Official Title: A Phase III, Multicenter, Randomized, Placebo-Controlled Study of Atezolizumab (Anti-PD-L1 Antibody) in Combination With Nab-Paclitaxel Compared With Placebo With Nab-Paclitaxel for Patients With Previously Untreated Metastatic Triple-Negative Breast Cancer

NCT Number: NCT02425891

Document Date: Protocol Version 9: 31-January-2020

PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH NAB-PACLITAXEL COMPARED WITH PLACEBO WITH NAB-PACLITAXEL FOR PATIENTS WITH PREVIOUSLY UNTREATED METASTATIC TRIPLE-NEGATIVE BREAST CANCER**
PROTOCOL NUMBER:	WO29522
VERSION NUMBER:	9
EUDRACT NUMBER:	2014-005490-37
IND NUMBER:	123,277
TEST PRODUCT:	Atezolizumab
MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	14 January 2015
DATES AMENDED:	Version 2 (UK only): 5 May 2015 Version 2 (Germany only): 22 May 2015 Version 3 (Global): 3 August 2015 Version 4: 20 November 2015 Version 4 (France only): 7 June 2016 Version 5 (France only): 7 September 2016 Version 5 (Global): 7 September 2016 Version 6 (France): 27 October 2017 Version 7 (Global): 2 March 2018 Version 8 (Global): 28 September 2018 Version 9 (Global): See electronic date stamp below.

FINAL PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
31-Jan-2020 18:20:26	Company Signatory	[redacted]

PROTOCOL AMENDMENT, VERSION 9
RATIONALE

Protocol WO29522 has been amended to align with Investigator's Brochure, version 15, and with the nab-paclitaxel (Abraxane®) prescribing information. Changes to the protocol, along with a rationale for each change, are summarized below:

- Background information on atezolizumab has been updated to account for additional approved indications (Section 1.2).
- To align with the Atezolizumab Investigator's Brochure, Version 15, "immune-related" has been changed to "immune-mediated" when describing events associated with atezolizumab (Sections 1.2.2.2, 5.1.1, and 5.1.6 and Appendix 10).
- The list of atezolizumab risks has been updated to include myositis for consistency with the list of identified risks in the Atezolizumab Investigator's Brochure (Section 5.1.1), and guidelines for managing patients who experience atezolizumab-associated adverse events have been revised to include myositis (Appendix 10).

  To align with the nab-paclitaxel (Abraxane®) prescribing information (SmPC), the risk of tumour lysis syndrome has been included (Section 5.1.2).
- To address a request by the French National Agency for the Safety of Medicines and Health Products (ANSM), systemic immune activation has been replaced by hemophagocytic lymphohistiocytosis and macrophage activation syndrome in the list of potential risks for atezolizumab (Section 5.1.1) and the management guidelines for systemic immune activation have been replaced with management guidelines for hemophagocytic lymphohistiocytosis and macrophage activation syndrome (Appendix 10). As a result, Section 5.1.6.1 Systemic Immune Activation has been deleted.
- Section 5.4.3 on reporting requirements for pregnancy has been updated with clarified definitions of spontaneous versus elective abortions.
- The reference document for the expectedness of adverse event assessement for nab–paclitaxel has been specified. (Summary of Product Characteristics) (Section 5.7)
- To address a request by the French ANSM, the atezolizumab adverse event management guidelines have been updated to add laboratory (e.g., B-type natriuretic peptide) and cardiac imaging abnormalities as signs or symptoms that are suggestive of myocarditis (Appendix 10).
- The Medical Monitor name and associated contact information has been updated throughout the document.

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH NAB-PACLITAXEL COMPARED WITH PLACEBO WITH NAB-PACLITAXEL FOR PATIENTS WITH PREVIOUSLY UNTREATED METASTATIC TRIPLE-NEGATIVE BREAST CANCER**
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MEDICAL MONITOR:	[redacted], M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ATEZOLIZUMAB (ANTI–PD-L1 ANTIBODY) IN COMBINATION WITH NAB-PACLITAXEL COMPARED WITH PLACEBO WITH NAB-PACLITAXEL FOR PATIENTS WITH PREVIOUSLY UNTREATED METASTATIC TRIPLE-NEGATIVE BREAST CANCER**
PROTOCOL NUMBER:	WO29522
VERSION NUMBER:	9
EUDRACT NUMBER:	2014-005490-37
IND NUMBER:	123,277
TEST PRODUCT:	Atezolizumab
PHASE:	III
INDICATION:	Triple-negative breast cancer (TNBC)
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, and pharmacokinetics of atezolizumab with nab-paclitaxel compared with placebo with nab-paclitaxel in patients with metastatic or locally advanced triple-negative adenocarcinoma of the breast who have not received prior systemic therapy for metastatic breast cancer (mBC). Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objectives

The following efficacy objectives will be evaluated in both the intent-to-treat (ITT) population (i.e., all randomized patients) and the subpopulation with programmed death–ligand 1 (PD-L1)–selected tumor status.

The co-primary efficacy objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab +nab-paclitaxel compared with placebo+nab-paclitaxel as measured by PFS
- To evaluate the efficacy of atezolizumab+nab-paclitaxel compared with placebo+nab-paclitaxel as measured by overall survival (OS)

The secondary efficacy objectives for this study are as follows:

- To evaluate the efficacy of atezolizumab+nab-paclitaxel compared with placebo+nab-paclitaxel as measured by objective response rate (ORR; per investigator assessment using RECIST v1.1)
- To evaluate the efficacy of atezolizumab+nab-paclitaxel compared with placebo+nab-paclitaxel as measured by duration of objective response (DOR; per investigator using RECIST v1.1) among patients with an objective response
- To evaluate patient-reported outcomes (PROs) of health status/health-related quality of life (HRQoL) associated with atezolizumab + nab-paclitaxel compared with placebo+nab-paclitaxel, as measured by the time to deterioration (TTD) in Items 29 and 30 of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30)

Safety Objectives

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of atezolizumab+nab-paclitaxel compared with placebo+nab-paclitaxel
- To evaluate the incidence of anti-therapeutic antibodies (ATAs) against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, pharmacodynamics, safety, and efficacy

Pharmacokinetic Objectives

The pharmacokinetic (PK) objectives for this study are as follows:

- To characterize the pharmacokinetics of atezolizumab when administered with nab-paclitaxel
- To characterize the pharmacokinetics of nab-paclitaxel when administered with atezolizumab

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To evaluate PROs of function and disease/treatment-related symptoms associated with atezolizumab+nab-paclitaxel compared with placebo+nab-paclitaxel, as measured by the EORTC QLQ-C30 and its breast cancer module (QLQ-BR23)
- To evaluate health utility as measured by the EuroQoL 5 Dimension (EQ-5D-5L) questionnaire for health economic modeling of atezolizumab + nab-paclitaxel compared with placebo + nab-paclitaxel
- To assess predictive, prognostic, and pharmacodynamic (PD) exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status and/or response to study treatment

Study Design

Description of Study

This is a Phase III, global, multicenter, double-blind, two-arm, randomized, placebo-controlled study designed to evaluate the efficacy and safety of atezolizumab administered with nab-paclitaxel compared with placebo in combination with nab-paclitaxel in patients with locally advanced or metastatic TNBC who have not received prior systemic therapy for mBC.

Eligible patients will be randomized in a 1:1 ratio to receive atezolizumab (840 mg) or placebo IV infusions on Days 1 and 15 of every 28-day cycle plus nab-paclitaxel (100 mg/m^2) administered via IV infusion on Days 1, 8, and 15 of every 28-day cycle. Randomization will be stratified by the following three factors: presence of liver metastases (yes vs. no); prior taxane treatment (yes vs. no); and tumor PD-L1 status (IC0 vs. IC1/2/3).

In the absence of disease progression or unacceptable toxicity, nab-paclitaxel will be administered for a target of at least 6 cycles, with no maximum. nab-Paclitaxel and atezolizumab or placebo may be discontinued for toxicity independently of each other in the absence of disease progression. The Sponsor, patients, and investigators will not be aware of each patient's treatment assignment prior to unblinding. Once treatment unblinding has occurred, investigators may request crossover to the atezolizumab+ nab-paclitaxel arm for patients who were randomized to the placebo + nab-paclitaxel arm, who have not yet experienced disease progression, and who have not started any other systemic anti-cancer agents beyond those offered in this study. Patients must still meet the safety-related eligibility criteria for the study prior to initiating atezolizumab.

In order to interrogate the mechanism of action of the drug combination in the tumor microenvironment and possible resistance mechanisms, tumor tissue may be optionally collected before dosing on Cycle 2, Day 1.

To test the mechanisms of resistance to the drug combination in the tumor microenvironment, all patients will undergo a mandatory tumor biopsy collection (if clinically feasible) at first

evidence of radiographic disease progression per RECIST v1.1. DNA sequencing of cancer-related genes will be performed on these specimens by Foundation Medicine, Inc. (Cambridge, MA). The research report may be obtained by the Investigator, if desired, directly from Foundation Medicine, Inc. and will describe results from investigational tests that are not intended to be used to guide future treatment decisions.

Tumor assessments per RECIST v1.1 will be performed approximately every 8 weeks (±1 week) for the first 12 months after Cycle 1, Day 1 and every 12 weeks (± 1 week) thereafter until disease progression or treatment discontinuation, whichever is later. Tumor assessments will be performed on the specified schedule regardless of treatment delays.

Treatment will be discontinued upon radiographic disease progression per RECIST v1.1. For equivocal findings of progression (e.g., very small or uncertain new lesions or lymph nodes; 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.

For estimation of PFS, ORR, and DOR, tumor response will be based on RECIST v1.1. The imaging data used for tumor assessment will be collected by the Sponsor to enable centralized, independent review of response endpoints by an Independent Review Committee (IRC) in the future, if necessary.

All patients will be followed for survival approximately every 3 months after the treatment discontinuation visit until death, withdrawal of consent, loss to follow-up, or study termination by the Sponsor. In addition, information regarding use of subsequent anti-cancer agents for metastatic TNBC during the survival follow-up period will be collected.

The pharmacokinetics of atezolizumab and nab-paclitaxel will be determined.

Safety assessments will include the incidence, nature, and severity of adverse events and laboratory abnormalities graded per NCI CTCAE v4.0. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry. Serum samples will be collected to monitor atezolizumab pharmacokinetics and to detect the presence of antibodies to atezolizumab. Patient samples, including tumor tissues, as well as serum and plasma and whole blood, will be collected for exploratory biomarker assessments.

Number of Patients

Up to 900 patients will be enrolled at approximately 257 sites globally.

Target Population

Patients with metastatic or locally advanced TNBC who have not received prior systemic cytotoxic therapy for mBC may be eligible for this study. Locally advanced disease must not be amenable to resection with curative intent. Patients may have received prior chemotherapy in the neoadjuvant/adjuvant setting if treatment was completed ≥12 months prior to randomization. Patients must comply with all eligibility criteria to be enrolled.

Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry:

- Signed Informed Consent Form
- Women or men aged ≥18 years
- Metastatic or locally advanced, histologically documented TNBC (absence of HER2, ER, and PR expression)

  HER2 negativity is defined as either of the following by local laboratory assessment:

  In situ hybridization (ISH) non-amplified (ratio of HER2 to CEP17 <2.0 or single probe average HER2 gene copy number <4 signals/cell), or

  IHC 0 or IHC 1+ (if more than one test result is available and not all results meet the inclusion criterion definition, all results should be discussed with the Medical Monitor to establish eligibility of the patient)

  ER and PR negativity are defined as <1% of cells expressing hormonal receptors via IHC analysis.
- No prior chemotherapy or targeted systemic therapy for inoperable locally advanced or metastatic TNBC

Radiation therapy for metastatic disease is permitted. There is no required minimum washout period for radiation therapy. Patients should be recovered from the effects of radiation.

Prior chemotherapy (including taxanes) in the neoadjuvant or adjuvant setting is allowable if treatment was completed ≥12 months prior to randomization.

- Eligible for taxane monotherapy (i.e., absence of rapid clinical progression, life-threatening visceral metastases, or the need for rapid symptom and/or disease control)
- Representative FFPE tumor specimens (either an archival specimen or fresh pre-treatment tissue from relapsed disease) in paraffin blocks (preferred) or at least 15 unstained slides, with an associated pathology report documenting ER, PR, and HER2 negativity

  Patients with fewer than 20 unstained slides available at baseline (but no fewer than 12) 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.

  If multiple tumor specimens are submitted (e.g., an archival specimen and tissue from relapsed disease), 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.

  A tumor specimen obtained from relapsed metastatic or locally advanced disease (if applicable) must also be submitted, if clinically feasible.

    Acceptable samples include core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

    FFPE tumor specimens in paraffin blocks are preferred

    Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable.

    Tumor tissue from bone metastases is not evaluable for PD-L1 expression and is therefore not acceptable.
- ECOG performance status of 0 or 1
- Life expectancy ≥12 weeks
- Measurable disease, as defined by RECIST v1.1

  Previously irradiated lesions can be considered as measurable disease only if disease progression has been unequivocally documented at that site since radiation.
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment (Cycle 1, Day 1):

  ANC ≥1500 cells/μL (without granulocyte colony-stimulating factor [G-CSF] support within 2 weeks prior to Cycle 1, Day 1)

  Lymphocyte count ≥500/μL

  Platelet count ≥100,000/μL (without transfusion within 2 weeks prior to Cycle 1, Day 1)

  Hemoglobin ≥9.0 g/dL

    Patients may be transfused or receive erythropoietic treatment to meet this criterion.

  AST, ALT, and alkaline phosphatase ≤2.5× the upper limit of normal (ULN), with the following exceptions:

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

    Patients with documented liver or bone metastases: alkaline phosphatase ≤5×ULN

  Serum bilirubin ≤1.25×ULN

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

INR and aPTT ≤1.5×ULN

This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.

Calculated creatinine clearance ≥30 mL/min

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year, during the treatment period and for at least 5 months after the last dose of atezolizumab/placebo or 1 month after the last dose of nab-paclitaxel, whichever is later.

  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 and/or uterus).

  Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices (IUDs), and copper IUDs.

  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.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 6 months after the last dose of nab-paclitaxel. Men must refrain from donating sperm during this same period.

  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.

- Women who are not postmenopausal (≥12 months of non–therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of study drug

<u>Exclusion Criteria</u>

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

Cancer-Specific Exclusion Criteria

- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for >2 weeks prior to randomization
- Known CNS disease, except for treated asymptomatic CNS metastases, provided <u>all</u> of the following criteria are met:

  Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla, or spinal cord)

  No ongoing requirement for corticosteroids as therapy for CNS disease

  No stereotactic radiation within 7 days or whole brain radiation within 14 days prior to randomization

  No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

  Note: Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to enrollment, if all other criteria are met.

