outlined in the schedules of assessments.

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 (Appendix 1 and Appendix 2), 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., country records) to obtain only information about survival status.

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to exclude a patient from the study at any time. If patients withdraw from study treatment, they will still continue follow-up, disease surveillance activities.

Reasons for withdrawal from the study may include but are not limited to:

- Withdrawal of consent for the study (i.e., from the study treatment regimens **and** any follow-up and/or surveillance activities associated with the study)
- Study termination or site closure
- Patient non-compliance (e.g., missed doses and/or missed visits)

Every effort should be made to obtain information on patients who withdraw or are excluded from the study. The primary reason for withdrawal or exclusion from the study should be documented on the appropriate eCRF. Patients who withdraw or are excluded from the study will not be replaced.

Withdrawal or exclusion from the study must differentiate between either withdrawal or exclusion from study treatment with continued follow-up and/or surveillance (i.e., survival, post-study treatments), or withdrawal or exclusion from study treatment with no follow-up and/or surveillance (i.e., survival, post-study treatments).

4.6.3 Participants Lost to Follow-Up

If a participant does not return to the clinic for a required study visit, site personnel must attempt to contact the participant as soon as possible to reschedule the missed visit and counsel the participant on the importance of maintaining the visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel may determine if there are ways to support participant participation. If a participant does not return to the clinic for scheduled visits and is not in contact with the site, site personnel must make every effort to regain contact with the participant. Whenever possible, attempts should include three telephone calls followed by a certified letter (or equivalent) to the participant's last known mailing address. These contact attempts should be

documented in the participant's medical record. If the participant continues to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study.

4.6.4 Study Discontinuation

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

- 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.

4.6.5 Site Discontinuation

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (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 plan for patients in this study is on the basis of clinical experience with atezolizumab in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections 5.1.1–5.1.4).

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 atezolizumab 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. Guidelines for managing patients who experience anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided in Appendix 9 and Appendix 10. All adverse events will be reported as described in Sections 5.2–5.6.

Patients with active infection are excluded from study participation. In the setting of a pandemic or epidemic, screening for active infections (including SARS-CoV-2) prior to and during study participation should be considered according to local or institutional guidelines or guidelines of applicable professional societies (e.g., American Society of Clinical Oncology or European Society for Medical Oncology).

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome，which are considered to be potential risks for atezolizumab. See Appendix 9 of the protocol and refer to Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks and the management guidelines for atezolizumab.

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. Patients will be monitored for carboplatin-related adverse events.

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

5.1.4 Risks Associated with Bevacizumab

The most common (≥ 1 of 10) side effects associated with bevacizumab include febrile neutropenia, leucopenia, neutropenia, thrombocytopenia, anorexia, hypomagnesaemia, hyponatremia, peripheral sensory neuropathy, dysarthria, headache, dysguesia, eye disorder, lacrimation increased, hypertension, thromboembolism (venous), dyspnea, rhinitis, epistaxis, cough, rectal hemorrhage, stomatitis, constipation, diarrhea, nausea, vomiting, abdominal pain, wound healing complications, exfoliative dermatitis, dry skin, skin discoloration, arthralgia, myalgia, proteinuria, ovarian failure, asthenia, fatigue, pyrexia, pain, mucosal inflammation, and weight decreased.

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

5.1.5 Bevacizumab Dose Modification and Management of Specific Adverse Events

At the start of each cycle without cytotoxic chemotherapy, the ANC must be >1000/µL and the platelet count must be ≥75,000 cells/µL. Dose adjustments for bevacizumab are permitted if the body weight changes > 10% from the baseline body weight provided that this aligns with institutional guidelines; all subsequent doses should be modified accordingly. Dose reductions for adverse events are not recommended. Criteria for treatment modifications and guidelines for the management of toxicities are summarized in Appendix 10. If adverse events occur that necessitate withholding bevacizumab from patients, the dose will remain unchanged once treatment resumes.

Bevacizumab treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. If bevacizumab has been withheld for ≥ 42 days from the date of the first missed dose because of toxicity, the patient should be discontinued from bevacizumab, unless resumption of treatment is approved following investigator discussion with the Medical Monitor. Bevacizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit-risk* by the investigator *and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.* The Medical Monitor *is available to advise as needed.*

5.1.6 Carboplatin and Paclitaxel Dose Modification and Management of Specific Adverse Events

At the start of each cycle with cytotoxic chemotherapy, the ANC must be ≥ 1500/µL and the platelet count must be ≥ 100,000 cells/µL. Treatment may be delayed for up to 42 days from the last dose to allow sufficient time for recovery. Growth factors may be used in lieu of and/or in addition to a dose reduction for neutropenic fever or

Grade 4 neutropenia in accordance with institutional practice guidelines and/or the American Society of Clinical Oncology and the National Comprehensive Cancer Network guidelines (Smith et al. 2015; NCCN 2016).

5.1.6.1 Carboplatin

Therapy with carboplatin should be discontinued in the case of an unresponsive tumor, progressive disease and/or occurrence of not tolerable side effects. Reduction of the initial dosage by 20%–25% or institutional guidelines (e.g., AUC 6, AUC 5, AUC 4) is recommended for patients present with risk factors such as prior myelosuppressive treatment.

For detailed information regarding the management of adverse events that are associated with carboplatin, refer to the prescribing information for carboplatin.

5.1.6.2 Paclitaxel

Subsequent doses of paclitaxel should be administered in accordance with individual patient tolerance to the treatment. Patients who experience severe neutropenia (neutrophil count $< 500/\mu L$ for ≥ 1 week) or severe peripheral neuropathy should receive a dose reduction of 20% or institutional guidelines (e.g., 175 mg/m2, 135 mg/m2, 110 mg/m2) for subsequent doses.

For detailed information regarding the management of adverse events associated with paclitaxel, refer to the prescribing information for paclitaxel.

5.1.7 Potential Overlapping Toxicities

The risk of overlapping toxicities between atezolizumab, bevacizumab, carboplatin, and paclitaxel is thought to be minimal. Nevertheless, the attribution and management of certain adverse events that have been associated with each agent separately (e.g., hepatotoxicity, skin, and gastrointestinal toxicity) may not be unambiguous when the agents are administered in combination. It is theoretically possible that allergic or inflammatory adverse events associated with bevacizumab and these chemotherapeutic agents (e.g., hepatotoxicity) could be exacerbated by the immunostimulatory activity of atezolizumab.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of the monitoring and recording of adverse events (includes serious adverse events and adverse events of special interest), performance of protocol-specified safety laboratory assessments, measurement of protocol-specified vital signs, and completion of other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require to be immediately reported 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 who is administered a pharmaceutical product, regardless of causal attribution. An adverse event can be any of the following:

- Any unfavorable and unintended sign (includes 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 (i.e., deterioration 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) that was not present at baseline
- Any deterioration in a laboratory test value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms, or leads to a change in the study treatment or the concomitant treatment, or discontinuation from the study treatment
- Adverse events that are related to a protocol-mandated intervention, including those events that occur prior to the assignment of the 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 causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at an 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 or incapacity (i.e., the adverse event results in the substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly or birth defect in a neonate or infant born to a mother who was exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or require medical and/or surgical intervention to prevent one of the outcomes listed)

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., $<$24 hours after the notification of the event; see Section 5.4.2 instructions on how to report).

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., $<$24 hours after learning of the event; see Section 5.4.2 for instructions on how to report). Adverse events of special interest for this study include the following:

5.2.3.1 General Adverse Events of Special Interest

- 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) and based on the following observations:

  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

- Suspected transmission of an infectious agent by the study treatment, defined as:

  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 test result findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

5.2.3.2 Adverse Events of Special Interest for Atezolizumab

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hypothyroidism and hyperthyroidism
- Hepatitis, which includes AST or ALT $>10\times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis

- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, and systemic inflammatory response syndrome
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

5.2.3.3 Adverse Events of Special Interest for Bevacizumab

- Grade ≥3 hypertension
- Grade ≥3 proteinuria
- Any grade gastrointestinal perforation, abscesses, or gastrointestinal-fistulae
- Grade ≥2 non-gastrointestinal 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

5.3 METHODS AND TIMING TO CAPTURE AND ASSESS SAFETY PARAMETERS

The investigator is responsible to ensure that all adverse events (see Section 5.2.1) 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), 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 the study treatment, serious adverse events caused only by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, or discontinuation of medications) should be reported (see Section 5.4.2).

After the initiation of the study treatment, all adverse events will be reported until 30 days after the last dose of the study treatment (which includes study-related surgery) 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 (which includes study-related surgery) or until starting a new anti-cancer therapy, whichever occurs first. After this reporting period, serious adverse events believed to be related to prior exposure to study treatment, including study-related surgery, should be reported.

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

5.3.2 Eliciting of Adverse Event Information

A consistent methodology for non-directive questions should be adopted to elicit adverse event information during all patient evaluation visits. Examples of non-directive questions include:

- "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 to assess the severity of an adverse event. Table 5 will be used to assess the severity of adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Severity Grading Scale for Adverse 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; disabled; or limited to perform 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: This information is on the basis of the most recent version of NCI CTCAE (v4.0), found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living include the preparation of meals, shopping for groceries or clothes, use of the telephone, money management, etc.

[b] Examples of self-care activities of daily living include bathing, (un)dressing, 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 5.2.2 and Section 5.4.2).

[d] Grade 4 and Grade 5 events must be reported as serious adverse events (see Section 5.2.2 and Section 5.4.2).

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 treatment and indicate "yes" or "no" accordingly. Guidance should be taken into consideration as follows:

- Temporal relationship of event onset to the initiation of the study treatment
- Course of the event, with special consideration of the effects of the dose reduction, discontinuation of the study treatment, or re-initiation of the study treatment (as applicable)
- Known association of the event with the study treatment or with similar treatments
- Known association of the event with the disease of interest in this 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

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

5.3.5 Procedures to Record Adverse Events

Investigators should use correct medical terminology and concepts when recording adverse events on the Adverse Event eCRF, and avoid colloquialisms and abbreviations. Only one adverse event term should be recorded only in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions and Cytokine-Release Syndrome

There may be significant overlap in signs and symptoms of IRRs and CRS. While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as delayed hypersensitivity reactions, sepsis or infections, HLH, tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured on the Adverse Event eCRF as a diagnosis (e.g., "infusion-related reaction" or "cytokine–release syndrome"). Avoid ambiguous terms such as "systemic reaction." Cases of late-onset CRS should be reported as "cytokine-release syndrome" on the Adverse Event eCRF. Associated signs and symptoms of an IRR should be recorded on the dedicated Infusion-Related Reaction eCRF.

If a patient experiences both a local and systemic reaction to a single administration ofstudy treatment, each reaction should be recorded separately on the Adverse Event eCRF, with associated signs and symptoms of an IRR also recorded separately on the dedicated Infusion-Related Reaction eCRF.

In recognition of the challenges in clinically distinguishing between IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix 9.

5.3.5.2 Diagnosis versus Signs and Symptoms

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 the report, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently identified, 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

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 initial event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If a healthy adult patient vomits and experiences mild dehydration without additional treatment, vomiting should be reported only on the eCRF.
- If a patient vomits and experiences severe dehydration, both events should be reported separately on the eCRF.
- If a patient experiences a severe gastrointestinal hemorrhage that leads to renal failure, both events should be reported separately on the eCRF.
- If a patient experiences dizziness that leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If a patient experiences neutropenia that 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 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 visits. Such events should be recorded only once on the Adverse Event eCRF. The initial severity (i.e., 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., $<$24 hours after learning that the event became serious; see Section 5.4.2). The Adverse Event eCRF should be updated and the event changed to “serious” with all data fields related to the serious adverse events completed.

A recurrent adverse event is one that resolves between patient evaluation visits and then 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 Test Result Values

Not every laboratory test result 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 the 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

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

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

If a clinically significant laboratory test result 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 test result 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 test result abnormality from patient visit to visit should be recorded only once on the Adverse Event eCRF (see Section 5.3.5.4 for details on how to record 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 the 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 result findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign value abnormality should be classified as an adverse event.

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

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

5.3.5.7 Abnormal Liver Function Test Results

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 an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report the occurrence of the following as an adverse event:

- 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 test result values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., <24 hours after notification 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) and that are attributed by the investigator solely to the progression of ovarian, fallopian tube, or primary peritoneal cancer should be recorded on the Death Attributed to Progressive Disease eCRF. All other patient deaths during the study, regardless of the relationship to the study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). The iDMC 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, only one such event should be reported. 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 conclusion of 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 in a patient at the time of 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 only as an adverse event if the frequency, severity, or character of the condition deteriorates 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 with the inclusion of applicable descriptors (e.g., “more frequent headaches”).