- Leptomeningeal disease

- Uncontrolled pleural effusion, pericardial effusion, or ascites

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled tumor-related pain

  Patients requiring narcotic pain medication must be on a stable regimen at study entry.

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to randomization. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

  Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to randomization.
- Uncontrolled hypercalcemia (>1.5 mmol/L ionized calcium or calcium >12 mg/dL or corrected serum calcium >ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy

  Patients who are receiving denosumab must discontinue denosumab use and replace it with a bisphosphonate instead while on study. There is no required minimum washout period for denosumab.

  Patients who are receiving bisphosphonate therapy specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.
- Malignancies other than TNBC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix or basal or squamous cell skin cancer)

General Medical Exclusion Criteria

- Pregnancy or lactation
- Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome)
- Significant cardiovascular disease, such as New York Heart Association (NYHA) cardiac disease (Class II or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina

  Patients with a known left ventricular ejection fraction (LVEF) <40% will be excluded.

  Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF <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.
- Severe infection within 4 weeks prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1

  Patients receiving routine antibiotic prophylaxis (e.g., to prevent chronic obstructive pulmonary disease exacerbation or for dental extraction) are eligible.
- Major surgical procedure within 28 days prior to randomization or anticipation of the need for a major surgical procedure during the course of the study other than for diagnosis

  Placement of central venous access catheter(s) (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted
- Known hypersensitivity to nab-paclitaxel or to any of the excipients.

Exclusion Criteria Related to Atezolizumab

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins

- Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis

    Patients with a history of autoimmune-mediated hypothyroidism on a stable dose of thyroid replacement hormone are eligible for this study.

    Patients with controlled Type 1 diabetes mellitus on a stable insulin dosing regimen are eligible for this study.

    Patients with eczema, psoriasis, lichen simplex chronicus or vitiligo with dermatologic manifestations only (e.g., no psoriatic arthritis) are permitted provided that they meet the following conditions:

        Rash must cover less than 10% of body surface area (BSA)

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

        No acute exacerbations of underlying condition within the last 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)
- Prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan

    History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Positive test for HIV
- Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C

    Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible.

    Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Active tuberculosis
- Receipt of a live, attenuated vaccine within 4 weeks prior to randomization or anticipation that such a live, attenuated vaccine will be required during the study

    Patients must agree not to receive live, attenuated vaccine (e.g., FluMist®) within 28 days prior to randomization, during treatment, or within 5 months following the last dose of atezolizumab/placebo.
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, or anti–PD-L1 therapeutic antibodies
- Treatment with systemic immunostimulatory agents (including but not limited to interferons or IL-2) within 4 weeks or five half-lives of the drug (whichever is shorter) prior to randomization
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor [TNF] agents) within 2 weeks prior to randomization, or anticipated requirement for systemic immunosuppressive medications during the study

    Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study

Patients with a history of allergic reaction to IV contrast requiring steroid pre-treatment should have baseline and subsequent tumor assessments performed using MRI.

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

End of Study

The end of the study is expected to occur about 53 months after FPI when approximately the pre-planned number of deaths will have been observed.

OS events will be monitored throughout the course of the study, and study timelines might be updated as indicated.

Length of Study

The end of the study is expected to occur about 53 months after FPI.

Investigational Medicinal Products

Test Products

- Atezolizumab 840-mg flat dose or placebo administered via IV infusion on Day 1 and Day 15 of every 28-day cycle
- nab-Paclitaxel 100 mg/m^2 administered via IV infusion on Days 1, 8, and 15 of every 28-day cycle. Doses of nab-paclitaxel should not be administered more frequently than every 7 days.

Statistical Methods

Primary Analysis

Efficacy analyses will be performed separately for the ITT population and the PD-L1–selected subpopulation.

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. PFS is simultaneously assessed in the ITT and PD-L1–selected subgroup.

For United States registration purposes, the co-primary efficacy endpoint of PFS will be defined as described above with an additional censoring rule for missed visits. Data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits. Type I error control will be applied to this analysis of PFS. The following analyses will be performed for both PFS endpoints described above. PFS will be compared between treatment arms with use of the stratified log-rank test. The HR for disease progression or death will be estimated using a stratified Cox proportional hazards model. The 95% CI for the HR will be provided. The stratification factors will be the same as the randomization stratification factors: presence of liver metastases (yes vs. no), prior taxane treatment (yes vs. no), and tumor PD-L1 status (IC0 vs. IC1/2/3). Results from an unstratified analysis will also be provided. Kaplan-Meier methodology will be used to estimate the median PFS for each treatment arm, and Kaplan-Meier curves will be produced. 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 death from any cause. Testing of OS is outlined in the protocol and analysis of OS is performed analogously to PFS.

OS will be analyzed in a similar manner as PFS.

Determination of Sample Size

Up to 900 patients in total will be randomized into the study.

Type I Error Control

The type I error (α) for this study is 0.05 (two-sided). Type I error will be controlled for the following efficacy endpoints:

- Co-primary efficacy endpoint of investigator-assessed PFS by RECIST v1.1 (as defined for United States registrational purposes; ITT and PD-L1–selected subgroups)
- Co-primary efficacy endpoint of OS (ITT and PD-L1–selected subgroups)
- Secondary efficacy endpoint: Investigator-assessed ORR by RECIST v1.1 (measurable disease population)

Type I error will be controlled by comparing these endpoints between treatment arms according to the following testing procedure.

At the time of the analysis of PFS, the co-primary endpoints of PFS and OS and the secondary endpoint of ORR are tested in the ITT population and in the PD-L1–selected subpopulation, as follows:

1. α (0.05) will be allocated between PFS (0.01) and OS (0.04). The allocated type I error for PFS is further allocated to PFS in the ITT (0.005) and PFS in the PD-L1–selected subgroup (0.005).

Testing of PFS and ORR

2. Test the null hypothesis of no difference in PFS between the two arms using the stratified log-rank test in the ITT population and the PD-L1–selected subgroup with the allocated type I error.
3. If one or both of the null hypotheses from the step above is rejected, ORR will subsequently be compared between the two arms in the corresponding populations (one or both) using the stratified Cochran-Mantel-Haenszel test using a Type I error of 0.001 for each correspondingly.

Testing of OS

4. At the time of the analysis of PFS, an interim analysis of OS in the ITT (OS [ITT]) will be performed. The interim analysis of OS (ITT) will be performed regardless of the results of the analyses of PFS and ORR. The interim analysis boundary for statistical significance will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming use function according to the type I error allocated to the comparison of OS (ITT). Allocation of the type I error to the comparison of OS (ITT) will depend on the outcome of the testing of PFS and ORR outlined in the Steps 1–3 above. Details for the different type I error allocations to the OS (ITT) testing are provided in the protocol.
5. If hypothesis of no difference in OS in the ITT population can be rejected, OS in the PD-L1–selected subgroup will be compared by recycling the type I error used for OS (ITT) testing.

Interim Analyses

There are no planned interim analyses of the co-primary endpoint of PFS.

Overall Survival

A total of three analyses of OS will be performed (two interim analyses and one final analysis). The timing and the two interim analyses and the final analysis for OS depends on the results of the definitive analysis of the co-primary endpoint PFS as well as the secondary endpoint ORR as described in the protocol, where the pre-specified boundaries for OS of all different scenarios are also presented.

The boundary for statistical significance at each interim analysis and the final analysis will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming use function.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
anti-HBc	antibody to hepatitis B core antigen
anti-HBs	antibody to hepatitis B surface antigen
ASCO	American Society of Clinical Oncology
ATA	anti-therapeutic antibody
CL	clearance
C_{max}	maximum observed serum concentration
C_{min}	minimum observed serum concentration
CR	complete response
CRC	colorectal cancer
CRP	C-reactive protein
CT	computed tomography
C_{trough}	trough concentration
CYP	cytochrome P450
DLT	dose-limiting toxicity
DOR	duration of objective response
DRB	Data Review Board
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	electronic patient-reported outcome
EQ-5D-5L	European Quality of Life 5 Dimension, 5-level version
ER	estrogen receptor
ESMO	European Society of Medical Oncology
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
FOLFOX	oxaliplatin, leucovorin, and 5-fluorouracil
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor 2
HIPAA	Health Insurance Portability and Accountability Act
HR	hazard ratio

Abbreviation	Definition
HRQoL	health-related quality of life
IC	tumor-infiltrating immune cell
ICH	International Conference on Harmonisation
iDCC	independent Data Coordinating Committee
iDMC	independent Data Monitoring Committee
IHC	immunohistochemistry
Ig	immunoglobulin
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug application
ISH	in situ hybridization
ITT	intent to treat
IV	intravenous
IxRS	interactive voice or Web response system
LFT	liver function test
LVEF	left ventricular ejection fraction
mBC	metastatic breast cancer
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE v4.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
pCR	pathologic complete response
PCR	polymerase chain reaction
PD	pharmacodynamic
PD–1	programmed death–1
PD–L1	programmed death–ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PR	progesterone receptor/partial response
PRO	patient-reported outcome
PVC	polyvinylchloride
q2w	every 2 weeks
q3w	every 3 weeks

Abbreviation	Definition
QLQ-BR23	breast cancer module for QLQ-C30
QLQ-C30	Quality-of-Life Questionnaire Core 30
RCC	renal cell carcinoma
RCR	Roche Clinical Repository
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
sb	solvent based
SD	stable disease
TIF	tumor interstitial fluid
TNBC	triple-negative breast cancer
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
TTD	time to deterioration
ULN	upper limit of normal
V_{ss}	volume of distribution at steady state

1. BACKGROUND

1.1 BACKGROUND ON BREAST CANCER

Globally, breast cancer is the second most common invasive malignancy and the most common cause of cancer-related mortality in women, with a 5-year survival rate following metastatic diagnosis of approximately15% (Jemal et al. 2011; Ferlay et al. 2012).

The treatment algorithm for patients with metastatic breast cancer (mBC) is based on several factors that include clinical, pathologic, and histologic characteristics such as the presence or absence of human epidermal growth factor 2 (HER2) amplification; hormone receptor status; prior response to and/or failure of hormonal agents; number and specific sites of metastatic disease; and treatment history in both the metastatic and adjuvant settings.

Several cytotoxic chemotherapy agents have shown activity in mBC, including anthracyclines, taxanes, gemcitabine, capecitabine, vinorelbine, eribulin, and ixabepilone. The response rates and progression-free intervals observed with these agents vary depending on the extent and type of prior therapy and extent of metastatic disease, as well as the biology of the disease. In general, anthracycline-based combination therapy and taxanes such as paclitaxel and docetaxel are believed to show the greatest activity (Piccart-Gebhart et al. 2008). Given the use of regimens containing anthracyclines in the adjuvant setting and the risk of cardiotoxicity associated with repeated courses, taxanes are now the most commonly used agent for patients with locally advanced or metastatic disease, particularly in the front-line setting (Greene and Hennessy 2014).

1.1.1 Triple-Negative Breast Cancer

Triple-negative breast cancer (TNBC) may be simply defined by the absence of immunostaining for estrogen receptor (ER), progesterone receptor (PR), and HER2. Overall, approximately 15%–20% of breast cancers are classified as TNBC. Large-scale comprehensive genomic analyses have characterized the heterogeneous nature of TNBCs and their diverse gene-expression patterns and underlying genomic changes, but these insights have not yet provided clear guidance for the identification of clinically effective targeted therapies currently under laboratory and clinical investigation. Unfortunately, TNBCs are more likely to have aggressive features, such as a high proliferative rate, and exhibit an invasive phenotype. Patients with metastatic TNBCs exhibit a poor clinical outcome, generally with rapid progression and a median overall survival (OS) of less than 1 year (Rodler et al. 2010).

Although TNBC may respond to chemotherapy, including taxanes, there are no targeted therapies with widespread global approval available for patients with this specific subtype of breast cancer. Recent Phase II and III clinical studies in TNBC have been disappointing, with the failure of iniparib and targeted therapies in combination with

chemotherapy (Carey et al. 2012; O'Shaughnessy et al. 2014). There is a pressing need for clinically active agents for the triple-negative subtype of mBC.

1.1.2 Taxanes and nab-Paclitaxel in Breast Cancer

Taxane-based regimens are considered a standard of care in first-line therapy for patients with mBC, including TNBC (Cardoso et al. 2012). No standard approach exists for second or further-line treatment, and options for cytotoxic chemotherapy are the same as those for other subtypes. Single-agent cytotoxic chemotherapeutic agents are generally regarded as the primary option for patients with metastatic TNBC, although combination chemotherapy may be used when there is aggressive disease and visceral involvement.

The role of paclitaxel in the treatment of breast cancer has been well established. The response rates for paclitaxel administered as a single agent to patients with mBC are approximately 25% in first-line treatment (Wilson et al. 1994; Seidman et al. 1995; Nabholtz et al. 1996; Gradishar et al. 2005).

Nanoparticle albumin-bound (nab)-paclitaxel is an albumin-bound formulation of paclitaxel that was developed to avoid the toxicities associated with the vehicles that are necessary for parenteral administration of solvent-based (sb)-paclitaxel (polyethylated castor oil and polysorbate 80). nab-Paclitaxel has a shorter infusion time (30 minutes) than sb-paclitaxel and can be administered without steroid or antihistamine premedication. In addition, it has an advantageous PK profile compared with sb-paclitaxel and achieves a 33% higher tumor uptake in preclinical models (Yardley et al. 2013). nab-Paclitaxel was approved for the treatment of mBC on the basis of a randomized Phase III study in which patients received either nab-paclitaxel or sb-paclitaxel (control) administered every 3 weeks (q3w) (n=460; Gradishar et al. 2005). The primary efficacy endpoint of the study was response rate. Patients receiving nab-paclitaxel achieved a higher response rate (21.5% vs. 11.1% for those receiving sb-paclitaxel). The median time to disease progression was longer for patients who received nab-paclitaxel than for those randomized to the sb-paclitaxel arm (23.0 vs. 16.9 weeks, respectively). Although a higher paclitaxel dose was achieved in the nab-paclitaxel arm, the incidence of Grade 4 neutropenia was significantly lower in the nab-paclitaxel arm than in the sb-paclitaxel (control) arm (9% vs. 22%, respectively). Grade 3 sensory neuropathy was more common with nab-paclitaxel than with sb-paclitaxel (10% vs. 2%, respectively) but was reported to be manageable and self-limiting with treatment interruption and dose reduction.