5.3.5.10 Lack of Efficacy or Deterioration 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 only as efficacy assessment data. In most cases, the expected pattern of progression will be on the basis of RECIST v1.1 criteria. In rare cases, the determination of the clinical progression will be on the basis of the symptomatic deterioration. However, every effort should be made to document the progression through the use of objective criteria. If there is any uncertainty 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 the hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization of a patient should be documented and reported as a serious adverse event (see 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 the administration of the study treatment 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 Reporting Requirements for Cases of Accidental Overdose or Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately 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). For atezolizumab/placebo or bevacizumab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with atezolizumab/placebo or bevacizumab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require the completion of two Adverse Event eCRF pages, one to report the accidental overdose

and one to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both eCRF pages.

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 with the use of PRO data. Sites are not expected to review the PRO data for adverse events.

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 study. The investigator must report such events to the Sponsor immediately, and under no circumstances should the reporting take place > 24 hours after the investigator is notified of the event. Events that the investigator must report to the Sponsor within 24 hours after notification of the event, regardless of the relationship to the study treatment include:

- 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 5.2.1; 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., < 24 hours after notification of the information). New significant information includes:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality on the basis of 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 to report serious adverse events to the local health authority and IRB and/or EC.

5.4.1 Medical Monitors and Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

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

Mobile Telephone No.: [redacted]

Email: [redacted]

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

Mobile Telephone No.: [redacted]

Email: [redacted]

To ensure the safety of the 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, and 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 the Initiation of the Study Treatment

After informed consent has been obtained from the patient but prior to the initiation of the study treatment, serious adverse events caused only by a protocol-mandated intervention should be reported. The Serious Adverse Event or Adverse Event of Special Interest Reporting Form provided to the investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., $<$24 hours after the notification of the event), either by fax or emailed scan of the form via the fax number or email address provided to the investigators.

5.4.2.2 Events That Occur after the Initiation of the Study Treatment

After the initiation of the study treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the last dose of the study treatment (which includes study-related surgery) is administered or until initiation of a new anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the notification of the event) on the Adverse Event eCRF and submit the report via the EDC system. A report will be generated and sent to the Roche Safety Risk Management team 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 the investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., $<$ 24 hours after the notification of the event), either by fax or emailed scan of the form via the fax number or email address provided to the 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 after the reporting period 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 5 months after the administration of the last dose of atezolizumab, and/or 6 months after the administration the last dose of bevacizumab, paclitaxel, or carboplatin, whichever is later. A paper Clinical Study 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 with use of the fax number or email address provided to the investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue the administration of the study treatment and counsel the patient on 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 and/or the mother during or after the pregnancy, or a congenital anomaly and/or 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.

Attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

5.4.3.2 Abortions

The Sponsor considers spontaneous abortions medically significant events, and they should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., $<$24 hours after the notification 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 and/or Birth Defects

Any congenital anomaly and/or birth defect in a child born to a female patient who is exposed to the study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., $<$24 hours after the notification 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 up on each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient completed the follow-up study period, or the patient withdraws consent. Every effort should be made to follow up on all serious adverse events that are considered related to the study treatment or study-related procedures until a final outcome can be reported.

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

All pregnancies reported during the study period 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 administration of 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 treatment, 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 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 on the basis of applicable legislation.

To determine the reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events with the use of reference documents:

- Atezolizumab Investigator's Brochure
- AVASTIN® (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 on the basis of the investigator's assessment of causality and seriousness, with permission to upgrade by the Sponsor as needed.

An iDMC will monitor the safety data during the study. An aggregate report of any clinically-relevant imbalances that do not favor the test product will be submitted to health authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary analysis populations for efficacy are the ITT population, defined as all patients randomized in the study, and the PD-L1–positive subgroup, defined as the patients in the ITT population whose PD-L1 status is IC1/2/3 at the time of randomization. Patients will be grouped in accordance with the treatment assigned at randomization.

The primary analysis population for safety is the Safety Population, defined as all randomized patients who receive at least one dose of the study medication. Patients will be grouped in accordance with the treatment they actually receive, and all patients who received any dose of atezolizumab will be included in the atezolizumab treatment arm for analysis.

If the China extension phase is initiated, data from this phase will not be included in the primary analysis of the main study. A separate analysis will be performed for the China subgroup, where data from the China extension phase and from the patients in the global enrollment phase from China will be combined and summarized (see Section 6.9 and the statistical analysis plan [SAP] for further details). All analyses

discussed in this section will be restricted to the patients recruited in the global study only, unless noted.

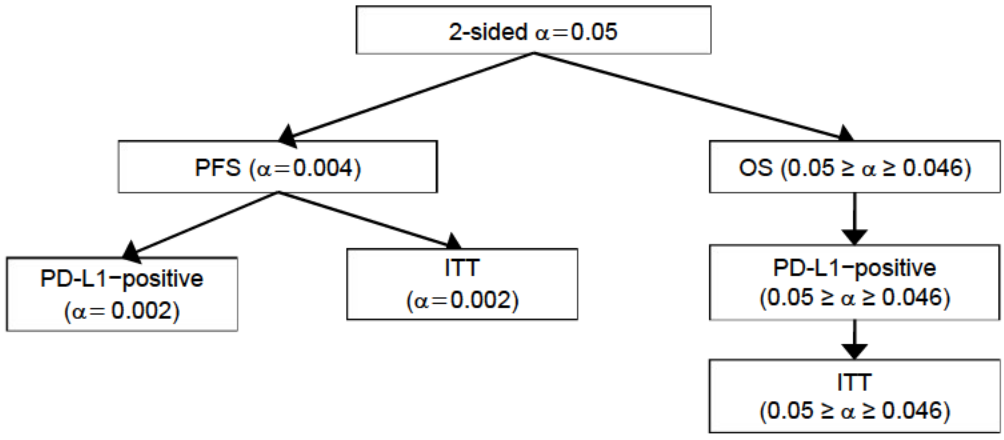
6.1 DETERMINATION OF SAMPLE SIZE

Approximately 1300 patients will be randomized in the global study in a 1:1 ratio to the two treatment arms.

There are two co-primary efficacy endpoints: investigator-assessed PFS and OS. The overall Type I error rate will be controlled at a two-sided level of 0.05 to test PFS and OS in the PD-L1–positive subgroup and the ITT population (see Figure 3). PFS in both the ITT and PD-L1–positive subgroup will be tested in parallel at the same significance level of 0.002 (two-sided). To test OS in both these specified populations, a hierarchical testing approach will be applied. The alpha allocated to OS will be used first to test OS in the PD-L1–positive subgroup. If the significance is reached, the same alpha as used for the PD-L1–positive subgroup OS testing will be passed to OS in the ITT. Note that the OS testing sequence of the populations may be inverted (see Section 6.4.1). The OS test in the PD-L1–positive subgroup is initially assigned with an alpha level of 0.046 and the actual alpha level will be determined by the results of the PFS tests. If the PFS test in either the ITT or PD-L1–positive population reaches significance, its assigned alpha of 0.002 will be additively passed to OS.

- The alpha level for OS will be 0.046 if neither of the PFS tests (in the ITT and PD-L1–positive subgroup) reaches significance.
- The alpha level for OS will be 0.048 if only one PFS test (in either the ITT or the PD-L1–positive subgroup) reaches significance.
- The alpha level for OS will be 0.05 if both the PFS tests (in the ITT and the PD-L1–positive subgroup) reach significance.

Figure 3 Overview of the Type I Error Control



ITT=intent-to-treat; PFS=progression-free survival; OS =overall survival.

The sample size of the study is determined by the number of patient deaths required to demonstrate efficacy in terms of OS in the PD-L1–positive subgroup and the ITT population. To detect an improvement in OS with the use of a log-rank test at a two-sided significance level of 0.046, approximately 311 deaths in the PD-L1–positive subgroup will be required to achieve 81% power with a target HR of 0.72, and approximately 534 deaths in the ITT population to achieve 80% power with a target HR of 0.78. The numbers of patient deaths needed for the OS analyses in the PD-L1–positive subgroup and the ITT population are listed in Appendix 4 for other significance levels that could be assigned to the OS analyses.

There will be no interim analysis for PFS. The primary analysis of PFS will take place when approximately 601 PFS events in the ITT and 347 PFS events in the PD-L1–positive subgroup have occurred (whichever is later), which is expected at approximately 36 months after the first patient is enrolled in the study. This provides 90% power to detect a PFS improvement of HR=0.7 in the ITT, and 91% power in the PD-L1–positive subgroup with HR=0.62, at a two-sided significance level of 0.002.

Two interim analyses of OS will be performed on patients who are in the ITT and PD-L1–positive populations. The timing of the two interim analyses and the final analysis for OS depends on the results from the primary analysis of the co-primary endpoint of PFS, which is listed in Appendix 4 and includes the pre-specified boundaries for the different scenarios.

The calculation of the sample size and estimates of the analysis timelines are based on the following assumptions:

- PFS and OS are exponentially distributed.
- The median duration of PFS in the control arm is 18 months.
- The median duration of OS in the control arm is 43 months.
- The prevalence of PD-L1–positive (IC1/2/3) patients is 60%.
- The two interim and final analyses of OS use the Lan-DeMets alpha spending function to approximate the O'Brien-Fleming boundary.
- The dropout rate is 5% over 12 months for PFS and OS.
- The recruitment of 1300 patients will take place over 25 months.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, major protocol violations such as major deviations of the inclusion and/or exclusion criteria, and the discontinuation from the study will be summarized overall and by treatment arm for all randomized patients. The reasons for study discontinuation will be tabulated.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic variables such as age, sex, race/ethnicity, and baseline characteristics (including the stratification variables) will be summarized by treatment arm for all randomized patients. Continuous variables will be summarized with use of means, SDs, medians, and ranges. Categorical variables will be summarized by proportions.

The baseline value of any variable will be defined as the last available value prior to the first administration of the study treatment.

6.4 EFFICACY ANALYSES

The primary efficacy analyses will be performed separately for the ITT population and the PD-L1–positive subpopulation. For both analyses, patients are grouped according to the treatment assigned at randomization.

6.4.1 Primary Efficacy Endpoint

The two co-primary efficacy endpoints of investigator-assessed PFS and OS will be tested with the overall type I error controlled at a two-sided level of 0.05. Tests of PFS will be simultaneously performed in the ITT population and the PD-L1–positive subgroup at a two-sided alpha of 0.002. OS will be assessed hierarchically: if the null hypothesis to compare OS in the PD-L1–positive subgroup is rejected, OS in the ITT population will be tested, with a two-sided alpha between 0.046 and 0.05 used in both tests (see Section 6.1). The sequence of the populations to test OS may be inverted from PD-L1➔ITT to ITT➔PD-L1 depending on data that are external to the study and/or the proportion of the patients in the PD-L1 subgroup within the ITT population. The final hierarchical testing sequence for OS and any changes in the statistical design specifications that result from this potential change will be described in the SAP prior to the first lock of the database for the primary PFS analysis.

The null and alternative hypotheses regarding PFS or OS in the ITT population or PD-L1–positive subpopulation can be phrased in terms of the survival functions $S_A(t)$ and $S_B(t)$ for Arm A (atezolizumab with paclitaxel + carboplatin + bevacizumab) and Arm B (placebo with paclitaxel + carboplatin + bevacizumab), respectively:

$$H0 : S_A(t) = S_B(t) \text{ versus } H1 : S_A(t) \neq S_B(t)$$

Progression-Free Survival

PFS is defined as the time from randomization to the occurrence of disease progression, as determined by investigators from tumor assessments, per RECIST v1.1, or death from any cause, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. Patients with no post-baseline tumor assessment will be censored on the date of randomization plus 1 day.

PFS will be compared between the treatment arms with the use of the stratified log-rank test. The hazard ratio (HR) for disease progression or death will be estimated with the use of a stratified Cox proportional hazards model. The 95% CI for the HR will be provided. The stratification factors will be the same as those of the randomization stratification factors: stage and/or surgical status (Stage III vs. Stage IV), ECOG performance status (0 vs. 1 or 2), tumor PD-L1 status (IC0 vs. IC1/2/3), and treatment strategy (adjuvant vs. neoadjuvant). Results from an unstratified analysis will also be provided. The Kaplan-Meier methodology will be applied to estimate the median PFS for each treatment arm, and Kaplan-Meier curves will be developed. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS for each treatment arm.