The pivotal study for nab-paclitaxel (Gradishar et al. 2005) enrolled patients who had not received a taxane for metastatic disease and who had not relapsed within 1 year of receiving a taxane for adjuvant disease. Forty-one percent (n=186) of the patients in the study received study drug as a first-line therapy. Among first-line patients, those who received nab-paclitaxel achieved a significantly higher response rate than those in the sb-paclitaxel group (34% vs. 18%, p=0.013) (Abraxis BioScience, Inc. 2006; EMA 2007).

There was also a trend for prolonged progression-free survival (PFS) among first-line patients in the experimental group, although this was not statistically significant (23.7 vs. 19.7 weeks, p=0.173). There was no benefit in OS among first-line patients (71.0 vs. 77.9 weeks, HR=1.215, p=0.264).

Based on the results of the pivotal study, nab-paclitaxel was approved for the treatment of mBC after failure of front-line combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Although it is not labeled for use in the front-line metastatic setting, National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) clinical practice guidelines include nab-paclitaxel as a standard of care that may be administered as a single agent to patients with recurrent or metastatic breast cancer (Cardoso et al. 2014; NCCN 2014; see Section 3.3.2).

1.2 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab (TECENTRIQ™, formerly known as MPDL3280A) is a humanized immunoglobulin IgG1 mAb consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human programmed death–ligand 1 (PD-L1) and inhibits its interaction with its receptors, programmed death–1 (PD-1) and B7.1 (CD80, B7-1). Both of these interactions are reported to provide inhibitory signals to T cells.

Atezolizumab is being investigated as a potential therapy against solid tumors and hematologic malignancies in humans. Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer, *small-cell lung cancer, and TNBC.*

1.2.1 Summary of Nonclinical Studies

The nonclinical strategy of the atezolizumab program was to demonstrate in vitro and in vivo activity, to determine in vivo pharmacokinetic (PK) behavior, to demonstrate an acceptable safety profile, and to identify a Phase I starting dose. Comprehensive pharmacology, PK, and toxicology evaluations were, thus, undertaken with atezolizumab.

The safety, pharmacokinetics, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab with cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, pharmacokinetics, and toxicokinetics of atezolizumab.

Overall, the nonclinical pharmacokinetics and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of downmodulating the PD-L1/PD-1 pathway and supported entry into clinical studies in patients.

Refer to the atezolizumab Investigator's Brochure for details on the nonclinical studies.

1.2.2 Clinical Experience with Atezolizumab

1.2.2.1 Ongoing Clinical Studies

Atezolizumab is currently being tested in multiple Phase I, II, and III studies, both as monotherapy and in combination with several anti-cancer therapies (see the atezolizumab Investigator's Brochure for study descriptions). Much of the safety and efficacy data summarized below are from Phase Ia Study PCD4989g, a multicenter, first-in-human, open-label, dose-escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered as a single agent by IV infusion q3w to patients with locally advanced or metastatic solid malignancies or hematologic malignancies.

1.2.2.2 Clinical Safety as a Single Agent

As of 15 December 2015, single-agent safety information was available for 629 safety-evaluable patients enrolled in the Phase Ia Study PCD4989g from all lines of therapy, including for the following tumor types: NSCLC=89, urothelial carcinoma=95, renal cell carcinoma (RCC)=72, TNBC=111, and small-cell lung cancer=17. These safety-evaluable patients received a range of atezolizumab doses: ≤ mg/kg q3w=9, 3 mg/kg q3w=3, 10 mg/kg q3w=36, 15 mg/kg q3w=236, 20 mg/kg q3w=46, and 1200 mg q3w=199. To date, no maximum tolerated dose (MTD), dose-limiting toxicities (DLTs), or clear dose-related trends in the incidence of adverse events have been determined.

Adverse Events

Of the 629 treated patients in Study PCD4989g, 619 patients (98.4%) experienced an adverse event regardless of attribution to atezolizumab. Treatment-related adverse events (per investigator's assessment of causality) were reported in 444 patients (70.6%). Approximately half of the 629 patients (50.2%) experienced an adverse event of Grade 3–4 in severity, based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0).

The most frequently observed adverse events (≥ 10% of patients) included fatigue, decreased appetite, nausea, pyrexia, constipation, cough, dyspnea, diarrhea, headache, back pain, vomiting, anemia, arthralgia, rash, insomnia, asthenia, abdominal pain, chills, pruritus, generalized pain, and peripheral edema.

Most of the Grade 3–4 adverse events occurred in ≤3 patients (≤0.5%). Those that were reported in ≥10 patients (≥1.6%) included dyspnea (4.8%), anemia (4.6%), hyponatremia (3.8%), fatigue (3.2%), asthenia (2.5%), dehydration (2.4%), hyperglycemia, AST increased and abdominal pain (1.9% each), ALT increased (1.7%), and urinary tract infection (1.6%). Related Grade 3–4 events were reported in 13.7% of patients, with fatigue and asthenia (1.3% each), AST increased and dyspnea (1.1% each), and hyponatremia (0.8%) as the most frequently occurring (≥ 0.8% or ≥5 patients).

Overall, atezolizumab as a single agent was well tolerated, with low rates of treatment-related Grade 3–4 events, Grade 5 events, treatment-related serious adverse events, and adverse events leading to treatment withdrawals. Safety findings in the TNBC cohort of Study PCD4989g are consistent with the data observed in the overall study population.

Refer to the Atezolizumab Investigator's Brochure for additional details regarding clinical safety.

Immune-Mediated Adverse Events

Immune-mediated adverse events are consistent with the role of the PD-L1/PD-1 pathway in regulating peripheral tolerance. Given the mechanism of action of atezolizumab, events associated with inflammation and/or *immune-mediated* adverse events are closely monitored in the atezolizumab clinical program. *Immune-mediated* adverse events associated with atezolizumab include dermatologic, hepatic, endocrine, gastrointestinal, respiratory, and neurological events.

Refer to the Atezolizumab Investigator's Brochure for additional details regarding *immune-mediated* adverse events observed in patients treated with atezolizumab.

1.2.2.3 Clinical Safety in Combination with Chemotherapy

Study GP28328 is a Phase Ib study of the safety and pharmacology of atezolizumab administered with bevacizumab and/or chemotherapy in patients with advanced solid tumors. Arm A is evaluating 1200 mg atezolizumab + bevacizumab administered q3w in patients with multiple solid tumor types, including separate expansion cohorts in colorectal cancer (CRC) and renal cell carcinoma (RCC). Arm B is evaluating atezolizumab + bevacizumab and oxaliplatin, leucovorin, and 5-fluorouracil (FOLFOX) administered every 2 weeks (q2w) in patients with multiple solid tumor types, including breast cancer. Arms C, D, and E are evaluating atezolizumab administered q3w in chemotherapy-naïve non–small cell cancer (NSCLC) patients in combination with carboplatin + paclitaxel, carboplatin + pemetrexed, and carboplatin + nab-paclitaxel, respectively. Arm F is evaluating atezolizumab administered q2w in combination with weekly nab-paclitaxel in patients with TNBC. Patients in Arms B, C, D, E, and F received cytotoxic chemotherapy in combination with atezolizumab.

As of 14 January 2016, preliminary safety data were available from 208 patients in Study GP28328 (n=144 in arms B, C, D, E, and F and n=64 in arm A). Of these patients, 144 patients received cytotoxic chemotherapy in combination with atezolizumab and 100.0% of patients reported one or more adverse effects. The most frequently reported adverse effects (≥10% of patients), regardless of attribution to study treatment, included fatigue, nausea, diarrhea, neutropenia, peripheral neuropathy, constipation, vomiting, cough, anemia, arthralgia, headache, alopecia, pyrexia and decreased appetite. The most frequently reported adverse effects were mainly assessed as Grade 1 or Grade 2 in maximum severity (excluding neutropenia). Fifty-two patients (36.1%) discontinued a study treatment (i.e., chemotherapy or atezolizumab) due to an adverse effect, including 9 patients (6.25%) who discontinued atezolizumab because of an adverse effect. The most commonly reported adverse effects leading to discontinuation of a study treatment were bone marrow suppression (neutropenia [10.4%] and thrombocytopenia [4.2%]), peripheral neuropathy (5.6%), and fatigue (4.9%).

Safety data from 32 TNBC patients (Arm F) in Study GP28328 indicate that the combination appears to be well tolerated and is consistent with the known risks of nab-paclitaxel and atezolizumab (Adams et al. 2016). Nineteen (19% of patients (6/32) experienced adverse events leading to discontinuation of nab-paclitaxel and 1 patient discontinued atezolizumab after prolonged asymptomatic Grade 2 AST elevation. The most frequent AEs attributed to atezolizumab (≥10%) included fatigue, pyrexia, diarrhea, nausea, alopecia, pruritis, headache, peripheral neuropathy and peripheral sensory neuropathy, and decreased neutrophil count.

The safety data to date suggest that atezolizumab can be safely combined with standard chemotherapy treatments. Several combinations have been evaluated and have been generally well-tolerated. Atezolizumab in combination with nab-paclitaxel has not been associated with additive severe (Grade 3 or higher) toxicities compared to that which is observed with nab-paclitaxel or atezolizumab alone. The AEs observed for atezolizumab in combination with chemotherapy are consistent with the known risks of each study treatment.

Refer to the Atezolizumab Investigator's Brochure for additional details regarding clinical safety.

1.2.3 Clinical Activity

Anti-tumor activity, including Response Evaluation Criteria in Solid Tumors (RECIST)–based responses (i.e., RECIST v1.1 responses), have been observed in patients with different tumor types, including NSCLC, RCC, melanoma, bladder cancer, CRC, head and neck cancer, gastric cancer, breast cancer (including TNBC), and sarcoma treated with atezolizumab monotherapy in Study PCD4989g. Among 386 evaluable patients enrolled prior to 1 July 2013 (data cutoff of 1 January 2014), there were 47 patients with responses with a median duration of response of 75.7 weeks (range: 11.7+ to 85.9+ weeks, where "+" denotes a censored value). The majority of

these responses have been durable, with 72.3% (34 of 47 patients) of responses ongoing as of the clinical cutoff date.

Analyses of tumor-infiltrating immune cells (ICs) for PD-L1 expression on baseline tumor tissue have been performed for Study PCD4989g. Preliminary results from Study PCD4989g suggest that PD-L1 expression in ICs is likely to be associated with response to atezolizumab.

Clinical Activity in Patients with TNBC

Single Agent Activity

As of 2 September 2014, clinical activity analyses have been performed on 21 patients with PD-L1–selected (IC2/3) TNBC in Study PCD4989g who received atezolizumab treatment by 21 July 2014 (Emens et al. 2014).

Unconfirmed responses were recorded for 5 patients. Two of these patients experienced a complete response and 3 patients experienced a partial response. As of 2 September 2014, 4 of these 5 patients were still responding and 1 patient experienced disease progression. The median duration of response has not been reached. The Kaplan-Meier estimated overall 24-week PFS rate was 33% (95% CI: 12% to 53%).

Activity in Combination with Chemotherapy

Study GP28328 is a multi-arm Phase 1b study evaluating the safety and preliminary efficacy of a number of combinations of atezolizumab and chemotherapy with or without bevacizumab in patients with locally advanced or metastatic solid tumors. Arm F of the study is testing the combination of atezolizumab and nab-paclitaxel in female patients with metastatic TNBC. Patients receive 800 mg of atezolizumab on Days 1 and 15 of every 28-day cycle plus nab-paclitaxel (125 mg/m^2) on Days 1, 8, and 15 of every 28-day cycle. Up to two prior cytotoxic regimens for metastatic disease are allowed.

On the basis of a clinical cut-off of 14 January 2016, safety and preliminary efficacy data were available for 32 patients (Adams et al. 2016). Of the efficacy-evaluable patients, 13 received the treatment combination as first-line therapy, and 19 had received $\geq$1 prior cytotoxic regimens for metastatic disease. 88% had previously received taxanes. In the overall efficacy-evaluable population, 12 patients (38% [95% CI: 2% to 56%]) achieved confirmed RECIST v1.1 responses. Clinical responses were observed in patients with PD-L1 IC1/2/3/ tumors as well as in those with PD-L1 IC0.

Six of thirteen patients (46% [95% CI: 19% to 75%]) who received atezolizumab plus nab-paclitaxel as 1L therapy achieved investigator-assessed confirmed responses, comprising one complete response and five partial responses.

Two out of nine (22% [95% CI: 3%, to 60%]) and four out of 10 patients (40% [95% CI: 12% to 74%]) who received study treatment as 2L and 3L+ therapy, respectively, achieved investigator-assessed confirmed responses.

The median progression-free survival, overall survival, and duration of response had not yet been reached at the time of the cut-off date.

1.2.4 Clinical Pharmacokinetics and Immunogenicity

On the basis of available preliminary PK data (0.03–20 mg/kg), atezolizumab appeared to show linear pharmacokinetics at doses ≥1 mg/kg. For the 1 mg/kg and 20 mg/kg dose groups, the mean apparent clearance (CL) and the mean volume of distribution at steady state (V_{ss}) had a range of 3.11 to 4.14 mL/kg and 48.1 to 67.0 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

The development of anti-therapeutic antibodies (ATAs) has been observed in patients in all dose cohorts and was associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). The development of detectable ATAs has not had a significant impact on pharmacokinetics for doses from 10 to 20 mg/kg. Patients dosed at the 10, 15, and 20 mg/kg dose levels have maintained the expected target trough levels of drug despite the detection of ATAs. To date, no clear relationship between detection of ATAs and adverse events or infusion reactions has been observed.

1.2.5 Rationale for Atezolizumab Dosage

The fixed dose of 840 mg (equivalent to an average body weight–based dose of 15 mg/kg 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 nonclinical tissue distribution data in tumor-bearing mice, target-receptor occupancy in the tumor, the observed atezolizumab interim pharmacokinetics in humans, and other factors. The target trough concentration (C_{trough}) was projected to be 6 μg/mL on the basis of several assumptions, including the following: 1) 95% tumor-receptor saturation is needed for efficacy, and 2) the tumor interstitial fluid (TIF) concentration to plasma ratio is 0.30 based on tissue distribution data in tumor-bearing mice.