Overall Survival

OS is defined as the time from the date of randomization to the date of patient death from any cause. Patients who are alive at the time of the analysis data cutoff timepoint will be censored as of the last date they were known to be alive. Patients with no post-baseline information will be censored as of the date of randomization plus 1 day. Analyses of OS are performed analogously to PFS and details are outlined above for PFS.

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Objective Response Rate

An OR is defined as either a confirmed CR or PR as determined by the investigator with the use of RECIST v1.1. OR will be assessed only in patients from the primary tumor reduction surgery group with measurable residual disease status after primary surgery. Patients from the primary cytoreductive surgery group with measurable residual disease status but who do not have a confirmed CR or PR (includes patients without a post-baseline tumor assessment) will be considered non-responders. The ORR is defined as the proportion of patients with an OR.

The analysis population for ORR will be limited to all randomized patients who undergo primary cytoreductive surgery, but have residual measurable disease. Because of the nature of primary tumor reduction surgery for OC patient, most patients will not have radiographically-measurable disease but will certainly have gross residual disease, which places them at a high risk for cancer recurrence and poor outcomes and makes them eligible for the novel treatments in this study. This study is conducted in the front-line, postoperative setting, and the analysis population for the secondary endpoint of radiographically-determined ORR will be analyzed for all ITT patients who undergo primary tumor reduction surgery and have postoperative radiographically measurable residual disease.

An estimate of ORR and its 95% CI will be calculated with the use of the Clopper-Pearson method for each treatment arm. CIs for the difference in ORRs

between the two treatment arms will be determined with use of the normal approximation to the binomial distribution.

6.4.2.2 Duration of Response

Duration of response (DOR) will be assessed in patients from the primary tumor reduction surgery group who have residual measurable disease after primary surgery and who had an OR as determined by the investigator with the use of RECIST v1.1. DOR is defined as the time interval from the date of the first occurrence of a confirmed CR or PR, whichever status is recorded first, until the first date that progressive disease or death is documented, whichever occurs first. Patients who have not progressed or died at the time of the analysis will be censored at the time of the last tumor assessment. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, DOR will be censored as of the date of the first occurrence of a CR or PR plus 1 day. DOR is on the basis of a non-randomized subset of patients (i.e., patients who achieved an OR); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between the treatment arms will be made for descriptive purposes. The methodologies detailed for the PFS analysis will be used for the DOR analysis.

6.4.2.3 Patient-Reported Outcomes Disease Symptoms, Function and Health-Related Quality of Life EORTC Data

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

For patients in the neoadjuvant therapy group, the proportion of patients in each arm who report a clinically-meaningful improvement in patient-reported abdominal pain or bloating, defined as a $\geq$10-point decrease from the baseline score on each of two items from the EORTC QLQ-OV28 abdominal/gastrointestinal (GI) symptom scale (items 31 and 32), will be summarized at each post-baseline timepoint by treatment arm.

The Cochran-Mantel-Haenszel test, stratified by stage and/or residual disease status (Stage III vs. Stage IV), ECOG performance status (0 vs. 1 or 2), and tumor PD-L1 status (IC0 vs. IC1/2/3) will be used to compare the proportion of patients who report a clinically-meaningful improvement in patient-reported abdominal pain or bloating at 9 weeks after neoadjuvant therapy between the two treatment arms. 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 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 $\geq$ 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.

All EORTC QLQ-OV28 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.

Patient-Reported Function and HRQoL EORTC QLQ-C30

For patients in the neoadjuvant therapy subgroup, 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 QoL scales of the EORTC QLQ-C30, will be summarized at each post-baseline timepoint by treatment arm, and compared between treatment arms with the use of the stratified Cochran-Mantel-Haenszel test specified above.

For patients in the primary surgery group, the proportion of patients in each arm who improve, remain stable or deteriorate in patient-reported functions and HRQoL, defined as a $\geq$10-point increase, changes within 10 points, and a $\geq$10-point decrease, respectively, from the baseline score on each of the functional (physical, role, emotional, and social) and global health status and/or QoL scales of the EORTC QLQ-C30 will be summarized at each post-baseline timepoint by treatment arm, and compared between treatment arms with the use of the stratified Cochran-Mantel-Haenszel test specified above.

The EORTC QLQ-C30 and QLQ-OV28 will be scored according to the EORTC scoring manual (Fayers et al. 2001b). Per Fayers et al. in the event that incomplete data exists,

if the scale has more than 50% of the constituent items completed, a pro-rated score will be computed. 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 and surgery status.

6.4.3 Handling of Missing Data

For PFS, patients without a date of disease progression who have not died will be analyzed as censored observations on the date of the last tumor assessment visit. If no post-baseline tumor assessment is available, PFS will be censored as of the date of randomization plus 1 day. In the analysis of PFS for U.S. registration purposes, data for patients with a PFS event who missed two or more scheduled assessment visits immediately prior to the PFS event will be censored as of the last tumor assessment visit prior to the missed visits (see Section 6.4.1).

For OR, patients without a post-baseline assessment will be considered non-responders.

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 as of the date of randomization plus 1 day.

For DOR, patients who have not progressed or died at the time of the analysis will be censored on the date of the last tumor assessment visit. If no tumor assessment visits were conducted after the date of the first occurrence of a CR or PR, DOR will be censored as of the date of the first occurrence of a CR or PR plus 1 day.

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.

6.5 SAFETY ANALYSES

Safety analyses will include all patients who received at least one dose of the study treatment, with patients grouped in accordance with the treatment actually administered. If a patient receives any dose of atezolizumab, the patient will be included in the atezolizumab arm for analysis.

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital sign measurements, study treatment exposures, and immunogenicity as measured by ADAs and will be presented by treatment arm.

Verbatim descriptions of adverse events will be mapped to the MedDRA terms. Treatment-emergent events, defined as events that occur on or after the administration of the first dose of the study treatment will be summarized by MedDRA term, appropriate MedDRA levels, and NCI CTCAE v4.0 grade, regardless of the relationship to the study drug as assessed by the investigator. For each patient, if multiple incidences of the

same adverse events occur, the maximum severity reported will be used in the summaries.

The following treatment-emergent adverse events will be summarized separately:

- Adverse events that lead to the discontinuation of the study drug by the patient
- Adverse events that lead to the dose reduction or interruption of the study drug by the patient
- Grade $\geq$ 3 adverse events
- Grade 5 adverse events
- Serious adverse events
- Adverse events of special interest.

All deaths and causes of death will be summarized.

Relevant laboratory test result values will be summarized over time, with NCI CTCAE Grade 3 and Grade 4 values identified where appropriate. Changes in NCI CTCAE grade will be tabulated by treatment arm.

ADA results will be summarized and listed by patient and treatment cycle. The immunogenicity analyses will include all patients enrolled in the study with ADA results, with patients grouped in accordance to the treatment administered.

The numbers and proportions of patients who are ADA positive and ADA-negative at baseline (baseline prevalence) and after baseline (post-baseline incidence) will be summarized by treatment group. At the time of the determination of post-baseline incidence, patients are considered ADA positive if they are ADA negative or have missing data at baseline but develop an ADA response after study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 0.60 titer units greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered ADA negative if they are ADA negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have post-baseline samples with a titer that is at least 0.60 titer units greater than the titer of the baseline sample (treatment unaffected).

The relationship between ADA status and safety, efficacy, pharmacokinetics, and biomarker endpoints may be analyzed and reported via descriptive statistics.

6.6 PHARMACOKINETIC ANALYSES

PK samples will be collected in this study as outlined in Appendix 3. Minimum and maximum atezolizumab serum concentration data will be tabulated and summarized. Descriptive statistics will include means, medians, ranges, and SDs, as appropriate.

Additional PK and pharmacodynamic analyses will be conducted as appropriate.

6.7 EXPLORATORY ANALYSES

6.7.1 Exploratory Analyses of Progression-Free Survival

6.7.1.1 Non-Protocol-Specified Anti-Cancer Therapy

The impact of non-protocol–specified anti-cancer therapy on PFS will be assessed dependent on the number of patients who are administered non-protocol–specified anti-cancer therapy before a PFS event. If > 5% of patients were administered a non-protocol–specified anti-cancer therapy before a PFS event in either treatment arm, a sensitivity analysis will be performed for the comparison between treatment arms in which patients who are administered non-protocol–specified anti-cancer therapy before a PFS event will be censored as of the last tumor assessment visit date before receipt of the non-protocol–specified anti-cancer therapy.

6.7.1.2 Sensitivity Analyses

Sensitivity analyses will be conducted to evaluate the potential impact of missing scheduled tumor assessment visits by patients on the primary analysis of PFS, as determined by the investigator with the use of a PFS event imputation rule.

If a patient misses two or more assessment visits that are scheduled immediately prior to the date of the PFS event, there will be two sets of sensitivity analyses conducted. In the first set, the patient will be counted as progressed as of the date of the first of these missing assessment visits. In the second set, the patient will be censored at the last tumor assessment prior to the missed visits.

Statistical methodologies that are analogous to those methodologies used in the primary analysis of PFS as specified in Section 6.4 will be applied for this sensitivity analysis.

6.7.2 Pathologic and Clinical Response

The pathologic and clinical response (PCR) status is defined as the extent of residual disease assessed at the time of interval cytoreductive surgery (i.e., clinico-pathologic response). The PCR status will be determined with clinical parameters that are observed at the time of the interval tumor reduction surgery, postoperative radiographic findings, and histologic parameters assessed centrally based on the surgical specimens from the interval tumor reduction surgery (Samrao et al. 2012; Burger et al. 2015; Nick et al. 2015; Fagotti et al. 2016). The analysis will include only the patients from the neoadjuvant subgroup. The PCR status will be summarized for both treatment arms. The relationship between PCR status and clinical outcome (e.g., PFS, OS, DOR) will be examined.

Guidance and examples for histopathologic evaluation of surgical specimens after interval cytoreduction are provided in the Ovarian Pathology Handbook and in Appendix 13.

6.7.3 Analysis of Overall Survival at 3 Years

The OS rate at 3 years after randomization will be estimated with the use of the Kaplan-Meier methodology for each treatment arm, along with 95% CIs that are calculated with use of the standard error derived from Greenwood's formula. The 95% CI for the difference in the OS rate between the two treatment arms will be estimated with use of the normal approximation method.

6.7.4 Exploratory Patient-Reported Outcomes Analyses

6.7.4.1 Patient-Reported Outcomes Disease and/or Treatment-Related Symptoms–EORTC Data

Summary statistics (mean, SD, 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 and surgery status.

6.7.4.2 FACT-G, GP5 Single Item 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 and surgery status.

6.7.4.3 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 clinical study report as they will be used in pharmacoeconomic analyses only.

6.7.5 Exploratory Biomarker Analyses

Exploratory biomarker analyses in tumor tissues and plasma, whole blood, or serum will be conducted in an effort to understand the association of these markers with the study drug response, including efficacy and/or adverse events. Results will be presented in a separate report.

NGS data will be analyzed in the context of this study and explored in aggregate with data from other studies to increase researchers' understanding of disease pathobiology and guide the development of new therapeutic approaches.

6.7.6 Subgroup Analyses

To assess the consistency of study results in the subgroups defined by demographic and baseline characteristics, PFS and OS in these subgroups will be examined. Summaries of PFS and OS, including unstratified HRs estimated with the use of Cox proportional hazards models and Kaplan-Meier estimates of the median, will be produced separately for each level of the categorical variables.

6.8 INTERIM ANALYSES

6.8.1 Planned Interim Analyses

There are no interim analyses planned for PFS in this study.

A total of three analyses of OS will be conducted: two interim analyses and one final analysis. The timing of the two interim analyses and the final analysis for OS will depend on the results from the definitive analysis of the co-primary endpoint of PFS as described in Appendix 4.

To control the type I error for OS, the stopping boundaries for the OS interim and final analyses are to be computed with use of the Lan-DeMets approximation to the O'Brien-Fleming boundary (DeMets and Lan 1994).

6.8.2 Optional Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one interim efficacy analysis that includes the analysis of the co-primary endpoints of PFS and OS before the primary analysis of PFS. Below are the specifications in place to ensure that the study continues to meet the highest standards of integrity when an optional interim analysis is conducted.

The Sponsor will remain blinded. The interim analysis will be conducted by an external statistical group and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the SAP, and the SAP will be submitted to the relevant health authorities at least 3 months prior to the conduct of

the interim analysis. The iDMC Charter will document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., terminate the study for positive efficacy, or for futility), and the iDMC Charter will be made available to the relevant health authorities.