The atezolizumab dose is also informed by available clinical activity, safety, pharmacokinetics, and immunogenicity data. Anti-tumor activity has been observed across doses from 1 mg/kg to 20 mg/kg. The maximum tolerated dose (MTD) of atezolizumab was not reached, and no DLTs have been observed at any dose in Study PCD4989g. Available preliminary PK data (0.03–20 mg/kg) from Study PCD4989g suggest that for doses ≥1 mg/kg q3w, atezolizumab generally exhibits pharmacokinetics that are both linear and consistent with typical IgG1 antibodies. Detectable ATAs were observed in patients at all dose levels but were associated with

changes in pharmacokinetics for some patients in the lower dose cohorts only (0.3, 1, and 3 mg/kg q3w). It is unclear from currently available data in these lower dose cohorts whether administration of higher doses to patients with both detectable ATAs and reduced exposure would necessarily restore exposure to expected levels. Available data suggest that the development of detectable ATAs does not appear to have a significant impact on the pharmacokinetics for doses from 10 to 20 mg/kg q3w in most patients. Correspondingly, patients dosed at the 10, 15, and 20 mg/kg q3w dose levels have maintained target trough levels of drug despite the detection of ATAs. Currently available PK and ATA data suggest that the 15 mg/kg atezolizumab q3w regimen (or fixed-dose equivalent) would be sufficient to maintain $C_{trough} \geq 6$ μg/mL and further safeguard against both interpatient variability and the potential effect of ATAs that could lead to subtherapeutic levels of atezolizumab relative to the 10 mg/kg atezolizumab q3w regimen (or fixed-dose equivalent). From inspection of available observed C_{trough} data, moving further to the 20 mg/kg atezolizumab q3w regimen does not appear to be warranted to maintain targeted C_{trough} levels relative to the proposed 15 mg/kg atezolizumab q3w level.

Simulations (Bai et al. 2012) do not suggest any clinically meaningful differences in exposure following a fixed dose or a dose adjusted for weight. On the basis of this analysis, a fixed dose of 1200 mg has been selected for when atezolizumab is administered q3w (equivalent to an average body weight–based dose of 15 mg/kg). For the q2w dosing interval used in this study, the corresponding fixed dose is 800 mg.

Because atezolizumab is formulated at a concentration of 60 mg/mL, 800 mg corresponds to a volume of 13.33 mL. In the interest of simplifying administration, the exact dose used in this study will be 840 mg, corresponding to a volume of 14 mL, which can be accurately administered with a single syringe. The 840-mg dose is not expected to result in meaningfully different exposures compared with an 800-mg dose.

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

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Atezolizumab

Encouraging clinical data emerging in the field of tumor immunotherapy have demonstrated that therapies focused on enhancing T-cell responses against cancer can result in a significant survival benefit in patients with advanced malignancies (Hodi et al. 2010; Kantoff et al. 2010; Chen et al. 2012).

PD-L1 is an extracellular protein that downregulates immune responses primarily in peripheral tissues through binding to its two receptors: PD-1 and B7.1. Many human tumors have been found to overexpress PD-L1, which acts to suppress anti-tumor immunity. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, which is sustained in states of chronic stimulation such as in chronic infection or cancer

(Blank et al. 2005; Keir et al. 2008). Ligation of PD-L1 with PD-1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells. B7.1 is a molecule expressed on antigen-presenting cells and activated T cells. PD-L1 binding to B7.1 on T cells and antigen-presenting cells can mediate downregulation of immune responses, including inhibition of T-cell activation and cytokine production (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, interruption of the PD-L1/PD-1 and the PD-L1/B7.1 pathways represents an attractive strategy to reinvigorate tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies, including patients with TNBC (see Section 1.2.3).

The observation that high CD8+ T-cell density in primary breast tumors is correlated with improved OS, and that metastatic TNBC tumors have fewer tumor-infiltrating lymphocytes than their matched primary tumors, suggests that the immune system is able to partially restrain human breast cancer but that immune suppression becomes more prevalent with increasing growth and metastasis (Cimino-Mathews et al. 2013; Adams et al. 2014; Loi 2014). The identification of immune-enriched subtypes of TNBC underscores the potential to harness preexisting host anti-tumor immunity in this disease (Lehmann et al. 2011). In this setting, invigorating T-cell activity with atezolizumab may be an effective treatment strategy.

Atezolizumab has been generally well tolerated (see Sections 1.2.2.2 and 1.2.2.3); adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, hypothyroidism, hepatitis/transaminitis, colitis, and myasthenia gravis, have been observed in ongoing studies of atezolizumab. To date, the majority of these events have been manageable without requiring treatment discontinuation.

1.3.2 nab-Paclitaxel and Combination Treatment with Atezolizumab

Because of the opportunity to avoid immunosuppressive effects from steroids, nab-paclitaxel potentially represents a preferred chemotherapy for combination with immunomodulatory drugs such as atezolizumab.

Preliminary safety data from Study GP28328 indicate that atezolizumab can be safely combined with chemotherapy (several combinations have been evaluated and determined to be well tolerated; refer to the Atezolizumab Investigator's Brochure for details). Specifically, atezolizumab was tested in combination with carboplatin+nab-paclitaxel in patients with previously untreated NSCLC and in

combination with nab-paclitaxel in patients with TNBC. No exacerbation of chemotherapy-associated adverse events was reported.

The safety of single-agent nab-paclitaxel in patients with mBC has been demonstrated in several studies. Although a higher paclitaxel dose was achieved in the nab-paclitaxel arm in the Phase III study comparing sb-paclitaxel to nab-paclitaxel, the incidence of Grade 4 neutropenia was significantly lower in the nab-paclitaxel arm than in the sb-paclitaxel (control) arm (9% vs. 22%, respectively; Gradishar et al. 2005). Grade 3 sensory neuropathy was more common with nab-paclitaxel than with sb-paclitaxel (10% vs. 2%, respectively), but was reported to be manageable and self-limiting with treatment interruption and dose reduction.

There is increasing evidence that in addition to causing tumor cell death, certain conventional chemotherapies may have immunogenic effects (Zitvogel et al. 2008). Clinical evidence exists to suggest that T-cell and NK-cell functions are enhanced in patients with breast cancer (Stage II/III) treated with taxanes compared with patients who did not receive taxanes (Carson et al. 2004). In addition, tumor cell killing by cytotoxic chemotherapy can be expected to expose the immune system to high levels of tumor antigens, and invigorating tumor-specific T-cell immunity in this setting by inhibiting PD-L1/PD-1 signaling may result in deeper and more durable responses compared with standard chemotherapy alone.

Further rationale for the choice of nab-paclitaxel as the comparator and for the selected dose of nab-paclitaxel is provided in Sections 3.3.2 and 3.3.3.

In summary, combination treatment with atezolizumab and nab-paclitaxel offers the potential for clinical benefit in patients with mBC.

2. OBJECTIVES

The following objectives will be assessed in patients with metastatic or locally advanced triple-negative adenocarcinoma of the breast who have not received prior systemic therapy for mBC.

2.1 EFFICACY OBJECTIVES

The following efficacy objectives will be evaluated in both the intent-to-treat (ITT) population (i.e., all randomized patients) and the subpopulation with PD-L1–selected tumor status.

2.1.1 Co-Primary Efficacy Objectives

- To evaluate the efficacy of atezolizumab + nab-paclitaxel compared with placebo+nab-paclitaxel as measured by PFS (per investigator assessment using RECIST v1.1)

- To evaluate the efficacy of atezolizumab + nab-paclitaxel compared with placebo + nab-paclitaxel as measured by overall survival (OS)

2.1.2 Secondary Efficacy Objectives

- To evaluate the efficacy of atezolizumab+nab-paclitaxel compared with placebo+nab-paclitaxel as measured by objective response rate (ORR; per investigator assessment using RECIST v1.1)
- To evaluate the efficacy of atezolizumab+nab-paclitaxel compared with placebo+nab-paclitaxel as measured by duration of objective response (DOR; per investigator using RECIST v1.1) among patients with an objective response
- To evaluate patient-reported outcomes (PROs) of health status/health-related quality of life (HRQoL) associated with atezolizumab+nab-paclitaxel compared with placebo+nab-paclitaxel, as measured by the time to deterioration (TTD) in Items 29 and 30 of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30)

2.2 SAFETY OBJECTIVES

The safety objectives for this study are as follows:

- To evaluate the safety and tolerability of atezolizumab+nab-paclitaxel compared with placebo+nab-paclitaxel
- To evaluate the incidence of ATAs against atezolizumab and to explore the potential relationship of the immunogenicity response with pharmacokinetics, pharmacodynamics, safety, and efficacy

2.3 PHARMACOKINETIC OBJECTIVES

The PK objectives for this study are as follows:

- To characterize the pharmacokinetics of atezolizumab when administered with nab-paclitaxel
- To characterize the pharmacokinetics of nab-paclitaxel when administered with atezolizumab

2.4 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate PROs of function and disease/treatment-related symptoms associated with atezolizumab+nab-paclitaxel compared with placebo+nab-paclitaxel, as measured by the EORTC QLQ-C30 and its breast cancer module (QLQ-BR23)
- To evaluate health utility as measured by the EuroQoL 5 Dimension (EQ-5D-5L) questionnaire for health economic modeling of atezolizumab+nab-paclitaxel compared with placebo+nab-paclitaxel
- To assess predictive, prognostic, and pharmacodynamic (PD) exploratory biomarkers in archival and/or fresh tumor tissue and blood and their association with disease status and/or response to study treatment

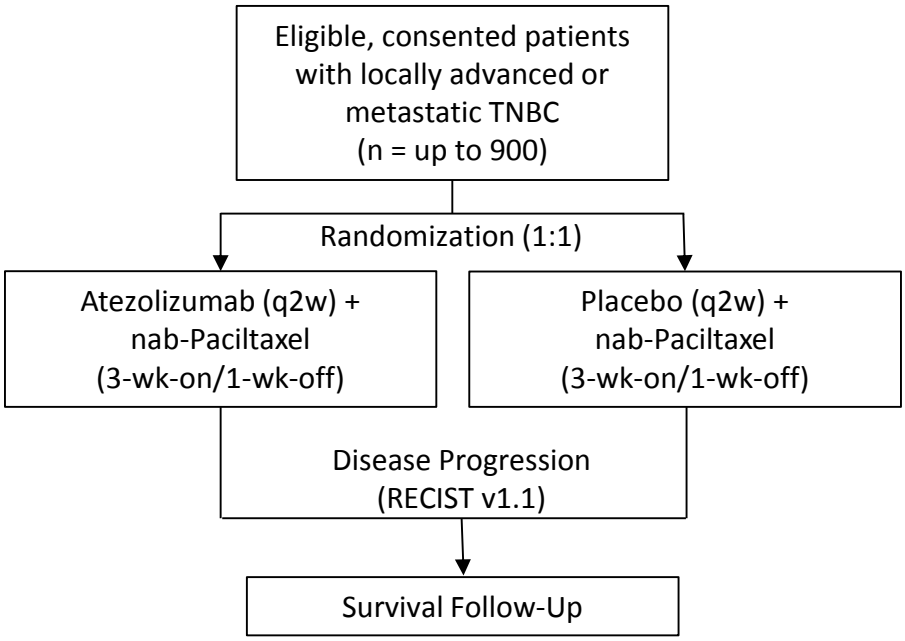
3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This is a Phase III, global, multicenter, double-blind, two-arm, randomized, placebo-controlled study designed to evaluate the efficacy and safety of atezolizumab administered with nab-paclitaxel compared with placebo in combination with nab-paclitaxel in patients with locally advanced or metastatic TNBC who have not received prior systemic therapy for mBC.

Patients who have a known ER-positive, PR-positive, or HER2-positive status are not eligible to participate in the study. Patients who have an unknown ER, PR, or HER2 status, and for whom determination of status is not possible, are also not eligible for this study. Figure 1 illustrates the study design.

Figure 1 Study Schema



ECOG=Eastern Cooperative Oncology Group; PS=performance status; q2w=every 2 weeks; RECIST v1.1=Response Evaluation Criteria in Solid Tumors, version 1.1; TNBC=triple-negative breast cancer; wk=week.

A representative formalin-fixed paraffin-embedded (FFPE) tumor specimen with an associated pathology report documenting ER, PR, and HER2 negativity must be submitted prior to enrollment. Tumor tissue should be of good quality based on total and viable tumor content and must be prospectively evaluated for PD-L1 expression prior to enrollment. A tumor specimen obtained from relapsed metastatic or locally advanced disease must also be submitted, if clinically feasible.

Up to 900 patients will be enrolled at approximately 257 sites globally. Patients will be randomized in a 1:1 ratio to receive atezolizumab (840 mg) or placebo IV infusions on Days 1 and 15 of every 28-day cycle plus nab-paclitaxel (100 mg/m^2) administered via IV infusion on Days 1, 8, and 15 of every 28-day cycle. Randomization will be stratified by the following three factors:

- Presence of liver metastases (yes vs. no)
- Prior taxane treatment (yes vs. no)
- Tumor PD-L1 status (IC0 vs. IC1/2/3)

In the absence of disease progression or unacceptable toxicity, nab-paclitaxel will be administered for a target of at least 6 cycles, with no maximum. nab-Paclitaxel and atezolizumab or placebo may be discontinued for toxicity independently of each other in the absence of disease progression. The Sponsor, patients, and investigators will not be aware of each patient's treatment assignment prior to unblinding (see Section 4.2). Once treatment unblinding has occurred, investigators may request crossover to the atezolizumab+nab-paclitaxel arm for patients who were randomized to the placebo+nab-paclitaxel arm, who have not yet experienced disease progression, and who have not started any other systemic anti-cancer agents beyond those offered in this study. Patients must still meet the safety-related eligibility criteria for the study prior to initiating atezolizumab.

In order to interrogate the mechanism of action of the drug combination in the tumor microenvironment and possible resistance mechanisms, tumor tissue may be optionally collected pre-dose on Cycle 2, Day 1.

To test the mechanisms of resistance to the drug combination in the tumor microenvironment, all patients will undergo a mandatory tumor biopsy collection (if clinically feasible) at first evidence of radiographic disease progression per RECIST v1.1. DNA sequencing of cancer-related genes will be performed on these specimens by Foundation Medicine, Inc. (Cambridge, MA). The research report may be obtained by the Investigator, if desired, directly from Foundation Medicine, Inc. and will describe results from investigational tests that are not intended to be used to guide future treatment decisions.

Tumor assessments per RECIST v1.1 (see Appendix 3) will be performed approximately every 8 weeks (±1 week) for the first 12 months after Cycle 1, Day 1 and every 12 weeks (±1 week) thereafter until disease progression or treatment discontinuation, whichever is later. Tumor assessments will be performed on the specified schedule regardless of treatment delays.

Treatment will be discontinued upon radiographic disease progression per RECIST v1.1. For equivocal findings of progression (e.g., very small or uncertain new lesions or lymph nodes; 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.

For estimation of PFS, ORR, and DOR, tumor response will be based on RECIST v1.1 (see Appendix 3). The imaging data used for tumor assessment will be collected by the Sponsor to enable centralized, independent review of response endpoints by an Independent Review Committee (IRC).

All patients will be followed for survival approximately every 3 months after the treatment discontinuation visit until death, withdrawal of consent, loss to follow-up, or study termination by the Sponsor. In addition, information regarding use of subsequent anti-cancer agents for metastatic TNBC during the survival follow-up period will be collected.

The pharmacokinetics of atezolizumab and nab-paclitaxel will be determined (see Appendix 2).

Safety assessments will include the incidence, nature, and severity of adverse events and laboratory abnormalities graded per NCI CTCAE v4.0. Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry. Serum samples will be collected to monitor atezolizumab pharmacokinetics and to detect the presence of antibodies to atezolizumab. Patient samples, including tumor tissues, as well as serum and plasma and whole blood, will be collected for exploratory biomarker assessments.

A schedule of assessments is provided in Appendix 1.

3.1.1 Independent Data Monitoring Committee

An independent data monitoring committee (iDMC) will monitor safety and study conduct on a periodic basis. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. The iDMC will meet approximately every 6 months from the point of first patient in (FPI) to review unblinded safety and study conduct data prepared by an independent Data Coordinating Center (iDCC). The safety data will include demographic data, adverse events, serious adverse events, and relevant laboratory data.

Following each data review, the iDMC will provide recommendations to the Sponsor as to whether the study should continue or be amended, or whether the study should be stopped on the basis of safety (i.e., evidence of harm). The Sponsor's Data Review Board (DRB; a group consisting of employees of the Sponsor empowered to make critical decisions) will make a decision on the basis of the iDMC's recommendations. The final decision will rest with the Sponsor.

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

There are two interim analyses planned for the co-primary endpoint of OS. No interim efficacy analysis is planned for the co-primary endpoint of PFS. The final analysis of PFS will occur at the time of the first OS interim analysis. The first interim analysis of OS together with the final analysis of PFS, and if necessary, the second interim analysis, will be carried out by the iDCC in a blinded fashion and provided to the iDMC. The iDMC will review these data and will recommend or not recommend to release the trial results and to unblind the study to the sponsor. The DRB of the sponsor will either accept or reject this recommendation. Details are specified in the iDMC charter.

3.2 END OF STUDY

The end of the study is expected to occur about 53 months after FPI when approximately the pre-planned number of deaths will have been observed (see Section 6.1.3).

OS events will be monitored throughout the course of the study, and study timelines might be updated as indicated.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Atezolizumab Dosage

The fixed dose of 840 mg q2w was selected on the basis of both nonclinical studies and available clinical data from Study PCD4989g (see Section 1.2.5).

3.3.2 Rationale for Use of nab-Paclitaxel Comparator

The taxane class of cytotoxic agents (paclitaxel, docetaxel, nab-paclitaxel) have significant antitumor activity in breast cancer. Although combinations of cytotoxic agents may be administered to patients with severe symptomatic disease or imminent visceral crisis, combination regimens are associated with increased toxicity and have not demonstrated an OS benefit compared with the sequential administration of single agents. The response rates and progression-free intervals observed with available agents vary depending on the extent and type of prior therapy and extent of metastatic disease, as well as the biology of disease. In general, taxanes such as paclitaxel and docetaxel are believed to show the greatest activity and are now the most commonly used agents for patients with locally advanced or metastatic disease, particularly in the front-line setting (Greene and Hennessy 2014).

nab-Paclitaxel is an albumin-bound formulation of paclitaxel that was developed to mitigate the significant toxicities associated with the vehicles that are necessary for parenteral administration of solvent-based (sb) paclitaxel (polyethylated castor oil and polysorbate 80). In addition, it has an advantageous PK profile compared with

sb-paclitaxel and achieves a 33% higher tumor uptake in preclinical models (Yardley et al. 2013). Steroids are routinely administered with sb-paclitaxel to lower the risk of hypersensitivity allergic reactions, but steroid premedication is not required with the use of nab-paclitaxel.

nab-Paclitaxel received a label from the U.S. Food and Drug Administration (FDA) for the treatment of mBC after failure of front-line combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, based on the pivotal Phase III study performed by Gradishar et al. (2005). However, in real-world practice, nab-paclitaxel is used throughout the continuum of care for patients with mBC. Both the NCCN and ESMO clinical practice guidelines include nab-paclitaxel as a standard of care that may be administered as a single agent to patients with newly diagnosed recurrent or metastatic breast cancer (Cardoso et al. 2014; NCCN 2014).

The recently reported randomized Phase III GeparSepto study compared the efficacy of nab-paclitaxel versus paclitaxel when the agents were administered to women with early-stage breast cancer as part of a neoadjuvant regimen (Untch et al. 2014). Overall, 38% of patients who received nab-paclitaxel achieved a pathologic complete response (pCR), compared with 29% of those who received conventional paclitaxel. Notably, the pCR rate among patients with TNBC who received nab-paclitaxel was twice that of women who received paclitaxel. The GeparSepto study was started with a weekly nab-paclitaxel dose of 150 mg/m^2, which was lowered to 125 mg/m^2 after an interim safety analysis determined that the higher dose was not tolerated. Although these data are from the neoadjuvant setting, they support the position that nab-paclitaxel constitutes an appropriate standard of care for women with TNBC and a suitable comparator in the present study.

nab-Paclitaxel represents the preferred chemotherapy for combination with immunomodulatory drugs such as atezolizumab because of both 1) the opportunity to avoid immunosuppressive effects from the concurrent steroid use required with other taxanes, and 2) the high rate of tumor cell death achieved by nab-paclitaxel, which can be expected to expose the immune system to high levels of tumor antigens, thereby enhancing the degree and duration of cancer-specific T-cell immunity by inhibition of PD-L1-mediated immune suppression by atezolizumab.

3.3.3 Rationale for nab-Paclitaxel Dosage and Regimen

The q3w dose of nab-paclitaxel (260 mg/m^2) in the FDA label established from the Phase III study comparing sb-paclitaxel with nab-paclitaxel (Gradishar et al. 2005) is not generally used in current clinical practice. Instead, weekly dosing of nab-paclitaxel is the most commonly utilized schedule given the better tolerability and suggestions of increased efficacy of weekly dosing compared to q3w dosing.

The superiority of the weekly regimen of nab-paclitaxel was first demonstrated in a randomized Phase II study conducted in patients with previously untreated mBC

(Gradishar et al 2009). In the four arms of this study, the ORRs were 37% with q3w nab-paclitaxel, 45% with weekly nab-paclitaxel 100 mg/m^2 (3-weeks-on/1-week-off schedule), 49% with weekly nab-paclitaxel 150 mg/m^2 (3-weeks-on/1-week-off schedule), and 35% with q3w docetaxel 100 mg/m^2 (independent radiologist assessment), illustrating the anti-tumor advantages of the weekly dosing schedule. PFS was 11.0 months, 12.8 months, 12.9 months, and 7.5 months (independent radiologist assessment) for each of the four arms, respectively. The difference in PFS and ORR between the 100 and 150 mg/m^2 weekly dose levels of nab-paclitaxel was not statistically significant, but patients receiving the higher dose experienced a greater incidence of Grade 3 or 4 neutropenia (44% vs. 25%) and Grade 3 sensory neuropathy (14% vs. 8%).

Subsequent clinical studies have not clearly demonstrated that weekly doses of nab-paclitaxel greater than 100 mg/m^2 are more efficacious. Furthermore, higher doses of nab-paclitaxel are associated with greater toxicities. The CALGB 40502 Phase III study randomized patients with chemotherapy-naive, HER2-negative mBC to receive weekly paclitaxel, weekly nab-paclitaxel at a higher dose of 150 mg/m^2, or ixabepilone, with all agents given in combination with bevacizumab, and on a 3-weeks-on/1-week-off schedule (Rugo et al. 2012). Nab-paclitaxel was not tolerable at this higher weekly dose and did not improve PFS in any subtype over standard dose paclitaxel, leading to the conclusion that 150 mg/m^2 should not be utilized.

To date, 100 mg/m^2 of nab-paclitaxel weekly on a 3-weeks-on/1-week-off schedule is the best-studied and tolerated dose, with suggestions of improved efficacy and decreased toxicities in mBC compared with both higher weekly doses and the every 3-week dosing schedule of the same drug. As a result, subjects on this study will receive nab-paclitaxel 100 mg/m^2 via IV infusion on Days 1, 8, and 15 of an every 28-day cycle. In the absence of disease progression or unacceptable toxicity, nab-paclitaxel will be administered for a target of six cycles, with no maximum number of cycles mandated by the study.

3.3.4 Rationale for Collection of Archival and Pre-Treatment Tumor Specimens

A portion of archival and pre-treatment tumor specimens will be used for confirmation of ER, PR, and HER2 triple-negative status by a central testing laboratory.

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-1 therapy (Herbst et al. 2014). This correlation is also observed with atezolizumab in preliminary data from Phase Ia Study PCD4989g (see Section 1.2.3).

To evaluate the potential predictive significance of PD-L1 expression in TNBC, representative tumor specimens in paraffin blocks (preferred) or at least 20 unstained slides (with an associated pathology report) must be submitted prior to

study randomization. Patients will be stratified on the basis of tumor PD-L1 expression determined by IHC (IC0 vs. IC1/2/3).

To enable evaluation of the potential for prior therapies to alter expression of PD-L1, patients will also be required to submit tumor specimens obtained from relapsed metastatic or locally advanced disease if clinically feasible, in addition to archival tumor tissue.

In addition to the assessment of PD-L1 status, other exploratory markers such as potential predictive and prognostic markers related to the clinical benefit of atezolizumab +nab-paclitaxel, tumor immunobiology, mechanisms of resistance, or tumor type, may also be analyzed.

3.3.5 Rationale for the Collection of Biopsy at the Time of Radiographic Progression

All patients will undergo a mandatory tumor biopsy collection (if clinically feasible) at the first evidence of radiographic disease progression. Analysis of biological material (including but not restricted to DNA and RNA) from these specimens will help elucidate molecular changes associated with resistance to or disease progression after treatment with nab-paclitaxel or nab-paclitaxel+atezolizumab in patients with TNBC. DNA sequencing of cancer-related genes will be performed on these specimens by Foundation Medicine, Inc. (Cambridge, MA). The research report may be obtained by the Investigator, if desired, directly from Foundation Medicine, Inc. and will describe results from investigational tests that are not intended to be used to guide future treatment decisions.

3.3.6 Rationale for Optional Biopsies

Optional tumor tissue samples collected at Cycle 2, Day 1 will be analyzed for molecular changes occurring after treatment with nab-paclitaxel+placebo or nab-paclitaxel+atezolizumab. These analyses will help elucidate early mechanisms of action and resistance to study treatment. The conclusions obtained from these studies will aid in the development of therapies to improve anti-tumor immune response in patients with TNBC.

3.3.7 Rationale for Blood Sampling for Biomarkers

Changes in different blood biomarkers may provide evidence for biologic activity of atezolizumab in combination with nab-paclitaxel in humans and may allow for the development of a blood-based biomarker to help predict which patients may benefit from atezolizumab + nab-paclitaxel. An exploratory objective of this study is to evaluate changes in surrogate biomarkers in blood samples.

In addition, potential correlations of these PD markers with the dose, safety, and anti-tumor activity of atezolizumab will be explored.

3.3.8 Rationale for Patient-Reported Outcome Assessments

As mBC is not curable with currently approved and available therapies, the main goals of treatment are to prolong survival and maintain or improve quality-of-life (Cardoso et al. 2012). PROs of global health status, function, and disease/treatment related symptoms will be assessed using the EORTC QLQ-C30 in conjunction with the QLQ-BR23 breast cancer module, as well as the EQ-5D-5L (see Section 5.3.5.13 and Appendix 4).

The EORTC QLQ-C30 and its breast cancer–specific module, the QLQ-BR23, are validated and reliable self-report measures (Aaronson et al.1993; Sprangers et al. 1996; Osoba et al. 1997). The EQ-5D-5L is a validated, generalized HRQoL measure that assesses patient's health status related to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Herdman et al. 2011; Janssen et al. 2013). A utility measure is obtained that is used to inform pharmacoeconomic evaluations.

The EORTC QLQ-C30, QLQ-BR23, and EQ-5D-5L will be assessed at baseline (Cycle 1, Day 1); at Day 1 of each subsequent cycle; and at the treatment discontinuation visit. In addition, all patients will complete the PRO questionnaires every 28 days for 1 year after treatment discontinuation, regardless of whether the patient is receiving subsequent anti-cancer therapy. Questionnaires will be completed after treatment discontinuation by the patient at home on an ePRO handheld device provisioned to the patient at the time of treatment discontinuation visit. As the QLQ-BR23 was not developed or tested and validated with men, male patients in this study will not complete the QLQ-BR23 measure.

3.4 OUTCOME MEASURES

3.4.1 Efficacy Outcome Measures

3.4.1.1 Co-Primary Efficacy Outcome Measures

The co-primary efficacy outcome measures to be assessed in the ITT population and in the PD-L1–selected subpopulation are as follows:

- PFS, defined as the time from randomization to the time of radiographic progression or death from any cause during the study, whichever occurs first
- OS, defined as the time from the date of randomization to the date of death from any cause

Progression will be assessed by the investigator using RECIST v1.1.