If there is a potential for the study to be terminated for positive efficacy as a result of the interim analysis, the type I error rate will be controlled to ensure that statistical validity is maintained. Specifically, the Lan-DeMets alpha-spending function that approximates the O'Brien-Fleming boundary will be applied to determine the critical value for terminating due to positive efficacy at the interim analysis (DeMets and Lan 1994). Additional criteria to recommend that the study be terminated for positive efficacy may be added to the iDMC charter. If the study continues beyond the interim analysis, the critical value at the time of the final analysis would be adjusted accordingly to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology.

6.9 CHINA SUBGROUP ANALYSIS

Patients from China enrolled in the global enrollment phase and China extension phase will be combined in China subgroup analysis. The objective of the China subgroup analyses is to assess the efficacy of atezolizumab in combination with paclitaxel + carboplatin + bevacizumab as measured by PFS and OS in the subset of patients from China and to investigate the consistency in the treatment effects between the China subpopulation and the global population.

Based on the current protocol assumptions a clinical cut-off for the China subpopulation is planned after approximately 76 primary endpoint (PFS) events have occurred in the ITT population and 43 events in PD-L1−positive subgroup of the China subgroup, whichever occurs later. Analyses based on the China subgroup will be reported separately from the global study. The 76 PFS events in the China subgroup will provide an approximately 80% probability of observing at least 50% of the PFS risk reduction benefit (HR $\leq$ 0.85) compared with that estimated for the global study (HR = 0.7) in the ITT population. The 43 PFS events in the PD-L1−positive subgroup of China subgroup will provide an approximately 81% probability of observing at least 50% of the PFS risk reduction benefit (HR $\leq$ 0.81) compared with that estimated for the global study (HR = 0.62) in PD-L1−positive subgroup. The CCOD for China subgroup analysis may be revisited based on the data maturity from the China subpopulation to ensure a desired probability of observing a consistent treatment effect in reducing PFS risk estimated from global main study.

PK and ADA samples will not be collected for the patients enrolled in the sites in China.

Further details can be found in the SAP.

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 control process to be performed on the data. Electronic data will be sent directly to the Sponsor, with the use of 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 the use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual that details 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 the patient data for his or her site in a readable format on a compact disc that must be kept with the study records.
An 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) that are entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents, whether in paper or electronic format, are those documents 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 test results notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are verified and certified as

accurate and complete, microfiches, photographic negatives, microfilms or magnetic media, X-rays, patient files, and records maintained at pharmacies, laboratories, and medico-technical departments involved in the clinical study.

Before the 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, but retained per the policy for retention of records described in Section 7.5.

To facilitate source data review and verification, the investigators and institutions must provide the Sponsor with direct access to the applicable source documents and reports for study-related monitoring, Sponsor audits, and IRB and/or EC review. The study site must also allow inspection by the 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 the original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with the health authority requirements that pertain to computerized systems used in clinical research. An acceptable computerized data collection system allows the preservation of the original entry of data. If the 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, the name of the person making the change, and the date of the change.

7.5 RETENTION OF RECORDS

Records and documents that pertain to the conduct of this study and the distribution of the IMP, including eCRFs, PRO data, ICFs, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for a period of 15 years after the completion or discontinuation of the study or for the length of time required by the 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 transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported 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 applicable 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 on 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 and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample ICF and the ancillary sample ICFs, such as a Child's Informed Assent Form or Mobile Nursing ICF if applicable, will be provided to each site. If applicable, the forms 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 ICFs or any alternate consent forms proposed by the site (collectively known as the "Consent Forms") before IRB and/or EC submission. The final IRB and/or EC-approved Consent Forms must be provided to the Sponsor for submission to the health authorities according to local requirements.

If applicable, the ICF will contain separate sections for optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be informed 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 their participation in the study. The case history or clinical records for each patient will document the informed consent process and that written informed consent was obtained prior to the participation in the study.

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

Patients must re-consent to the most current version of the Consent Forms or to a significant new information and/or findings addendum in accordance with the applicable

laws and IRB and/or EC policy during their participation in the study within the adverse event reporting period. For any updated or revised Consent Forms, the case history or clinical records for each patient will document the informed consent process and that written informed consent was obtained with the use of the updated and/or revised Consent Forms for the patient's 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.

For sites in the United States, each Consent Form may also include a patient authorization to allow the use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patients to authorize the use and disclosure of personal health information under the HIPAA regulations, the review, approval and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

The Sponsor maintains the confidentiality standards by coding each patient that is enrolled in the study through the assignment of a unique patient identification number.

This means that patient names are not included in the datasets that are transmitted to any Sponsor location.

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

Medical information may be provided to a patient's personal physician or other appropriate medical personnel who are responsible for the patient's welfare and for treatment purposes.

Given the complexity and exploratory nature of biomarker analyses, data derived from these analyses will generally not be provided to the study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with the local regulations to allow the Sponsor to submit complete and accurate financial certifications or disclosure statements to the appropriate health authorities. Investigators are responsible to provide information on financial interests during the course of the study and for 1 year after the completion of the study (i.e., last patient, last visit).

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, ICFs, and documentation of IRB and/or EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail that contains a complete record of all changes made to the 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 the safety of patients

and the integrity of the data to the Sponsor and IRB and/or EC in accordance with established IRB and/or 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 to inspect the study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs and/or ECs to inspect facilities and records that are relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored and managed by F. Hoffmann-La Roche Ltd. Approximately 300 sites globally will participate in the study, and approximately 1300 patients will be randomized to the study.

Randomization will occur through the IWRS. Central facilities will be used for study assessments throughout the study (e.g., specified laboratory tests and PK analyses). Accredited local laboratories will be used for routine monitoring and local laboratory ranges will be collected.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for the publication of the study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following Web site:

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 studies in patients that involve an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript that reports on the primary clinical study results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical studies on patients that involve an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from the analyses of the 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 on the basis of the information from other studies that may not yet be available to the investigator.

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

Authorship for publications will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication resulting from 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 the data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed upon otherwise.

9.6 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Assessments for
Patients Who Underwent Primary Surgery

	Screening		Concurrent Treatment						Maintenance Treatment																Treatment Completion/ Early Termination [a]	Post-Treatment Follow-up [a]
			Cycle [a]						Cycle [a]																	
	Day –28 to –1	Day –14 to –1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Within 30 days of the last dose of the study treatment	Q3Mo for 2 yr after the treatment completion visit, then Q6Mo for 3 yr, then annually
Signed informed consent [b]	x																									
Demographic data	x																									
Medical history and baseline conditions	x																									
Complete physical examination [c]	x																									
Limited physical examination [d]			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECOG PS	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Vital signs [e]	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events [f]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications		x [g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Hematology [h]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Urinalysis [i]		x																								
Urine protein [i]					x		x		x		x		x		x		x		x		x		x		x	

Appendix 1
Schedule of Assessments for
Patients Who Underwent Primary Surgery (cont.)

	Screening		Concurrent Treatment						Maintenance Treatment																Treatment Completion/ Early Termination [a]	Post-Treatment Follow-up [a]
			Cycle [a]						Cycle [a]																	
	Day –28 to –1	Day –14 to –1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Within 30 days of the last dose of the study treatment	Q3Mo for 2 yr after the treatment completion visit, then Q6Mo for 3 yr, then annually
Serum chemistry [j]		x	x	x	x	x	x	x	x	x [j]	x	x [j]	x	x [j]	x	x [j]	x	x [j]	x	x [j]	x	x [j]	x	x [j]	x [j]	
TSH, free T3, free T4	x					x				x				x				x				x			x	
HIV, HBV, HCV serology [k]	x																									
Urine pregnancy test (for patients of childbearing potential [l]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PT/INR, aPTT		x																								
12-lead ECG	x																									
Radiologic disease assessment [m,n,o]	x				x			x				x				x				x				x	x	x
Serum CA-125 level [p]	x		x	x	x	x	x	x	x		x		x		x		x		x		x		x		x	x
EORTC QLQ-C30, QLQ-OV28, EQ-5D-5L [q]			x		x		x			x				x				x				x			x	x [q]
FACT-G, GP5 single item [r]					x		x			x				x				x				x			x	x [r]
Samples for PK, ADA, and biomarkers	See Appendix 3 for Schedule of PK, ADA, and biomarker sampling																									

Appendix 1
Schedule of Assessments for
Patients Who Underwent Primary Surgery (cont.)

	Screening		Concurrent Treatment						Maintenance Treatment																Treatment Completion/ Early Termination [a]	Post-Treatment Follow-up [a]
			Cycle [a]						Cycle [a]																	
	Day –28 to –1	Day –14 to –1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Within 30 days of the last dose of the study treatment	Q3Mo for 2 yr after the treatment completion visit, then Q6Mo for 3 yr, then annually
Optional whole blood sample for RBR [s]			x																							
Atezolizumab/ placebo administration			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Bevacizumab administration				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Paclitaxel administration			x	x	x	x	x	x																		
Carboplatin administration			x	x	x	x	x	x																		
Screening baseline FFPE tumor tissue block or 20 unstained slides [t]	x																									
Mandatory FFPE tumor tissue specimen at disease progression [u]																									x	

Appendix 1
Schedule of Assessments for
Patients Who Underwent Primary Surgery (cont.)

ADA = anti-drug antibody; CA = cancer antigen; CR = complete response; CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic Case Report Form; EORTC = European Organisation for Research and Treatment of Cancer; FACT-G = Functional Assessment of Cancer Therapy-General; FFPE = formalin-fixed, paraffin-embedded; HBV = hepatitis B virus; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PK = pharmacokinetic; PR = partial response; PRO = patient-reported outcome; Q3Mo = every 3 months; Q6Mo = every 6 months; QLQ-OV28 = Quality of Life Questionnaire Ovarian Cancer Module 28; RECIST = Response Evaluation Criteria in Solid Tumors; UPCR = urine protein-to-creatinine ratio; yr = year.

Note: Study assessments/cycles may be adjusted slightly to accommodate holidays, vacations, and unforeseen major life events. Documentation to justify this decision should be provided.

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 period (Cycle 1 through Cycle 22) must occur within 3 days prior to the administration (e.g., activities/assessments for Cycle 1, except the actual drug infusion, must be performed within 3 days before infusion of Cycle 1). 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 (±21 days) for the first 2 years after the treatment completion visit, then every 6 months (±21 days) for 3 years, and then annually (±21 days). Post-treatment visits can be performed via telephone or clinic visit as indicated by assessment requirements.

b The Informed consent must be obtained prior to any study-specific procedure and within 28 days (± 7 days) before randomization.

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

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

e Vital signs will include measurements of the respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and body temperature. Vital signs should be measured prior to the first study treatment infusion of the cycle, as clinically indicated, and at other specified timepoints as outlined in the schedule of activities.

Appendix 1
Schedule of Assessments for
Patients Who Underwent Primary Surgery (cont.)

[f] 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.

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

[h] Hematology consists of CBC, including hemoglobin, WBC count with differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count.

[i] Patients must demonstrate negativity for proteinuria (see Section 4.1.2). Urine protein is no longer required for patients who discontinue bevacizumab for reasons other than proteinuria. However, for those who discontinue bevacizumab due to proteinuria, urine protein is required until proteinuria returns to baseline or until the end of the study, whichever occurs first.

[j] Serum chemistry includes BUN, creatinine, sodium, potassium, magnesium, calcium, glucose, total bilirubin, ALT, AST, ALP, and albumin. Serum chemistry eligibility must be confirmed during the screening period before randomization. After Cycle 1, serum magnesium may be performed as clinically indicated. Serum chemistry samples performed during the maintenance phase and at treatment discontinuation may be performed at each cycle, instead of every other cycle, in accordance to country-specific health authority mandates (e.g., Spain).

[k] All patients will be tested for HIV infection prior to enrollment into the study, and HIV-positive patients will be excluded from the study. All patients will be tested for HBsAg and total HBcAb at the baseline. 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.

[l] Urine pregnancy tests beyond Cycle 1 for Cycles 2–22, at treatment discontinuation, and at 3 and 6 months after treatment discontinuation must be performed in accordance to country-specific health authority mandates (e.g., Spain, Norway, Czech Republic, Poland, Germany, and Belgium).

Appendix 1
Schedule of Assessments for
Patients Who Underwent Primary Surgery (cont.)