3.4.1.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures to be assessed in the ITT population and in the PD-L1–selected subpopulation are as follows:

- ORR, defined as the proportion of patients with an objective tumor response (either partial response [PR] or complete response [CR] per investigator using RECIST v1.1)

- DOR, defined as the time from the first occurrence of a documented objective tumor response to the time of radiographic progression (per investigator using RECIST v1.1) or death from any cause on study, whichever occurs first
- TTD in global health status/HRQoL, defined by a minimally important decrease of ≥10 points on the global health status/HRQoL scale of the EORTC QLQ-C30

3.4.2 Safety Outcome Measures

The safety outcome measures are as follows:

- Incidence, nature, and severity of adverse events graded according to NCI CTCAE v4.0
- Changes in vital signs, physical findings, and clinical laboratory results
- Incidence of ATA response to atezolizumab and potential correlation with PK, PD, safety, and efficacy parameters

3.4.3 Pharmacokinetic Outcome Measures

The PK outcome measures are as follows:

- Atezolizumab maximum observed serum concentration (C_{max}) and minimum observed serum concentration (C_{min}) within a dosing interval at specified timepoints during treatment and at treatment termination
- Plasma concentration of nab-paclitaxel (reported as total paclitaxel)

3.4.4 Exploratory Outcome Measures

The exploratory outcome measures are as follows:

- Association of tumor immune-mediated or disease type–related exploratory biomarkers in archival and/or freshly obtained tumor tissues with disease status and/or response to atezolizumab+nab-paclitaxel
- Association of exploratory biomarkers in plasma, whole blood, or serum (including but not limited to cytokines such as interleukin [IL]-6) collected before treatment, during treatment with atezolizumab+nab-paclitaxel, or at disease progression with disease status and/or response to atezolizumab+nab-paclitaxel
- TTD in the functional (physical, role, cognitive) subscales of the EORTC QLQ-C30
- Assessment of mean changes in function and disease/treatment-related symptoms in all scales of the EORTC QLQ-C30 and QLQ-BR23 by treatment arm
- Health utility assessment as measured by the EQ-5D-5L during the study for health economic evaluations

4. MATERIALS AND METHODS

4.1 PATIENTS

Patients with metastatic or locally advanced TNBC who have not received prior systemic cytotoxic therapy for mBC may be eligible for this study. Locally advanced disease must not be amenable to resection with curative intent. Patients may have received prior

chemotherapy in the neoadjuvant/adjuvant setting if treatment was completed ≥12 months prior to randomization. Patients must comply with all eligibility criteria to be enrolled.

4.1.1 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study entry:

- Signed Informed Consent Form
- Women or men aged ≥18 years
- Metastatic or locally advanced, histologically documented TNBC (absence of HER2, ER, and PR expression)

  HER2 negativity is defined as either of the following (Wolff et al. 2013) by local laboratory assessment:

  In situ hybridization (ISH) non-amplified (ratio of HER2 to CEP17 <2.0 or single probe average HER2 gene copy number <4 signals/cell), or

  IHC 0 or IHC 1+. If more than one test result is available and not all results meet the inclusion criterion definition, all results should be discussed with the Medical Monitor to establish eligibility of the patient.

  ER and PR negativity are defined as <1% of cells expressing hormonal receptors via IHC analysis.
- No prior chemotherapy or targeted systemic therapy for inoperable locally advanced or metastatic TNBC

  Radiation therapy for metastatic disease is permitted. There is no required minimum washout period for radiation therapy. Patients should be recovered from the effects of radiation.

  Prior chemotherapy (including taxanes) in the neoadjuvant or adjuvant setting is allowable if treatment was completed ≥12 months prior to randomization
- Eligible for taxane monotherapy (i.e., absence of rapid clinical progression, life-threatening visceral metastases, or the need for rapid symptom and/or disease control)
- Representative FFPE tumor specimen (either an archival specimen or fresh pre-treatment tissue from relapsed disease) in paraffin blocks (preferred) or at least 20 unstained slides, with an associated pathology report documenting ER, PR, and HER2 negativity (see Appendix 8 for detailed tissue requirements at screening)

  Patients with fewer than 20 unstained slides available at baseline (but no fewer than 12) 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.

  If multiple tumor specimens are submitted (e.g., an archival specimen and tissue from relapsed disease), 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.

A tumor specimen obtained from relapsed metastatic or locally advanced disease (if applicable) must be submitted, if clinically feasible.

Acceptable samples include core needle biopsies for deep tumor tissue (minimum three cores) or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions.

FFPE tumor specimens in paraffin blocks are preferred.

Fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases, and lavage samples are not acceptable.

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

- ECOG performance status of 0 or 1 (see Appendix 7)
- Life expectancy ≥12 weeks
- Measurable disease, as defined by RECIST v1.1

  Previously irradiated lesions can be considered as measurable disease only if disease progression has been unequivocally documented at that site since radiation.
- Adequate hematologic and end-organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment (Cycle 1, Day 1):

  ANC ≥1500 cells/μL (without granulocyte colony-stimulating factor [G-CSF] support within 2 weeks prior to Cycle 1, Day 1)

  Lymphocyte count ≥ 500/μL

  Platelet count ≥100,000/μL (without transfusion within 2 weeks prior to Cycle 1, Day 1)

  Hemoglobin ≥9.0 g/dL

  Patients may be transfused or receive erythropoietic treatment to meet this criterion.

  AST, ALT, and alkaline phosphatase ≤2.5× the upper limit of normal (ULN), with the following exceptions:

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

  Patients with documented liver or bone metastases: alkaline phosphatase ≤5×ULN

  Serum bilirubin ≤1.25×ULN

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

  INR and aPTT ≤1.5×ULN

This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose.

Calculated creatinine clearance ≥30 mL/min

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of <1% per year, during the treatment period and for at least 5 months after the last dose of atezolizumab/placebo or 1 month after the last dose of nab-paclitaxel, whichever is later.

  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 and/or uterus).

  Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices (IUDs), and copper IUDs.

  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.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 6 months after the last dose of nab-paclitaxel. Men must refrain from donating sperm during this same period.

  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.

- Women who are not postmenopausal (≥12 months of non–therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 14 days prior to initiation of study drug.

4.1.2 Exclusion Criteria

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

4.1.2.1 Cancer-Specific Exclusion Criteria

- Spinal cord compression not definitively treated with surgery and/or radiation, or previously diagnosed and treated spinal cord compression without evidence that disease has been clinically stable for >2 weeks prior to randomization

- Known CNS disease, except for treated asymptomatic CNS metastases, provided all of the following criteria are met:

  Only supratentorial and cerebellar metastases allowed (i.e., no metastases to midbrain, pons, medulla, or spinal cord)

  No ongoing requirement for corticosteroids as therapy for CNS disease

  No stereotactic radiation within 7 days or whole brain radiation within 14 days prior to randomization

  No evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study

  Note: Patients with new asymptomatic CNS metastases detected at the screening scan must receive radiation therapy and/or surgery for CNS metastases. Following treatment, these patients may then be eligible without the need for an additional brain scan prior to enrollment, if all other criteria are met.

- Leptomeningeal disease
- Uncontrolled pleural effusion, pericardial effusion, or ascites

  Patients with indwelling catheters (e.g., PleurX®) are allowed.

- Uncontrolled tumor-related pain

  Patients requiring narcotic pain medication must be on a stable regimen at study entry.

  Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to randomization. Patients should be recovered from the effects of radiation. There is no required minimum recovery period.

  Asymptomatic metastatic lesions whose further growth would likely cause functional deficits or intractable pain (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to randomization.

- Uncontrolled hypercalcemia (>1.5 mmol/L ionized calcium or calcium >12 mg/dL or corrected serum calcium >ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy

  Patients who are receiving denosumab must discontinue denosumab use and replace it with a bisphosphonate instead while on study. There is no required minimum washout period for denosumab.

  Patients who are receiving bisphosphonate therapy specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible.

- Malignancies other than TNBC within 5 years prior to randomization, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix or basal or squamous cell skin cancer)

4.1.2.2 General Medical Exclusion Criteria

- Pregnancy or lactation
- Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome)
- Significant cardiovascular disease, such as New York Heart Association (NYHA) cardiac disease (Class II or greater), myocardial infarction within 3 months prior to randomization, unstable arrhythmias, or unstable angina

  Patients with a known left ventricular ejection fraction (LVEF) $<$40% will be excluded.

  Patients with known coronary artery disease, congestive heart failure not meeting the above criteria, or LVEF $<$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.
- Severe infection within 4 weeks prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1

  Patients receiving routine antibiotic prophylaxis (e.g., to prevent chronic obstructive pulmonary disease exacerbation or for dental extraction) are eligible.
- Major surgical procedure within 28 days prior to randomization or anticipation of the need for a major surgical procedure during the course of the study other than for diagnosis

  Placement of central venous access catheter(s) (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted
- Known hypersensitivity to nab-paclitaxel or to any of the excipients.

4.1.2.3 Exclusion Criteria Related to Atezolizumab

- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation
- History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome,

multiple sclerosis, vasculitis, or glomerulonephritis (see Appendix 5 for a more comprehensive list of autoimmune diseases)

Patients with a history of autoimmune-mediated hypothyroidism on a stable dose of thyroid replacement hormone are eligible for this study.

Patients with controlled Type 1 diabetes mellitus on a stable insulin dosing regimen are eligible for this study.

Patients with eczema, psoriasis, lichen simplex chronicus or vitiligo with dermatologic manifestations only (e.g., no psoriatic arthritis) are permitted provided that they meet the following conditions:

Rash must cover less than 10% of body surface area (BSA).

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

No acute exacerbations of underlying condition within the last 12 months (not requiring PUVA [psoralen plus ultraviolet A radiation], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids)

- Prior allogeneic stem cell or solid organ transplantation
- History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Positive test for HIV
- Active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible.

  Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Active tuberculosis
- Receipt of a live, attenuated vaccine within 4 weeks prior to randomization or anticipation that such a live, attenuated vaccine will be required during the study

  Patients must agree not to receive live, attenuated vaccine (e.g., FluMist®) within 28 days prior to randomization, during treatment, or within 5 months following the last dose of atezolizumab/placebo.
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, or anti–PD-L1 therapeutic antibodies

- Treatment with systemic immunostimulatory agents (including but not limited to interferons or IL-2) within 4 weeks or five half-lives of the drug (whichever is shorter) prior to randomization
- Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [TNF] agents) within 2 weeks prior to randomization, or anticipated requirement for systemic immunosuppressive medications during the study

  Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled in the study

  Patients with a history of allergic reaction to IV contrast requiring steroid pre-treatment should have baseline and subsequent tumor assessments performed using MRI.

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

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established, the study site will obtain the patient's identification number and treatment assignment from the interactive voice or Web response system (IxRS) for eligible patients.

Randomization will occur in a 1:1 ratio using a permuted-block randomization method. Patients will be randomized to one of two treatment arms: atezolizumab + nab-paclitaxel or placebo + nab-paclitaxel. The randomization scheme is designed to ensure that an approximately equal number of patients will be enrolled in each treatment arm within the baseline characteristics of the following stratification factors:

- Presence of liver metastases (yes vs. no)
- Prior taxane treatment (yes vs. no)
- Tumor PD-L1 status (IC0 vs. IC1/2/3)

Patients should receive their first dose of study treatment on the day of randomization if possible. If this is not possible, the first dose should occur no later than 3 days after randomization.

The Sponsor and its agents (with the exception of the IxRS service provider [the external independent statistical coordinating center responsible for verifying patient randomization and study treatment kit assignments], PK/PD laboratory personnel, and the iDMC members); the study site personnel, including the investigator; and the patient will be blinded to treatment assignment prior to unblinding (see Section 4.2.1).

The Sponsor and its agents (with the exception of the PD-L1 assay provider and the iDMC members); the study site personnel, including the investigators; and the patients will be blinded to PD-L1 status prior to study unblinding of the treatment assignment at the study level.

4.2.1 Unblinding

Unblinding of treatment assignment may occur under the following circumstances.

Emergency Unblinding

Per health authority reporting requirements, treatment assignment will be unblinded for serious, unexpected study drug-related toxicity (as part of the IND safety reporting process). In these instances, investigators will not be notified of individual patient's treatment assignment as a matter of course. Emergency unblinding by the investigator should be a last resort performed only in cases when knowledge of treatment assignment will affect the management of a patient who experiences a treatment-emergent adverse event. Investigators are encouraged to consult with the Medical Monitor prior to performing emergency unblinding. If unblinding is necessary for patient safety management, the investigator is credentialed to break the treatment code within the IxRS autonomously by means of a pin code which is issued to them at the start of the study. All such occurrences should be documented in the study file.

Unblinding should not result in the withdrawal of the patients from the study. Every effort should be made to retain unblinded patients and continue data collection as per protocol.

Unblinding at the Study Level

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

For the process related to the interim efficacy analyses, see Section 3.1.1.

4.3 STUDY TREATMENT

Atezolizumab/placebo and nab-paclitaxel are considered the investigational medicinal products (IMPs) in this study.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Atezolizumab/Placebo

Atezolizumab will be supplied by the Sponsor as sterile liquid in 20-mL glass vials. For information on the formulation and handling of atezolizumab, refer to the Investigator's Brochure and Pharmacy Manual. The vial contains 20 mL (1200 mg) of atezolizumab solution. Fourteen (14 mL) of atezolizumab solution will contain an 840-mg dose. Placebo will consist of the vehicle without the antibody. Placebo will be supplied in a single-use, 20-cc USP/Ph. Eur. Type 1 glass vial as a colorless, sterile, preservative-free clear liquid solution intended for IV administration. The vial contains approximately

20 mL of solution. The formulation contains 20 mM histidine acetate, 120 mM sucrose, and 0.04% polysorbate 20, pH 5.8.

For further details on the storage and preparation of atezolizumab/placebo, see the Pharmacy Manual and the Investigator's Brochure.

Atezolizumab/placebo will be supplied by the Sponsor.

4.3.1.2 nab-Paclitaxel

Refer to the nab-paclitaxel (Abraxane®) Package Insert for details on formulation and storage.

nab-Paclitaxel will be supplied by the Sponsor.

4.3.2 Dosage, Administration, and Compliance

On days of scheduled infusions of atezolizumab or placebo and nab-paclitaxel (i.e., Day 1 and Day 15 of every cycle; nab-paclitaxel will be administered alone on Day 8 of every cycle), chemotherapy is to be administered after infusion of atezolizumab/placebo.

4.3.2.1 Atezolizumab or Placebo

Patients will receive atezolizumab 840 mg or placebo administered by IV infusion q2w (every 14 [±3] days).

Administration of atezolizumab or placebo will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

Atezolizumab or placebo infusions will be administered per the instructions outlined in Table 1.

Table 1 Administration of First and Subsequent Infusions of Atezolizumab/Placebo

Administration of First and Subsequent Infusions of Atezolizumab/Placebo

First Infusion	Subsequent Infusions
• No premedication is administered. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. • Infuse 14 mL atezolizumab (840 mg) in 250 mL NaCl) over 60 (±15) minutes. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during and after the infusion if clinically indicated • Patients will be informed about the possibility of delayed symptoms following infusion and instructed to contact their study physician if they develop such symptoms.	• If patient experienced infusion-related reaction during any previous infusion, premedication with antihistamines may be administered for at subsequent infusions at the discretion of the treating physician. • Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) within 60 minutes before starting infusion. • If the patient tolerated the first infusion well without infusion-associated adverse events, the second infusion may be administered over 30 (± 10) minutes. • If no reaction occurs, subsequent infusions may be administered over 30 (±10) minutes Continue to record vital signs within 60 minutes before starting infusion and during and after the infusion if clinically indicated. • If the patient had an infusion-related reaction during the previous infusion, the subsequent infusion must be administered over 60 (± 15) minutes. Record patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) during and after the infusion if clinically indicated.