[m] All radiographic assessments will be performed according to the time interval (e.g., 9 weeks, 12 weeks, etc.) with the corresponding windows per Section 4.5.5 regardless of the treatment cycle. For patients who have had primary tumor reductive surgery, an initial CT scan or MRI of at least the chest, abdomen, and pelvis is required to establish postsurgical (i.e., primary cytoreductive surgery) baseline of the extent of residual disease within 28 days prior to randomization. In the absence of disease progression, imaging that uses the same modality and encompasses the same field as in the initial pre-treatment evaluation should be repeated (1) every 9 weeks during the concurrent treatment phase, (2) every 12 weeks in the maintenance phase (the first scan in the maintenance phase is performed 12 weeks after the last scan in the concurrent treatment phase), (3) every 3 months for the first 2 years after completion of all protocol therapy, (4) and then every 6 months for the next 3 years, regardless of whether the patient showed measurable disease on the initial CT or MRI. CT scans or MRIs after 5 years of survival follow-up may be done, as clinically indicated. Head/neck imaging at screening is dictated by clinical judgment. If a tumor assessment is performed within 30 days prior to the scan scheduled at the treatment completion/early termination visit, then a specific treatment completion/early termination tumor assessment does not need to be performed.

[n] A CT scan or MRI of at least the patient's chest, abdomen, and pelvis is required to establish the postsurgical (i.e., primary cytoreductive surgery) baseline for the extent of residual disease within 28 days prior to the initiation of study treatment (Scan 1).

[o] Follow-Up Radiographic Assessment of Disease: In the absence of disease progression and/or allergic reaction to IV contrast, imaging with the same modality and field as the initial pretreatment evaluation should be repeated at the following time intervals (i.e., 9 weeks, 12 weeks, etc.) with the corresponding windows per Section 4.5.5 regardless whether the patient had measurable disease on the initial CT or MRI and regardless of the treatment cycle.

Scans 2 and 3: Every 9 weeks from randomization during the concurrent treatment phase (approximately after Cycle 3 and Cycle 6, but may vary).

Scans 4, 5, 6, and 7: Every 12 weeks after the last scan during the concurrent treatment phase, which is now during the maintenance phase (approximately after Cycle 10, Cycle 14, Cycle 18, and Cycle 22).

After the treatment completion visit, every 3 months for 2 years, then every 6 months for 3 years. CT scans or MRIs after 5 years of survival follow-up may be done, as clinically indicated.

Appendix 1
Schedule of Assessments for
Patients Who Underwent Primary Surgery (cont.)

[p] Baseline prechemotherapy value is required. When available, also include the presurgical value. CA-125 after 5 years may be done as clinically indicated.

[q] 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 during each treatment and post-treatment period:

Concurrent treatment: At baseline (Cycle 1, Day 1) (±3 days), and on Day 1 (±3 days) of every other cycle thereafter until Cycle 6 (i.e., every 6 weeks)

Maintenance treatment: At Cycle 8, Day 1 (±3 days) and on Day 1 (±3 days) of each cycle every 12 weeks thereafter until Cycle 22

Treatment discontinuation or completion: At the end of the treatment or discontinuation visit within 30 days of the administration of the last dose of the study treatment

Post-treatment follow-up: Patients who discontinue study treatment for progressive disease or loss of clinical benefit or any other reason, regardless of receipt of subsequent anti-cancer therapy will complete the PROs after the treatment completion visit, every 3 months (±21 days) for the first year of the survival follow-up period; every 6 months (±21 days) for the second year of the survival follow-up period; and every year (±21 days) for the final 3 years of the survival follow-up period. Patients in the survival follow-up phase who are unable to visit the site in-person due to COVID-19 may complete the PRO questionnaires via phone interview by site staff.

[r] The single-item GP5 from the FACT-G questionnaire will be the final measure to be administered and must be completed by patients at the following assessment timepoints during each treatment and post-treatment period:

Concurrent treatment: At Cycle 3, Day 1 (±3 days), and on Cycle 5, Day 1 (±3 days)

Maintenance treatment: At Cycle 8, Day 1 (±3 days), and on Day 1 (±3 days) of each cycle every 12 weeks thereafter until Cycle 22

Treatment discontinuation or completion: At the end of the treatment or discontinuation visit within 30 days of the administration of the last dose of the study treatment

Post-treatment follow-up: Patients who discontinue study treatment for progressive disease or loss of clinical benefit or any other reason, regardless of receipt of subsequent anti-cancer therapy will complete FACT-G GP5 after the treatment completion visit, every 3 months (±21 days) for the first year of the survival follow-up period; every 6 months (±21 days) for the second year of the survival follow-up period; every year (±21 days) for the final 3 years of the survival follow-up period. Patients in the survival follow-up phase who are unable to visit the site in-person due to COVID-19 may complete the PRO questionnaires via phone interview by site staff.

Appendix 1
Schedule of Assessments for
Patients Who Underwent Primary Surgery (cont.)

[s] Whole blood for DNA isolation will be collected from patients who have consented to optional RBR sampling at Cycle 1, Day 1. If the RBR genetic blood sample is not collected during the scheduled visit, it may be collected after randomization during the clinical study.

[t] Tumor tissue should be of good quality based on the total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate to determine tumor PD-L1 status). An FFPE block or at least 20 unstained slides should be provided. Fine-needle aspiration, brushing, cell pellets from pleural effusion, lavage samples, and bone metastases are not acceptable. For core needle biopsy specimens, at least three cores (18 gauge minimum) should be submitted for evaluation. Submission of the screening tumor sample can occur outside the 28-day screening period in conjunction with obtaining the informed consent. Primary surgery must be within 42 days of randomization.

[u] The collection of a sample at disease progression is mandatory if clinically feasible. Preferably, samples collected at the time of radiographic progression should be collected from growing lesions. An FFPE block or at least 15 unstained slides should be provided. Fine-needle aspiration, brushing, cell pellets from pleural effusion, lavage samples, and bone metastases are not acceptable. For core needle biopsy specimens, at no fewer than two cores (18 gauge minimum) should be submitted for evaluation.

Appendix 2
Schedule of Assessments for
Patients Who Underwent Neoadjuvant Chemotherapy and Interval Surgery

	Screening		Concurrent Neoadjuvant Treatment			Presurgical/ Surgery Visit	Concurrent Post-neoadjuvant Treatment			Maintenance Treatment																Completion of Treatment/ Early Termination Visit [a]	Post-Treatment Follow-Up [a]
			Cycle [a]				Cycle [a]			Cycle [a]																	
	Day –28 to -1	Day –14 to –1	1	2	3		4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Within 30 days of last dose of study treatment	Q3Mo for 2 yr after the treatment completion visit, then Q6Mo for 3 yr, then annually
Written informed consent [b]	x																										
Demographic data	x																										
Medical history and baseline conditions	x																										
Complete physical examination [c]	x																										
Limited physical examination [d]			x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECOG PS	x		x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Vital signs [e]	x		x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events [f]		x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [g]		x [f]	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Hematology [h]		x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

Appendix 2
Schedule of Assessments for
Patients who Underwent Neoadjuvant Chemotherapy and Interval Surgery (cont.)

	Screening		Concurrent Neoadjuvant Treatment			Presurgical/ Surgery Visit	Concurrent Post-neoadjuvant Treatment			Maintenance Treatment																Completion of Treatment/ Early Termination Visit [a]	Post-Treatment Follow-Up [a]
			Cycle [a]				Cycle [a]			Cycle [a]																	
	Day –28 to -1	Day –14 to –1	1	2	3		4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Within 30 days of last dose of study treatment	Q3Mo for 2 yr after the treatment completion visit, then Q6Mo for 3 yr, then annually
Urinalysis [i]		x																									
Urine protein [i]				x				x		x		x		x		x		x		x		x		x		x	
Serum chemistry [j]		x	x	x	x		x	x	x	x	x [j]	x	x [j]	x	x [j]	x	x [j]	x	x [j]	x	x [j]	x	x [j]	x	x [j]	x [j]	
TSH, free T3, and free T4	x						x				x				x				x				x			x	
HIV, HBV, HCV serology [k]	x																										
Urine pregnancy test (if childbearing potential exists) [l]		x		x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PT/INR, aPTT		x																									
12-lead ECG	x																										
Radiographic disease assessment [m,n]					x		x		x				x				x				x				x	x	x
Serum CA-125 level [o]	x		x	x	x		x	x	x	x		x		x		x		x		x		x		x		x	x

Appendix 2
Schedule of Assessments for
Patients who Underwent Neoadjuvant Chemotherapy and Interval Surgery (cont.)

	Screening		Concurrent Neoadjuvant Treatment			Presurgical/ Surgery Visit	Concurrent Post-neoadjuvant Treatment			Maintenance Treatment																Completion of Treatment/ Early Termination Visit [a]	Post-Treatment Follow-Up [a]
			Cycle [a]				Cycle [a]			Cycle [a]																	
	Day –28 to -1	Day –14 to –1	1	2	3		4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Within 30 days of last dose of study treatment	Q3Mo for 2 yr after the treatment completion visit, then Q6Mo for 3 yr, then annually
EORTC QLQ-C30, QLQ-OV28, EQ-5D-5L [p]			x			x	x		x		x				x				x				x			x	x [p]
FACT-G, GP5 single item [q]						x			x		x				x				x				x			x	x [q]
Blood samples for PK, ADA , and biomarkers	See Appendix 3 for schedule of PK, ADA, and biomarker sampling.																										
Optional whole blood sample for RBR			x [r]																								
Atezolizumab/ placebo administration			x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Bevacizumab administration			x	x				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Paclitaxel administration			x	x	x		x	x	x																		

Appendix 2
Schedule of Assessments for
Patients who Underwent Neoadjuvant Chemotherapy and Interval Surgery (cont.)

	Screening		Concurrent Neoadjuvant Treatment			Presurgical/ Surgery Visit	Concurrent Post-neoadjuvant Treatment			Maintenance Treatment																Completion of Treatment/ Early Termination Visit [a]	Post-Treatment Follow-Up [a]
			Cycle [a]				Cycle [a]			Cycle [a]																	
	Day –28 to -1	Day –14 to –1	1	2	3		4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Within 30 days of last dose of study treatment	Q3Mo for 2 yr after the treatment completion visit, then Q6Mo for 3 yr, then annually
Carboplatin administration			x	x	x		x	x	x																		
Screening baseline FFPE tumor tissue block or 20 unstained slides [s]	x																										
Biopsy [t]			x																								
FFPE tumor tissue sample from surgical material						x																					
Mandatory FFPE tumor tissue specimen at disease progression [u]																										x	

Appendix 2
Schedule of Assessments for
Patients who Underwent Neoadjuvant Chemotherapy and Interval Surgery (cont.)

ADA = anti-drug antibody; CA = cancer antigen; CR = complete response; CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic Case Report Form; EORTC = European Organisation for Research and Treatment of Cancer; FACT-G = Functional Assessment of Cancer Therapy-General; FFPE = formalin-fixed, paraffin-embedded; HBV = hepatitis B virus; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PK = pharmacokinetic; PR = partial response; PRO = patient-reported outcome; Q3Mo = every 3 months; Q6Mo = every 6 months;; QLQ-OV28 = Quality of Life Questionnaire Ovarian Cancer Module 28; RECIST = Response Evaluation Criteria in Solid Tumors; UPCR = urine protein-to-creatinine ratio; $yr = year$.

Note: Study assessments/cycles may be adjusted slightly to accommodate holidays, vacations, and unforeseen major life events. Documentation to justify this decision should be provided.

[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 period (Cycle 1 through Cycle 22) must occur within 3 days prior to the administration (e.g., activities/assessments for Cycle 1, except the actual drug infusion, must be performed within 3 days before infusion of Cycle 1). 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 (±21 days) for the first 2 years after the treatment completion visit, then every 6 months (±21 days) for 3 years, and then annually (±21 days). Post-treatment visits can be performed via telephone or clinic visit as indicated by assessment requirements.

[b] The Informed consent must be obtained prior to any study-specific procedure and within 28 days (± 7 days) before randomization.

[c] A complete physical examination should include an evaluation of the patient's head, eyes, ears, nose, throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at the baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

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

[e] Vital signs will include measurements of the respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and body temperature. Vital signs should be measured prior to the first study treatment infusion of the cycle, as clinically indicated, and at other specified timepoints as outlined in the schedule of activities.

[f] 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.

Appendix 2
Schedule of Assessments for
Patients who Underwent Neoadjuvant Chemotherapy and Interval Surgery (cont.)

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

[h] Hematology consists of CBC, including hemoglobin, WBC count with differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells), and platelet count.

[i] Patients must demonstrate negativity for proteinuria (see Section 4.1.2). Urine protein is no longer required for patients who discontinue bevacizumab for reasons other than proteinuria. However, for those who discontinue bevacizumab due to proteinuria, urine protein is required until proteinuria returns to baseline or until the end of the study, whichever occurs first.