Dose reduction of atezolizumab/placebo is not permitted. Guidelines for treatment interruption or discontinuation and the management of specific adverse events are provided in Sections 5.1.5 and 5.1.6, respectively.

Refer to the Atezolizumab Investigator's Brochure and Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

4.3.2.2 nab-Paclitaxel

nab-Paclitaxel will be administered according to the local prescribing information. The starting dose level of nab-paclitaxel in this study will be 100 mg/m^2 administered intravenously over 30 minutes on Days 1, 8, and 15 of each 28-day cycle (3-weeks-on/1-week-off schedule). Doses of nab-paclitaxel should not be administered

more frequently than every 7 days. Dose modifications should be performed according to Section 5.1.7.

Sites should follow their institutional standard of care for determining the nab-paclitaxel dose for patients who are obese and for dose adjustments in the event of patient weight changes. The infusion site should be closely monitored for possible infiltration during drug administration.

In the absence of disease progression or unacceptable toxicity, nab-paclitaxel will be administered for a target of at least 6 cycles, with no maximum.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (atezolizumab, placebo, and nab-paclitaxel) will be provided by the Sponsor where required by local health authority regulations. The investigational site will acknowledge receipt of the IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced and must be reported immediately to the study monitor.

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

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

4.3.4 Post-Study Access to Atezolizumab

The Sponsor will offer continued access to Roche IMP (atezolizumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMP (atezolizumab) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Roche IMP (atezolizumab) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for metastatic or unresectable locally advanced TNBC that has not received prior chemotherapy for metastatic disease
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for metastatic or unresectable locally advanced TNBC that has not received prior chemotherapy for metastatic disease
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

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

4.4 CONCOMITANT THERAPY

4.4.1 Permitted Therapy

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to screening to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

Premedication with antihistamines may be administered for any atezolizumab/placebo infusions after Cycle 1, Day 1.

The following therapies are permitted on study:

- Prophylactic or therapeutic anticoagulation therapy (such as low–molecular weight heparin or warfarin at a stable dose level)
- Palliative radiotherapy (e.g., treatment of known bone metastases) provided it does not interfere with assessment of tumor target lesions

  It is not required to hold atezolizumab/placebo during palliative radiotherapy; nab-paclitaxel should be interrupted per institutional standard of care.
- Inactivated vaccinations (including for influenza)
- Megestrol administered as an appetite stimulant
- Inhaled corticosteroids for chronic obstructive pulmonary disease
- Mineralocorticoids (e.g., fludrocortisone)

- Low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency
- Bisphosphonates for the prevention of skeletal events

    Patients who are receiving denosumab must be willing and able to receive a bisphosphonate instead while on study. There is no required minimum washout period for patients who discontinue denosumab.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated and per local standards.

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H_2-receptor antagonist per standard practice (for sites outside the United States, equivalent medications may be substituted per local 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 6).

4.4.2 Excluded and Cautionary Therapy

The following medications are excluded while the patient is receiving study treatment:

- Other systemic anti-cancer therapy
- RANKL inhibitor (denosumab): patients who are receiving denosumab prior to randomization must be willing and eligible to receive a bisphosphonate instead while on study.
- Immunomodulatory agents, including but not limited to interferons or IL-2, during the entire study; these agents could potentially increase the risk for autoimmune conditions when received in combination with atezolizumab.
- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide; these agents could potentially alter the activity and the safety of atezolizumab.
- Use of steroids to premedicate patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance); in such patients, MRIs of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest must be performed.
- Any live, attenuated vaccine (e.g., FluMist®) within 28 days prior to randomization, treatment, or within 5 months following the last dose of atezolizumab/placebo.

Systemic corticosteroids and anti–TNF-α agents may also attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to these agents should be considered.

In addition, patients should not receive other immunomodulatory agents for 10 weeks after atezolizumab discontinuation.

The concomitant use of herbal therapies is not recommended, as their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, their use for patients in the study is allowed at the discretion of the investigator.

4.4.3 Concomitant Medications with nab-Paclitaxel

The metabolism of nab-paclitaxel is catalyzed by cytochrome P450 (CYP) isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when nab-paclitaxel is concomitantly administered with known inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) and inducers (e.g., rifampin and carbamazepine) of CYP3A4.

G-CSF treatment is permitted for patients receiving nab-paclitaxel. The primary prophylaxis should be administered per the American Society of Clinical Oncology (ASCO), EORTC, and ESMO guidelines; namely, in patients who are ≥60 years of age and/or with comorbidities (Smith et al. 2006; Crawford et al. 2009; Aapro et al. 2011).

Evidence supporting the use of long-acting (pegylated) forms of G-CSF in patients receiving weekly chemotherapy is limited, and investigators should consider giving preference to conventional formulations of G-CSF.

Anti-emetics, anti-allergic measures, and other treatments for concomitant nab-paclitaxel toxicities may be used at the discretion of the investigator, taking into account precautions from the Summary of Product Characteristics.

Refer to the Summary of Product Characteristics (package insert) for nab-paclitaxel for all boxed warnings and contraindications.

4.5 STUDY ASSESSMENTS

Flowcharts of scheduled study assessments are provided in Appendix 1 and Appendix 2. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each patient.

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.

If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations.

Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

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

4.5.2 Description of Study Assessments

4.5.2.1 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to the Cycle 1, Day 1 visit.

TNBC history will include prior cancer therapies, procedures, and an assessment of tumor mutational status.

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

4.5.2.2 Physical Examinations

A complete physical examination 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 electronic Case Report Form (eCRF).

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. 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.

4.5.2.3 Vital Signs

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

At all clinic visits where study treatment is administered, vital signs should be determined within 60 minutes before the first infusion. Vital signs will also be determined during and after the infusions if clinically indicated (see Table 1).

4.5.2.4 Tumor and Response Evaluations

All sites of measurable and non-measurable disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Tumor assessments are to be performed at the timepoints specified in Appendix 1, regardless of drug delays or interruptions. Tumor assessments will continue until disease progression, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

Initial screening assessments must include CT scans (with oral/IV contrast unless contraindicated) or MRI of the chest, abdomen, and pelvis. Bone scan or PET scan should also be performed to evaluate for bone metastases. A spiral CT scan of the chest may be obtained but is not a requirement. MRIs of the chest, abdomen, and pelvis with a noncontrast CT scan of the chest may be used in patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance).

A CT (with contrast) or MRI scan of the head must be performed at screening to evaluate CNS metastasis in all patients. An MRI scan of the brain is required to confirm or refute a diagnosis of CNS metastasis at screening in the event of an equivocal scan. Patients with active or untreated CNS metastasis are not eligible for this study (see Section 4.1.2.1 for CNS-related exclusion criteria).

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

CT scans of the neck should also be performed if clinically indicated during the screening period. At the investigator's discretion, other methods of assessment of measurable disease per RECIST v1.1 may be used.

After baseline tumor assessments, evaluation of tumor response per RECIST v1.1 (see Appendix 3) will be performed every 8 weeks for the first 12 months following randomization (±1 week) and every 12 weeks thereafter (±1 week), with additional scans performed as clinically indicated. The same radiographic procedures used to assess measurable disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans and/or MRI). All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits.

At the investigator's discretion, CT or other clinically appropriate scans may be repeated at any time if progressive disease is suspected. If the initial screening bone scan or PET scan does not show evidence of bone metastases, then these procedures do not need to be repeated unless clinically indicated or at the treating physician's discretion.

All primary imaging data used for tumor assessment will be collected by the Sponsor to enable centralized, independent review of response endpoints, if needed.

If treatment is discontinued prior to disease progression per RECIST v1.1, tumor response assessment should continue to be performed per the schedule specified above.

4.5.2.5 Laboratory, Biomarker, and Other Biological Samples

Refer to the laboratory manual for additional details on laboratory assessments and sample handling.

Local Laboratory Assessments

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

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential [neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells], and platelet count)
- Serum chemistries (glucose, BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, total bilirubin, ALT, AST, alkaline phosphatase, total protein, and albumin)

  Levels of magnesium and phosphorus must be tested during screening. During treatment, levels of magnesium and phosphorus should be tested as clinically indicated
- Coagulation (aPTT and INR)
- Serum pregnancy test for women of childbearing potential, including women who have had a tubal ligation; urine pregnancy tests will be performed at each cycle during treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  Childbearing potential is defined as not having undergone surgical sterilization, hysterectomy, and/or bilateral oophorectomy or not being postmenopausal (≥12 months of amenorrhea).
- Levels of magnesium and phosphorus must be tested during screening. During treatment, levels of magnesium and phosphorus should be tested as clinically indicated
- Thyroid function testing (thyroid-stimulating hormone [TSH], free T3, free T4)
- HIV (tested prior to inclusion into the study)

  HIV−positive patients will be excluded from study participation.
- HBV serology (HBsAg, antibody to HBsAg [anti-HBs], anti-HBc)

  HBV DNA testing is required on or before Cycle 1, Day 1 if the patient has negative serology for HBsAg and positive serology for anti-HBc.
- HCV serology (anti-HCV)

Central Laboratory Assessments

The assessments listed below will be performed at a central laboratory or by the Sponsor. Any residual material from samples collected to enable these central assessments may be used for additional atezolizumab-related safety assessments (e.g., ATA assay), exploratory biomarker profiling, identification, and PD assay development purposes. Instruction manuals and supply kits will be provided for all central laboratory assessments.

- C-reactive protein (CRP)
- ATA assays

  Serum samples will be assayed for the presence of ATAs to atezolizumab using validated immunoassays.
- PK assays

  Serum samples will be assayed for atezolizumab concentration using a validated immunoassay.

  Plasma samples will be assayed for nab-paclitaxel using validated methods.
- Auto-antibody testing; baseline sample to be collected on Cycle 1, Day 1 prior to the first dose of study drug. For patients who show evidence of immune-mediated toxicity, additional samples may be collected and all samples will be analyzed centrally.

  Anti–double-stranded DNA

  Circulating anti-neutrophil cytoplasmic antibody

  Perinuclear anti-neutrophil cytoplasmic antibody
- Biomarker assays

  Blood samples will be obtained for biomarker evaluation (including but not limited to biomarkers that are related to TNBC or tumor immune biology) from all eligible patients according to the schedule in Appendix 2. Samples will be processed to obtain plasma and serum for the determination of changes in blood-based biomarkers. Whole blood samples may be processed to obtain peripheral blood mononuclear cells (PBMCs) and their derivatives (e.g., RNA and DNA).
- Archival or fresh tumor tissue samples for eligibility

  Representative tumor specimens in paraffin blocks (preferred) or at least 20 unstained slides, with an associated pathology report, must be submitted for determination of PD-L1 status prior to study enrollment.

  Patients with fewer than 20 unstained slides available at baseline (but no fewer than 12) may be eligible upon discussion with the medical monitor.

  A portion of archival and pre-treatment tumor specimens will be used for confirmation of ER, PR, and HER2 triple-negative status by a central testing laboratory.

Tumor tissue should be of good quality based on total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate to determine tumor PD-L1 status). Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation.

Patients having additional tissue samples from procedures performed at different times during the course of their breast tumor will be requested (but not required) to also submit these samples for central testing. Tissue samples obtained at multiple times for individual patients will greatly contribute to an improved understanding of the dynamics of PD-L1 expression and relationship with intervening anticancer therapy.

The status of immune-mediated and tumor type–related, and other exploratory biomarkers (including but not limited to T-cell markers) in archival and fresh tumor tissue samples of enrolled patients may be evaluated.

For archival samples, the remaining tumor tissue block for all patients enrolled will be returned to the site upon request or 18 months after final closure of the study database, whichever is sooner. Tissue samples from patients who are not eligible to enroll in the study will be returned no later than 6 weeks after eligibility determination.

If clinically feasible, the Sponsor also requests fresh pre-treatment biopsy specimens obtained from either relapsed metastatic or locally advanced disease. Acceptable samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. For core needle biopsy specimens, at least three cores should be submitted for evaluation.

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

- Biopsy at radiographic progression

  All patients will undergo a mandatory tumor biopsy sample collection, if clinically feasible and if permitted by local guidelines and regulations, at the time of radiographic disease progression.

- Optional biopsy

  Patients may agree to provide optional tumor tissue samples for biopsy by providing consent on the Consent for Optional Biopsy, which is separate from the main study Informed Consent Form. For patients who agree to optional biopsies, biopsy samples may be collected prior to dosing on Cycle 2, Day 1 (±7 days) per investigator discretion

Acceptable samples include core needle biopsies for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. For core needle biopsy specimens, at least three cores should be submitted for evaluation.

Use and Storage of Remaining Samples from Study-Related Procedures

If a patient undergoes a medically indicated procedure (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy, etc.) any time during the course of the study that has the likelihood of yielding tumor tissue, any remaining samples or a portion of the sample not necessary for medical diagnosis (body fluid samples or leftover tumor tissue) may be used for exploratory analysis. Patients must provide specific consent in order for discarded samples from routine care to be obtained.

The remainder of samples obtained for study-related procedures will be destroyed no later than 5 years after the end of the study or earlier depending on local regulations. If the patient provides optional consent for storing samples in the RCR for future research (see Section 4.5.6), the samples will be destroyed no later than 15 years after the date of final closure of the clinical database.

4.5.3 Anti-Therapeutic Antibody Testing

Atezolizumab may elicit an immune response. Patients with signs of any potential immune response to atezolizumab will be closely monitored. Validated screening and confirmatory assays will be employed to detect ATAs at multiple timepoints before, during, and after study treatment (see Appendix 2 for the schedule). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Rosenberg and Worobec 2004; Koren et al. 2008) to characterize ATA responses to atezolizumab in support of the clinical development program. This tiered strategy will include an assessment of whether ATA responses correlate with relevant clinical endpoints. Implementation of ATA characterization assays will depend on the safety profile and clinical immunogenicity data.