[j] Serum chemistry includes BUN, creatinine, sodium, potassium, magnesium, calcium, glucose, total bilirubin, ALT, AST, ALP, and albumin. Serum chemistry eligibility must be confirmed during the screening period before randomization. After Cycle 1, serum magnesium may be performed as clinically indicated. Serum chemistry samples performed during the maintenance phase and at treatment discontinuation may be performed at each cycle, instead of every other cycle, in accordance to country-specific health authority mandates (e.g., Spain).

[k] All patients will be tested for HIV infection prior to enrollment into the study, and HIV-positive patients will be excluded from the study. All patients will be tested for HBsAg and total HBcAb at the baseline. 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.

[l] Urine pregnancy tests beyond Cycle 1 for Cycles 2–22, at treatment discontinuation, and at 3 and 6 months after treatment discontinuation must be performed in accordance to country-specific health authority mandates (e.g., Spain, Norway, Czech Republic, Poland, Germany, and Belgium).

[m] All radiographic assessments will be performed according to the time interval (e.g., 9 weeks, 12 weeks, etc.) with the corresponding windows per Section 4.5.5 regardless of the treatment cycle. The initial CT scan/MRI of at least the patient's chest, abdomen, and pelvis is required within 28 days of randomization to establish the first baseline prior to starting neoadjuvant therapy and interval cytoreductive surgery. A CT scan or MRI of at least the patient's chest, abdomen, and pelvis is required to establish the new baseline (i.e., postsurgical from interval cytoreductive surgery) for the extent of residual disease within 14 days prior to re-initiation of study treatment (Scan 3). CT scans or MRIs after 5 years of survival follow-up may be done as clinically indicated. Head/neck imaging at screening is dictated by clinical judgment. If a tumor assessment is performed within 30 days prior to the scan scheduled at the treatment completion/early termination visit, then a specific treatment completion/early termination tumor assessment does not need to be performed.

Appendix 2
Schedule of Assessments for
Patients who Underwent Neoadjuvant Chemotherapy and Interval Surgery (cont.)

[n] Follow-Up Radiographic Assessment of Disease: In the absence of disease progression and/or allergic reaction to IV contrast, imaging with the same modality and field as the initial pretreatment evaluation should be repeated at the following time intervals (i.e., 9 weeks, 12 weeks, etc.) with the corresponding windows per Section 4.5.5 regardless whether the patient had measurable disease on the initial CT or MRI and regardless of the treatment cycle:

Concurrent treatment phase Scan 2: 9 weeks from randomization during the concurrent treatment phase (approximately end of Cycle 3).

Scan 3: postsurgical scan done after interval cytoreductive surgery and as close as possible (within 14 days) to starting Cycle 4 during the concurrent treatment phase.

Scan 4: 9 weeks from Scan 3 (i.e., postsurgical scan done after interval cytoreductive surgery) during the concurrent treatment phase (approximately end of Cycle 6). Tumor assessment scans during the concurrent treatment phase must be done every 9 weeks, regardless of treatment cycle.

Maintenance phase Scans 5, 6, and 7: Every 12 weeks after the last scan during the concurrent treatment phase, which is now during the maintenance phase (approximately after Cycle 10, Cycle 14, Cycle 18, and Cycle 22).

After the treatment completion visit, every 3 months for 2 years, then every 6 months for 3 years. CT scans or MRIs after 5 years of survival follow-up may be done, as clinically indicated.

[o] Baseline prechemotherapy value is required. When available, also include the presurgical value. CA-125 after 5 years may be done as clinically indicated.

[p] 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 during each treatment and post-treatment period:

Concurrent Treatment: At baseline (Cycle 1, Day 1) (± 3 days); post Cycle 3/pre-Interval Surgery visit (± 3 days); post-Interval Surgery at Cycle 4, Day 1 (±3 days); Cycle 6, Day 1 (± 3 days)

Maintenance Treatment: At Cycle 8, Day 1 (± 3 days) and on Day 1 (± 3 days) of each cycle every 12 weeks thereafter until Cycle 22

Treatment Discontinuation or completion: At the end of treatment or discontinuation visit within 30 days of the administration of the last dose of the study treatment

Appendix 2
Schedule of Assessments for
Patients who Underwent Neoadjuvant Chemotherapy and Interval Surgery (cont.)

Post-Treatment Follow-up: Patients who discontinue study treatment for progressive disease or loss of clinical benefit or any other reason, regardless of receipt of subsequent anti-cancer therapy will complete the PROs after the treatment completion visit, every 3 months (±21 days) for the first year of the survival follow-up period; every 6 months (±21 days) for the second year of the survival follow-up period; and every year (±21 days) for the final 3 years of the survival follow-up period. Patients in the survival follow-up phase who are unable to visit the site in-person due to COVID-19 may complete the PRO questionnaires via phone interview by site staff.

[q] The single-item GP5 from the FACT-G questionnaire will be the final measure to be administered and must be completed by patients at the following assessment timepoints during each treatment and post-treatment period:

Concurrent treatment: At the post Cycle 3/pre-Interval Surgery visit (±3 days), and on Cycle 6, Day 1 (±3 days)

Maintenance treatment: At Cycle 8, Day 1 (±3 days), and on Day 1 (±3 days) of each cycle every 12 weeks thereafter until Cycle 22

Treatment discontinuation or completion: At the end of the treatment or discontinuation visit within 30 days of the administration of the last dose of the study treatment

Post-treatment follow-up: Patients who discontinue study treatment for progressive disease or loss of clinical benefit or any other reason, regardless of receipt of subsequent anti-cancer therapy will complete FACT-G GP5 after the treatment completion visit, every 3 months (±21 days) for the first year of the survival follow-up period; every 6 months (±21 days) for the second year of the survival follow-up period; every year (±21 days) for the final 3 years of the survival follow-up period. Patients in the survival follow-up phase who are unable to visit the site in-person due to COVID-19 may complete the PRO questionnaires via phone interview by site staff.

[r] Whole blood for DNA isolation will be collected from patients who have consented to optional RBR sampling at Cycle 1, Day 1. If the RBR genetic blood sample is not collected during the scheduled visit, it may be collected after randomization during the clinical study.

[s] Tumor tissue should be of good quality based on the total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate to determine tumor PD-L1 status). An FFPE block or at least 20 unstained slides should be provided. Fine-needle aspiration, brushing, cell pellets from pleural effusion, lavage samples, and bone metastases are not acceptable. For core needle biopsy specimens, at least three cores (18 gauge minimum) should be submitted for evaluation. Submission of the screening tumor sample from needle core biopsy or laparoscopy can occur outside the 28-day screening period in conjunction with obtaining the informed consent.

[t] For patients who are enrolled in the biomarker cohort; tumor biopsy samples should be collected by core needle (18 gauge minimum) or excisional biopsy at Cycle 1, Day 15. Three cores per paraffin block should be submitted for analysis.

[u] The collection of a sample at disease progression is mandatory if clinically feasible. Preferably, samples collected at the time of radiographic progression should be collected from growing lesions. An FFPE block or at least 15 unstained slides should be provided. Fine-needle aspiration, brushing, cell pellets from pleural effusion, lavage samples, and bone metastases are not acceptable. For core needle biopsy specimens, at no fewer than two cores (18 gauge minimum) should be submitted for evaluation.

Appendix 3
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples [a]

Visit	Timepoint	Sample Type	
		Patients who undergo primary surgery	Patients who undergo NACT interval surgery (and, where applicable, the biomarker cohort only; n = 100)
Screening (Day −28 to Day −1)	—	—	—
Randomization	—	Atezolizumab/placebo biomarker (tissue)	Atezolizumab/placebo biomarker (tissue)
Cycle 1, Day 1	Prior to the first infusion (up to 24 hours prior)	Atezolizumab/placebo pharmacokinetics (serum) [b] Atezolizumab/placebo ADA (serum) [b] Atezolizumab/placebo biomarker (blood, plasma [c])	Atezolizumab/placebo pharmacokinetics (serum) [b] Atezolizumab/placebo ADA (serum) [b] Atezolizumab/placebo biomarker (blood, plasma [c])
	30 minutes (± 15 minutes) after end of infusion	Atezolizumab/placebo pharmacokinetics (serum) [b]	Atezolizumab/placebo pharmacokinetics (serum) [b]
Cycle 1, Day 15	—	—	Atezolizumab/placebo biomarker (tissue) (biomarker cohort only; n = 100) Atezolizumab/placebo biomarker (plasma [c]) (biomarker cohort only; n = 100)
Cycle 2	Prior to the first infusion (up to 24 hours prior)	Atezolizumab/placebo pharmacokinetics (serum) [b] Atezolizumab/placebo ADA (serum) [b] Atezolizumab/placebo biomarker (plasma [c])	Atezolizumab/placebo pharmacokinetics (serum) [b] Atezolizumab/placebo ADA (serum) [b] Atezolizumab/placebo biomarker (plasma [c])
Cycle 3	Prior to the first infusion (up to 24 hours prior)	Atezolizumab/placebo pharmacokinetics (serum) [b] Atezolizumab/placebo ADA (serum) [b]	Atezolizumab/placebo pharmacokinetics (serum) [b] Atezolizumab/placebo ADA (serum) [b]
	30 minutes (± 15 minutes) after the end of infusion	Atezolizumab/placebo pharmacokinetics (serum) [b]	Atezolizumab/placebo pharmacokinetics (serum) [b]

Appendix 3
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples [a] (cont.)

		Sample Type	
Visit	Timepoint	Patients who undergo primary surgery	Patients who undergo NACT interval surgery (and, where applicable, the biomarker cohort only; n = 100)
Cycle 4	Prior to the first infusion (up to 24 hours prior)	Atezolizumab/placebo pharmacokinetics (serum) [b] Atezolizumab/placebo ADA (serum) [b] Atezolizumab/placebo biomarker (plasma [c, d])	Atezolizumab/placebo pharmacokinetics (serum) [b] Atezolizumab/placebo ADA (serum) [b] Atezolizumab/placebo biomarker (plasma [c, d])
Cycle 8 and Cycle 16	Prior to the first infusion (up to 24 hours prior)	Atezolizumab/placebo pharmacokinetics (serum) [b] Atezolizumab/placebo ADA (serum) [b]	—
At surgical visit	—	—	Atezolizumab/placebo biomarker (tissue) Atezolizumab/placebo biomarker (plasma [c, d])
At disease progression[e]	—	Atezolizumab/placebo biomarker (tissue, plasma [c, d])	Atezolizumab/placebo biomarker (tissue, plasma [c, d])
Treatment discontinuation/ completion visit [f]	(± 24 hours)	Atezolizumab/placebo pharmacokinetics (serum) [b] Atezolizumab/placebo ADA (serum) [b]	Atezolizumab/placebo biomarker (plasma [c, d]) Atezolizumab/placebo pharmacokinetics (serum) [b] Atezolizumab/placebo ADA (serum) [b]
≥ 90 days after last dose of atezolizumab[h]	(± 1 week[g])	Atezolizumab/placebo pharmacokinetics (serum) [b] Atezolizumab/placebo ADA (serum) [b]	Atezolizumab/placebo pharmacokinetics (serum) [b] Atezolizumab/placebo ADA (serum) [b]

Appendix 3
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples [a] (cont.)

ADA = anti-drug antibody; NACT = neoadjuvant chemotherapy.

Note: Study assessments/cycles may be adjusted slightly to accommodate holidays, vacations, and unforeseen major life events. Documentation to justify this decision should be provided.

[a] Pharmacokinetic and ADA samples will not be collected for the patients enrolled in the sites in China.

[b] Patients who discontinue atezolizumab/placebo no longer need to provide pharmacokinetics/ADA samples.

[c] EDTA plasma.

[d] This may include WGS and/or RBR samples. Refer to the laboratory manual for details.

[e] Samples should be collected from either RECIST progression or investigators-determined clinical progression

[f] Patients who complete the study treatment period will return to the clinic for a treatment completion visit at 30 days from the administration of the last dose of the study drug. Patients who discontinue the study drug prematurely will return to the clinic for a treatment discontinuation visit 30 days after the administration of the last dose of the study drug. The visit at which the response assessment shows progressive disease may be designated as the treatment discontinuation visit.

[g] Samples greater than one week are acceptable.

[h] Can be combined with the Month 3 Survival Follow-Up visit when appropriate.

Appendix 4 Interim and Final Analyses for Overall Survival

Different Scenarios of PFS Testing	Alpha Level	OS Analysis Type	Time from (months)	Information Fraction (%)	No. of Events	Stopping Boundary (HR)	Stopping Boundary (p-value)
PFS is not statistically significant in either PD-L1+ or ITT	0.046	1st IA	36	60	187 320	≤0.6728 ≤0.7382	≤0.0066
		2nd IA	45	80	249 427	≤0.7447 ≤0.7984	≤0.0200
		FA	56	100	311 534	≤0.7913 ≤0.8364	≤0.0390
PFS is statistically significant in either PD-L1+ or ITT, but not both	0.048	1st IA	36	60	185 317	≤0.6734 ≤0.7393	≤0.0072
		2nd IA	45	80	246 422	≤0.7449 ≤0.7987	≤0.0209
		FA	56	100	308 528	≤0.7920 ≤0.8368	≤0.0407
PFS is statistically significant in both PD-L1+ and ITT	0.050	1st IA	35	60	182 313	≤0.6729 ≤7395	≤0.0075
		2nd IA	44	80	243 418	≤0.7455 ≤0.7995	≤0.0220
		FA	55	100	304 522	≤0.7922 ≤0.8371	≤0.0423

FA=final analysis, FP=first patient in; HR=hazard ratio; IA=interim analysis, ITT=intent-to-treat; OS=overall survival; PFS=progression-free survival.

Appendix 5
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires

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Table 1 Quality of Life Questionnaire Core 30

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

<u>Please go on to the next page</u>

Appendix 5
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires (cont.)

Table 1 Quality of Life Questionnaire Core 30 (cont.)

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
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires (cont.)

Table 2 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
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires (cont.)

Table 2 Quality of Life Questionnaire Ovarian Cancer Module 28 (cont.)

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 EQ-5D-5L

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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

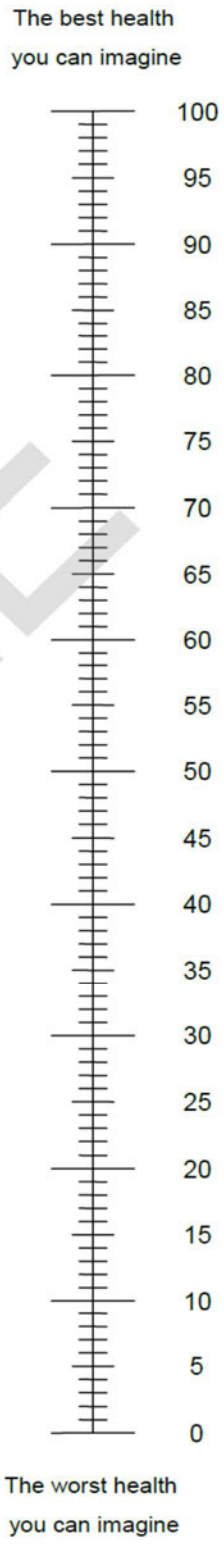
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

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 ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 7 Preexisting Autoimmune Diseases and Immune Deficiencies

Study patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease listed in the table are excluded from participating in the study. Possible exceptions to this exclusion could be subjects with a medical history of entities such as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid-replacement hormone may be eligible for enrollment in this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent (e.g., acute Lyme arthritis) are not excluded from the study. Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction while receiving another immunostimulatory anti-cancer agent. The Medical Monitor *is available to advise on* any uncertainty over autoimmune exclusion*s*.

Appendix 7
Preexisting Autoimmune Diseases and Immune Deficiencies (cont.)

Table 1 Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease - chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary *cholangitis* • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren's syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

Appendix 8 Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, IV, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event that a patient suffers a suspected anaphylactic reaction during a study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5 Administer antihistamines, epinephrine, or other medications as required by the patient's status and directed by the physician in charge.
6. Continue to observe the patient and document observations.

Appendix 9
Management of Atezolizumab-Specific Adverse Events

DOSE MODIFICATIONS

There will be no dose modifications for atezolizumab in this study.

TREATMENT INTERRUPTION

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks after event onset, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on the investigator's assessment of benefit-risk and documented by the investigator.* The Medical Monitor *is available to advise as needed.* Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit-risk* by the investigator *and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.* The Medical Monitor *is available to advise as needed.*

MANAGEMENT GUIDELINES

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology, when clinically indicated.

Although most immune-mediated adverse events observed with atezolizumab have been mild and limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the

investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed*.

PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 1.

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • *For Grade 1 pneumonitis, consider withholding atezolizumab.*
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]For recurrent events, *or events with no improvement after 48-72 hours of corticosteroids,* treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Bronchoscopy or BAL is recommended. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day *IV methylprednisolone*. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented* by the investigator. The Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

HEPATIC EVENTS

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 2.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table 2 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

Table 2 Management Guidelines for Hepatic Events (cont.)

Event	Management
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented* by the investigator. The Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by both the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

GASTROINTESTINAL EVENTS

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 3.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.* The Medical Monitor *is available to advise as needed*.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed*.

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

Event	Management
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.* The Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

ENDOCRINE EVENTS

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 4.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone, free triiodothyronine, and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

Table 4 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH *closely*.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH *closely*. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • *Consider patient referral to endocrinologist.* **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism. • *Consider patient referral to endocrinologist.*
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • *Evaluate for diabetic ketoacidosis and manage as per institutional guidelines.* • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

MRI = magnetic resonance imaging.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented* by the investigator. The Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated. event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

Table 4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented* by the investigator. The Medical Monitor *is available to advise as needed*.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed*.

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 5.

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to ophthalmologist. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented* by the investigator. The Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. *Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly.* Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of GI illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 6.

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

Table 6 Management Guidelines for Immune-Mediated Myocarditis

Event	Management
Immune-mediated myocarditis, Grade 2–4	• Permanently discontinue atezolizumab and contact Medical Monitor.[a] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). The Medical Monitor is available to advise as needed.

INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, anti-pyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported

with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in Table 5

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines IL-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

Table 5 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1 [a] Fever [b] with or without constitutional symptoms	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If the infusion is tolerated at the reduced rate for 30, the infusion rate may be increased to the original rate. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment, [c] including maintenance of IV fluids for hydration. • In case of rapid decline or prolonged CRS (>2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors and/or Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor. [e] • If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. • If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

Event	Management
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) and/or Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Permanently discontinue atezolizumab and contact Medical Monitor. [e] • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus and vasopressor as needed. • Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator and in consultation with the Medical Monitor.
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) and/or Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab and contact Medical Monitor. [e] • Administer symptomatic treatment. [c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator and in consultation with the Medical Monitor. • Hospitalize patient until complete resolution of symptoms.

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

Table 7 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: These management guidelines have been adapted from NCCN guidelines for management of CAR T-cell–related toxicities (Version 2.2019).

[a] Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed*. For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit–risk ratio.

[f] Refer to Riegler et al. (2019).

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 8.

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	Amylase and/or lipase $>1.5–2.0\times$ ULN: • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent. Asymptomatic with amylase and/or lipase $>2.0–5.0\times$ ULN: Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented* by the investigator. The Medical Monitor *is available to advise as needed*.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by both the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed*.

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

Table 8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented* by the investigator. The Medical Monitor *is available to advise as needed*.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed*.

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and *self*-limit*ing*, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 9.

Table 9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • *If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.*
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]

Stevens-Johnson syndrome or toxic epidermal necrolysis, (any grade)	Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis: • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented* by the investigator. The Medical Monitor *is available to advise as needed*.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit-risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed*.

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 10.

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

Table 10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-mediated neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology *and refer patient to neurologist*. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • *Refer patient to neurologist.* • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be *based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented* by the investigator. The Medical Monitor *is available to advise as needed*.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed*.

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

IMMUNE–MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 11.

Table 11 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact Medical Monitor. [a] • Refer patient to neurologist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed*.

RENAL EVENTS

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients

with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine *and urine protein*, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented* by the investigator. The Medical Monitor *is available to advise as needed.*

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.*

IMMUNE-MEDIATED MYOSITIS

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. *Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.*

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 13.

Table 13 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

Appendix 9
Management of Atezolizumab-Specific Adverse Events (cont.)

Table 13 Management Guidelines for Immune-Related Myositis (cont.)

Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented* by the investigator. The Medical Monitor *is available to advise as needed*.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed*.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab.

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever $\geq$ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin $<$ 90 g/L (9 g/dL) ($<$ 100 g/L [10 g/dL] for infants $<$ 4 weeks old)
  - Platelet count $<$ 100 $\times$ 109/L (100,000/μL)
  - ANC $<$ 1.0 $\times$ 109/L (1000/μL)
- Fasting triglycerides $>$ 2.992 mmol/L (265 mg/dL) and/or fibrinogen $<$ 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin $>$ 500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated $\geq$ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin $>$ 684 mg/L (684 ng/mL)

- At least two of the following:
  - Platelet count ≤ 181 × 109/L (181,000/μL)
  - AST ≥ 48 U/L
  - Triglycerides > 1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 14.

Table 14 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019).. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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Appendix 10
Guidelines for Management of Patients Who Experience Specific Adverse Events Associated with Bevacizumab

Event	Action to Be Taken
GI perforation, any grade	• Permanently discontinue bevacizumab.
Fistulae	
Internal fistula not arising in the GI tract	• Consider permanent discontinuation of bevacizumab.
Tracheoesophageal fistula, any grade	• Permanently discontinue bevacizumab.
Fistula, any type, Grade 4	• Permanently discontinue bevacizumab.
Hypertension	
Medically significant hypertension not adequately controlled with antihypertensive therapy	• Permanently discontinue bevacizumab.
Hypertensive crisis	• Permanently discontinue bevacizumab.
Hypertensive encephalopathy	• Permanently discontinue bevacizumab.
Congestive heart failure, Grade ≥ 3	• Permanently discontinue bevacizumab.
PRES	• Permanently discontinue bevacizumab.
Nephrotic syndrome	• Permanently discontinue bevacizumab.
Thrombosis/embolism	
Venous thrombosis, Grade 3	• Withhold bevacizumab until patient is on a stable dose of anticoagulation. [a]
Recurrent venous thrombosis, Grade ≥ 3	• Permanently discontinue bevacizumab.
Venous thrombosis, Grade 4	• Permanently discontinue bevacizumab.
Arterial thrombosis/embolism, any grade	• Permanently discontinue bevacizumab.
Hemorrhage	
Grade ≥ 2 hemoptysis (≥ 2.5 mL of bright red blood per episode)	• Permanently discontinue bevacizumab.
Grade 3, 4 bleeding	• Permanently discontinue bevacizumab.
Bleeding in patients on full-dose anticoagulant therapy	• Permanently discontinue bevacizumab. [b]
CNS bleeding, any grade	• Permanently discontinue bevacizumab.

Appendix 10
Guidelines for Management of Patients Who Experience Specific Adverse Events Associated with Bevacizumab (cont.)

Event	Action to Be Taken
Major surgery or wound-healing complication	• Withhold bevacizumab until the wound is fully healed. • If the wound does not fully heal despite withholding treatment, permanently discontinue bevacizumab.
Hypersensitivity/allergic reactions	• Permanently discontinue bevacizumab.
Infusion-associated events	• See footnote. [c]
Febrile neutropenia, Grade 4 [d]	• Withhold bevacizumab until resolution.
Decreased platelet count, Grade 4 [d]	• Withhold bevacizumab until resolution to Grade ≤ 1.

GI = gastrointestinal; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PRES = posterior reversible encephalopathy syndrome; ULN = upper limit of normal.

Note: All grades are per NCI CTCAE, Version 4.

The above events should be reported as adverse events.

[a] Patients on heparin treatment should have a therapeutic aPTT between 1.5 – 2.5 × ULN. Patients on coumadin derivatives should have an INR between 2.0 and 3.0 assessed in two consecutive measurements 1 – 4 days apart. Patients on full-dose low-molecular-weight heparins should receive the appropriate dose based on the weight of the patient according to package insert.

[b] Follow guidelines of the treating institution. Standard procedures such as antagonization with protamine or vitamin K and infusion of vitamin K dependent factors should be considered dependent on the severity of the bleeding.

[c] Instructions for Preparation, Administration, and Disposal of Bevacizumab.

[d] Bevacizumab should be temporarily withheld in the event of Grade 4 febrile neutropenia and/or Grade 4 thrombocytopenia (regardless of the relationship to treatment), because these conditions are predisposing factors for an increased bleeding tendency.

Preparation and disposal: Bevacizumab should be prepared per institutional standard by a healthcare professional using aseptic technique. Withdraw the necessary amount of bevacizumab and dilute in a total volume of 100 ml of 0.9% sodium chloride injection, USP. If the total bevacizumab dose exceeds 1000 mg, dilute the calculated bevacizumab dose 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 administered (i.e., minimize the infusion volume as much as possible). For patients who weigh more than 110 kg, refer to the Avastin® Investigator's Brochure for the infusion preparation for this protocol. Bevacizumab infusions should not be administered or mixed with dextrose or glucose solutions. Discard any unused portion left in a vial, as the product contains no preservatives. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Diluted bevacizumab should be used within 8 hours at room temperature or within 24 hours at 2°C–8°C.

Appendix 10
Guidelines for Management of Patients Who Experience Specific Adverse Events Associated with Bevacizumab (cont.)

Administration: Although no data are available specifically on bevacizumab, in general, patients experiencing mild to moderate hypersensitivity/infusion reactions (Grade 1 or 2 of the NCI CTCAE infusion-related reactions), in particular after the first exposure, may tolerate re-administration of the agent at reduced infusion rates and with treatment using antihistamines and corticosteroids after complete resolution of symptoms. Re-challenge is generally discouraged in patients who experienced a severe initial reaction (Grade 3 or 4).

A rate-regulating device should be used for all bevacizumab infusions. When the bevacizumab IV bag is empty, 50 ml of 0.9% sodium chloride solution, USP, will be added to the IV bag or an additional bag will be hung, and the infusion will be continued for a volume equal to that of the tubing to ensure complete delivery of the bevacizumab. The initial dose will be delivered over 90 (±15) minutes. If the first infusion is tolerated without any infusion-associated 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 infusions may be slowed or interrupted for patients who experience infusion-associated 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. The total infusion time, therefore, should always be either 90, 60, or 30 minutes. If more saline is infused, the extent of saline infusion does not factor into the trial drug infusion time.

Should extravasation of bevacizumab infusion occur, the following steps should be taken:

- Discontinue the infusion.
- Treat the extravasation according to institutional guidelines for extravasation of a non-caustic agent.
- If a significant volume of bevacizumab remains, restart the infusion at a more proximal site in the same limb or on the other side.
- Treat the infiltration according to institutional guidelines for infiltration of a non-caustic agent.

In the event of a suspected anaphylactic reaction during bevacizumab infusion:

1. Stop the trial drug infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of bevacizumab. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.

Appendix 10
Guidelines for Management of Patients Who Experience Specific Adverse Events Associated with Bevacizumab (cont.)

4. Administer antihistamines, corticosteroids, epinephrine, or other medications as required.
5. Continue to observe the patient, document observations and administer further treatment as required.
6. Permanently discontinue bevacizumab.

Event	Action to be Taken
Proteinuria [a]	
Grade 1 (urine dipstick 1+ **and** either urine protein/creatinine ratio of < 1.0 or 24-hr urine protein collection 0.15 to < 1.0 g/24 hr)	• No bevacizumab modifications.
Grade 2 (urine dipstick 2+ to 3+ **and** either urine protein/creatinine ratio of 1.0 to < 3.5 or 24-hr urine protein collection 1.0 to < 3.5 g/24 hr)	• For 2+ dipstick, may administer bevacizumab and obtain urine protein/creatinine ratio or 24-hr urine prior to next dose. • For 3+ dipstick, obtain urine protein/creatinine ratio or 24-hr urine prior to administration of bevacizumab. • Hold bevacizumab if urine protein/creatinine ratio > 2 or 24-hr urine protein > 2 g/24 hr. May resume bevacizumab when urine protein/creatinine ratio is ≤ 2 or 24-hr urine protein is ≤ 2 g/24 hr.
Grade 3 (urine dipstick 4+ **and** either urine protein/creatinine ratio of ≥ 3.5 or urinary protein collection ≥ 3.5 g/24 hr)	• Hold bevacizumab. Resume when protein/creatinine ratio is ≤ 2 or 24-hr urine protein is ≤ 2 g/24 hr.

[a] Performing only a urine protein/creatinine ratio or only a 24-hr urine protein collection may be performed in lieu of a urine dipstick. For urine dipstick of ≥ 2+, a confirmatory urine protein/creatinine ratio or 24-hr urine protein collection is required.

For context, urine protein/creatinine ratio may be used to establish and monitor proteinuria. The urine protein/creatinine ratio in a spot urine sample has been shown to adequately estimate the amount of protein (in grams) excreted in 24 hours of urine. For example, a urine protein/creatinine ratio of 1 is equivalent to a 24-hr urine protein of 1 gram.

Appendix 10
Guidelines for Management of Patients Who Experience Specific Adverse Events Associated with Bevacizumab (cont.)

If manually calculating the urine protein/creatinine ratio, one of the following formulae can be used, depending on the units in which the urine creatinine is reported:

1. If both urine protein and urine creatinine are reported in mg/dL, the urine protein/creatinine ratio = (urine protein) / (urine creatinine)
2. If urine creatinine is reported in mmol/L, the urine protein/creatinine ratio = [(urine protein)(0.088)] / (urine creatinine)

Appendix 11
Response Evaluation Criteria in Solid Tumors, Version 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 measurable or non-measurable as follows.

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 of:

- 10 mm by CT or 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 in 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.

b. Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), 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

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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.

masses/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 to measure 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 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 malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered 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.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

a. 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.

Appendix 11
Response Evaluation Criteria in Solid Tumors, Version 1.1: Modified Excerpt from Original Publication (cont.)

b. 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 study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will be considered measurable only when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules).

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 on the basis of 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 intravenous (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, if not, the patient should be considered not evaluable from that point forward. 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.

Appendix 11
Response Evaluation Criteria in Solid Tumors, Version 1.1: Modified Excerpt from Original Publication (cont.)

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 to 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 in instances where 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-target 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, additionally, 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 ≥ 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 scan, 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 ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Appendix 11
Response Evaluation Criteria in Solid Tumors, Version 1.1: Modified Excerpt from Original Publication (cont.)

Lesions irradiated within 3 weeks prior to Cycle 1, Day 1 may not be counted as target lesions.

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

a. 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

b. 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 CR criteria are met since a normal lymph node is defined as having a short axis < 10 mm.

Target Lesions That Become Too Small to Measure. While on 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 BML (below measurable limit) should be ticked. (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.)

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

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 maximal longest diameter for the coalesced lesion.

c. 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. Although 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.

- CR: 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 lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: unequivocal progression of existing non-target lesions

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

d. 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 studies 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. Although 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.

e. 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 PR 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.

EVALUATION OF RESPONSE

a. 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.

Appendix 11
Response Evaluation Criteria in Solid Tumors, Version 1.1: Modified Excerpt from Original Publication (cont.)

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 studies; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. 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 be most likely

to 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.

Appendix 11
Response Evaluation Criteria in Solid Tumors, Version 1.1: Modified Excerpt from Original Publication (cont.)

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

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

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

c. 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 1–3.

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.

If a patient undergoes an excisional biopsy or other appropriate approach (e.g., multiple passes with large core needle) of a new lesion or an existing solitary progressive lesion that following serial sectioning and pathological examination reveals no evidence of malignancy (e.g., inflammatory cells, fibrosis, etc.), then the new lesion or solitary progressive lesion will not constitute disease progression.

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 12
Patient Questionnaire FACT-G Item GP5

<u>Do not reproduce or distribute</u>. The Sponsor will provide sites with all instruments to be completed in this study.

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 13
Ovarian Pathology Handbook

Ovarian Pathology Handbook

YO39523/GOG-3015/ENGOT-ov39 Ovarian Pathology

This guide serves to help identify morphological changes indicative of residual disease in ovarian cancer patients following neoadjuvant treatment.

Background: Tumor cells may demonstrate nuclear alterations such as enlargement, hyperchromasia, chromatin clumping and smudging, eosinophilia, and vacuolization with foamy/clear cell changes. Stromal alterations consist of dense fibrosis, inflammation, foamy histiocytes, cholesterol clefts, necrosis, and dystrophic calcifications. Similar morphologic changes associated with neoadjuvant chemotherapy or chemoradiation in other sites (e.g., pancreas, breast, rectum, esophagus) have also been described [Chang 2008, Becker 2003, Junker 2001, Hartman 2012].

Four easily reproducible histological characteristics, seen by hematoxylin-eosin, have been identified and may be associated with clinical outcome: **Residual Tumor (RT), Fibrosis, Necrosis and Inflammation** [Samrao 2012]. A scoring system has been developed to assessing the parameters in each tissue section (see over the page).

Should you have any questions about the content or use of this material, please contact:

[redacted] **MD, MS at Genentech**
Email: [redacted]

All slides from each of the following sites must be evaluated by H&E:

1. Omentum
2. Left pericolic or pelvic peritoneum
3. Right pericolic or pelvic peritoneum
4. Cul de sac peritoneum
5. Left or Right ovary
6. The location of the disease initially making this disease unresectable to no gross residual disease (R0) in primary tumor reductive surgery

Slides from each site must be evaluated for:

- Residual Tumor
- Fibrosis
- Necrosis
- Inflammation

This handbook was developed by [redacted], MD, MS [redacted], Genentech – A member of the Roche family) and [redacted], MD [redacted])

Appendix 13
Ovarian Pathology Handbook (cont.)

YO39523/GOG-3015/ENGOT-ov39 Ovarian Pathology

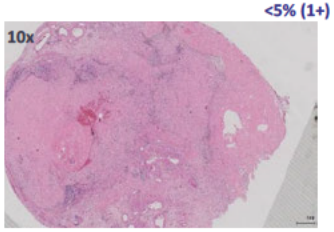
IMagyn050 OVARIAN

Residual Tumor

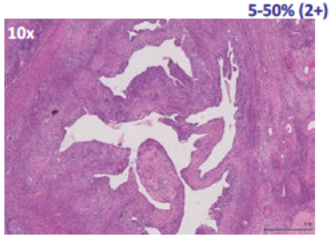
% Residual Tumor

No tissue to evaluate (0) ☐
<5% (1+) ☐
5-50% (2+) ☐
>50% (3+) ☐

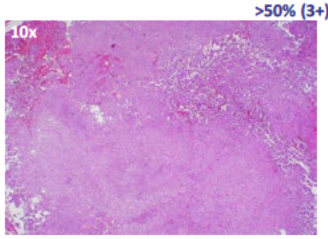
<5% (1+)



5-50% (2+)



>50% (3+)

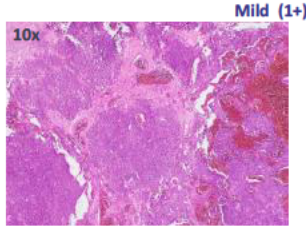


Fibrosis

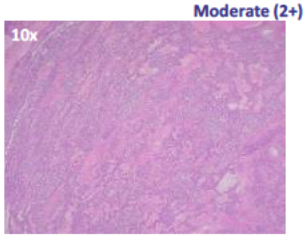
Fibrosis

No tissue to evaluate (0) ☐
Mild (1+) ☐
Moderate (2+) ☐
Severe (3+) ☐

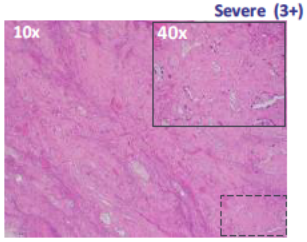
Mild (1+)



Moderate (2+)



Severe (3+)

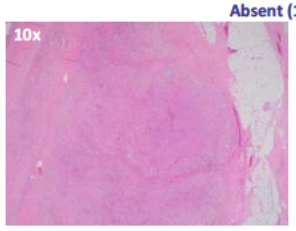


Necrosis

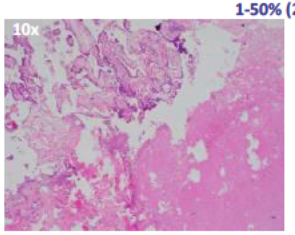
Necrosis

No tissue to evaluate (0) ☐
Absent (1+) ☐
1-50% (2+) ☐
>50% (3+) ☐

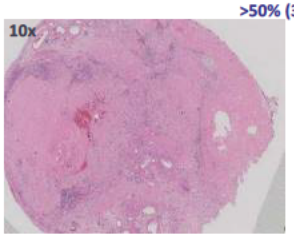
Absent (1+)



1-50% (2+)



>50% (3+)

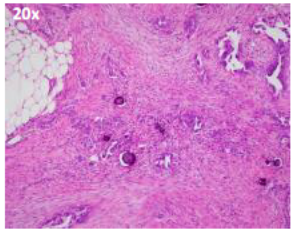


Inflammation

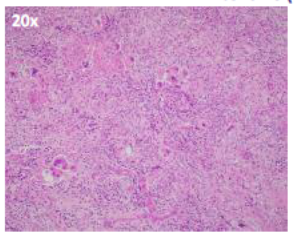
Inflammation

No tissue to evaluate (0) ☐
Mild (1+) ☐
Extensive (2+) ☐

Mild (1+)



Extensive (2+)



*If no tissue was taken at surgery, please select "No tissue to evaluate."