4.5.4 Electrocardiograms and Cardiac Function Assessment

A twelve-lead ECG is required at screening and when clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. ECG recordings must be performed after the patient has been resting 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 kept as part of the patient's permanent study file at the site. Any clinically significant morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.5 Patient-Reported Outcomes

The EORTC QLQ-C30, QLQ-BR23, and EQ-5D-5L questionnaires will be collected to more fully characterize the clinical profile of atezolizumab + nab-paclitaxel and nab paclitaxel.

The EORTC QLQ-C30 and the QLQ-BR23 (see Appendix 4) are validated and reliable self-report measures (Aaronson et al. 1993; Sprangers et al. 1996; Osoba et al. 1997).

The EORTC QLQ-C30 (version 3) consists of thirty questions that assess global HRQoL, including five aspects of patient functioning (physical, emotional, role, cognitive, and social); three symptom scales (fatigue, nausea and vomiting, and pain); and six single-items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of "the last week". Scale scores can be obtained for the multi-item scales. The breast cancer–specific QLQ-BR23 module consists of 23 additional items assessing disease/treatment symptoms (systemic therapy side effects, breast symptoms, arm symptoms, and hair loss) and aspects of patient functioning (body image, sexual functioning, and future perspective). Because the QLQ-BR23 was not developed or tested and validated with men, male patients in this study will not complete the QLQ-BR23 measure.

The EQ-5D-5L (see Appendix 4) is a generic, preference-based measure that assesses health status and is used to inform pharmacoeconomic evaluations. The EQ-5D-5L consists of two parts: the health state classification and the visual analogue scale (EQ VAS). The health state classification contains five dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Herdman et al. 2011; Janssen et al. 2013). From these five items, a utility measure is obtained for each patient. The EQ VAS records the respondent's self-rated health on a scale from 0 ("the worst health you can imagine") to 100 ("the best health you can imagine").

The PRO instruments will be translated as required in the local language and completed in their entirety by the patient. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires scheduled for administration during a clinic visit must be completed by the patient at the investigational site at the start of the clinic visit prior to other study assessments and before administration of study treatment. Interviewer assessment is allowed but can only be conducted by a member of the clinic staff if the patient is unable to complete the measure on their own. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site.

An electronic PRO (ePRO) data collection modality will be employed. To capture PRO data during study treatment, patients will complete the questionnaires on an ePRO tablet at the site. The ePRO device and instructions for completing the PRO questionnaires electronically will be provided by the investigator staff. The data will be transmitted via a pre-specified transmission method (e.g., Web or wireless) automatically after entry to a centralized database at the ePRO vendor. The data can be accessed securely by appropriate study personnel via the Internet.

The PRO questionnaires (EORTC QLQ-C30, QLQ-BR23, and EQ-5D-5L) will be completed on the ePRO device at the site at baseline (Cycle 1, Day 1) and Day 1 of each subsequent cycle, and at the end of treatment/discontinuation visit. In addition, all patients will complete the PRO questionnaires every 28 days for 1 year after treatment discontinuation, regardless of whether the patient is receiving subsequent anti-cancer

therapy. Questionnaires will be completed after treatment discontinuation by the patient at home on an ePRO handheld device provisioned to the patient at the time of the treatment discontinuation visit.

4.5.6 Samples for Roche Clinical Repository

4.5.6.1 Overview of the Roche Clinical Repository

The RCR is a centrally administered group of facilities for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR 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.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.6.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.5.6) will not be applicable at that site.

4.5.6.3 Sample Collection

The following samples will be collected for the identification of dynamic (non-inherited) biomarkers for patients who have signed the RCR optional consent:

- Remaining blood derivatives (serum, plasma, and PBMCs and their derivatives) after study-related tests have been performed
- Remaining FFPE tissue (with the exception of archival FFPE blocks, which will be returned to sites) after study-related tests have been performed
- Leftover tumor tissue samples (from clinically indicated procedures performed during the study)

A blood sample for DNA isolation and genetic biomarker analysis will be collected from patients who have consented to optional RCR sampling at baseline as shown in the schedule of assessments in Appendix 1. If, however, the RCR 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 may enable the evaluation of single nucleotide polymorphisms in genes associated with immune biology including but not restricted to the target and pathway associated genes such as PD-L1, PD-1, and B7.1. The sample may be processed using techniques such as kinetic PCR and DNA sequencing.

For all samples, the dates of consent should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

4.5.6.4 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A “linking key” between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

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

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate

authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

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

4.5.6.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told 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 RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether the patient has given consent to participate by completing the Informed Consent eCRF.

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

4.5.6.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes using the RCR Patient Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the study is closed. A patient's withdrawal from Study WO29522 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study WO29522.

4.5.6.7 Monitoring and Oversight

RCR 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

Informed Consent Form. Roche monitors (or their designees) and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.6 PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

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

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient noncompliance

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.1.1 Discontinuation from Study Drug

Patients must discontinue study drug if they experience any of the following:

- Intolerable toxicity related to study treatment
- Any medical condition that may jeopardize the patient's safety if he or she continues on study treatment
- Use of another systemic anti-cancer therapy (see Section 4.4.2)
- Pregnancy
- Radiographic disease progression per RECIST v1.1

The primary reason for study drug discontinuation should be documented on the appropriate eCRF.

4.6.2 Study and Site Discontinuation

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

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

The Sponsor will notify the investigator if the study is placed on hold or if the Sponsor decides to discontinue the study or the development program.

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria (see Sections 4.1.1 and 4.1.2) and close monitoring (as indicated below and in Section 4.5). Section 5.3 (Methods and Timing for Capturing and Assessing Safety Parameters) provides complete details regarding safety reporting for this study. An iDMC (see Section 3.1.1) has also been incorporated into the study design to periodically review aggregate safety data.

Administration of study treatment will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. All adverse events and serious adverse events will be recorded during the study and for up to 30 days after the last dose of study drug or until the initiation of another anti-cancer therapy, whichever occurs first. After this period, investigators should report serious adverse events and adverse events of special interest that are believed to be related to prior treatment with study drug. The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

This is a double-blind study. Study treatment assignment may be unblinded for a serious, unexpected study drug-related toxicity (as part of the IND safety reporting process; see Section 4.2.1). Emergency unblinding should be a last resort only performed in cases where knowledge of treatment assignment will affect the ongoing management of a patient who experiences a treatment-emergent adverse event.

5.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: infusion-related reactions (IRRs) and *immune-mediated* hepatitis, pneumonitis, colitis, pancreatitis,

diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, meningoencephalitis, myocarditis, nephritis*, and myositis. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome (considered to be potential risks for atezolizumab).* Refer to Appendix 10 of the protocol for the AE management guidelines and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated risks for atezolizumab.

5.1.2 Risks Associated with nab-Paclitaxel

In clinical studies and post-marketing experience, nab-paclitaxel has been associated with alopecia, myelosuppression (primarily neutropenia, anemia, thrombocytopenia), peripheral neuropathy, cranial nerve palsies, hypersensitivity reactions, pneumonitis, gastrointestinal events (i.e., nausea, vomiting, diarrhea), myalgia, arthralgia, cardiotoxicity (myocardial disorders, cardiac failure, angina, tachycardia, ventricular arrhythmia), cystoid macular edema, Stevens-Johnson syndrome/toxic epidermal necrolysis, sepsis, infusion site reactions/extravasation, hepatic toxicity (drug-induced liver injury), acute renal failure, hemolytic-uremic syndrome, drug-induced lupus erythematous, *and tumor lysis syndrome*.

Patients will be monitored for nab-paclitaxel–related adverse events, including hematologic, gastrointestinal, hepatic toxicities, and peripheral neuropathy.

For more details regarding the safety profile of nab-paclitaxel, refer to the local prescribing information. Other specific instructions can be found in Sections 4.4.3 and 5.1.7 for nab-paclitaxel.

5.1.3 General Plan to Manage Safety Concerns

5.1.3.1 Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies with atezolizumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were taken into account. Specifically, patients at risk for study-emergent autoimmune conditions or with a prior diagnosis of autoimmune disease, patients with evidence of acute infections, and patients who have received a live-attenuated viral vaccine within 4 weeks of randomization are excluded from the study (see Section 4.1 for additional details).

5.1.3.2 Monitoring

Safety will be evaluated in this study through the monitoring of all serious and non-serious adverse events defined and graded according to NCI CTCAE v4.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1. Laboratory values must be reviewed prior to each infusion.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see Appendix 1 and Appendix 2 for the list and timing of study assessments).

During the study, patients will be closely monitored for the development of any adverse events, including signs or symptoms of autoimmune conditions and infection.

All serious adverse events and protocol-defined events of special interest will be reported in an expedited fashion (see Sections 5.2.2 and 5.2.3).

Patients will be followed for safety for 30 days following their last dose of study drug or until they receive another anti-cancer therapy, whichever comes first.

Patients who have an ongoing study drug–related adverse event upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new anti-cancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the adverse event.

5.1.4 Dose Modification

5.1.4.1 General Notes Regarding Dose Modification

Reasons for dose modifications or delays, the supportive measures taken, and the outcomes will be documented in the patient's chart and recorded on the eCRF.
The severity of adverse events will be graded according to the NCI CTCAE v4.0 grading system.

- Dose reduction of atezolizumab/placebo is not permitted.
- For any concomitant conditions already apparent at baseline, the dose modifications will apply according to the corresponding shift in toxicity grade, if the investigator feels it is appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this will be considered a shift of one grade and treated as Grade 1 toxicity for dose-modification purposes.
- When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.
- If, in the opinion of the investigator, a toxicity is considered to be due solely to one component of the study treatment (i.e., atezolizumab/placebo or nab-paclitaxel) and the dose of that component is delayed or modified in accordance with the guidelines below, the other component may be administered if there is no contraindication.
- When treatment is temporarily interrupted because of toxicity caused by atezolizumab/placebo or nab-paclitaxel, the treatment cycles will be restarted such that the atezolizumab/placebo and nab-paclitaxel infusions remain synchronized.

- If it is anticipated that nab-paclitaxel will be delayed by ≥2 weeks, then atezolizumab/placebo should be given without the chemotherapy if there is no contraindication.
- In general, the start of a cycle may be delayed to allow recovery from toxicities, but there shall be no delay within cycles. Cycle length is fixed at 28 days, and dosing on Days 8 and 15 of a cycle may be skipped but shall not be delayed outside of the window specified in the Appendix 1 (i.e., +3 days).

The treating physician may use discretion in modifying or accelerating the dose modification guidelines described below depending on the severity of toxicity and an assessment of the risk versus benefit for the patient, with the goal of maximizing patient compliance and access to supportive care.

5.1.5 Atezolizumab/Placebo Dose Modification

There will be no dose reduction for atezolizumab or placebo in this study. Patients may temporarily suspend study treatment if they experience an adverse event that requires a dose to be held. If atezolizumab or placebo is held because of adverse events for >12 weeks after event onset, then the patient will be discontinued from atezolizumab or placebo treatment and will be followed for safety as specified in Section 5.5. If, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming atezolizumab after a hold >12 weeks, study drug may be restarted with the approval of the Medical Monitor.

If a patient must be tapered off steroids used to treat adverse events, atezolizumab or placebo may be held for >12 weeks until steroids are discontinued or reduced to prednisone dose (or dose equivalent) ≤10 mg/day. The acceptable length of interruption will depend on agreement between the investigator and the Medical Monitor.

Dose interruptions for reason(s) other than adverse events, such as surgical procedures, may be allowed with Medical Monitor approval. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption.

5.1.6 Management of Atezolizumab/Placebo-Specific Adverse Events

For details on the management of infusion-related reactions and all other *immune-mediated* adverse events, including but not limited to, gastrointestinal, dermatologic, endocrine, pulmonary toxicity, hepatotoxicity, pancreatic, or eye toxicity refer to the Appendix 10.

Refer to Section 5.1.7.5 and Table 6 for management of pulmonary events, including pneumonitis, for atezolizumab/placebo and nab-paclitaxel.

5.1.7 nab-Paclitaxel Dose Modification and Management of Specific Adverse Events

5.1.7.1 Hematologic Toxicity

In general, ANC must be ≥1500/μL and platelet count must be ≥100,000/μL on Day 1 of each cycle. When nab-paclitaxel is administered on Day 1, it should not be administered on Days 8 or 15 of the cycle unless ANC ≥500 cells/μL and platelets ≥50,000 cells/μL. In certain situations (see Section 5.1.4.1) a cycle may begin with the administration of atezolizumab/placebo alone (without nab-paclitaxel on Day 1). If Day 1 of a cycle begins with only atezolizumab/placebo but without the administration of nab-paclitaxel due to low platelet or ANC levels, nab-paclitaxel should not be administered subsequently within that cycle until ANC ≥1500/μLand platelet count ≥100,000/μL If the delay in re-starting nab-paclitaxel is >7 days (i.e., counts do not recover until Day 15) dosing should be resumed with applicable reductions according to the criteria in Table 2.

If the start of a cycle is delayed (i.e. both atezolizumab/placebo and nab-paclitaxel are held) for low counts, postpone Day 1 and resume dosing when counts recover with applicable reductions according to criteria in Table 2.

If nab-paclitaxel cannot be administered on Day 8 of the cycle, it may be administered on Day 15 if counts have recovered to permissible levels with applicable dose reductions according to the criteria in Table 2.

If nab-paclitaxel cannot be administered on Day 15 of the cycle, the next dose of nab-paclitaxel should be administered on Day 1 of the following cycle when ANC and platelets counts have recovered to permissible levels. When dosing resumes, the nab-paclitaxel doses should be permanently reduced as outlined in Table 2.

Table 2 nab-Paclitaxel Permanent Dose Reductions for Hematologic Toxicity

Hematologic Toxicity	Occurrence	Weekly nab-Paclitaxel Dose (mg/m^2)
Neutropenic fever (nadir ANC <500/μL with fever >38°C) or Delay of first administration of nab-paclitaxel in a cycle by >7 days for nadir ANC <1500/μL or Nadir ANC <500/μL for >7 days	First	75
	Second	50
	Third	Discontinue treatment
Nadir platelet count <50,000/μL	First	75
	Second	Discontinue treatment

ANC=absolute neutrophil count; AUC=area under the concentration-time curve.

5.1.7.2 Gastrointestinal Toxicity

For Grade 3 or 4 gastrointestinal toxicities, treatment should be delayed until resolution to less than or equal to the patient's baseline value. Dose reductions at the start of the subsequent cycle will be based on gastrointestinal toxicities from the dose administered in the preceding cycle. Table 3 provides the relevant dose adjustments for gastrointestinal toxicities.

Table 3 nab-Paclitaxel Dose Modification Based on Gastrointestinal Toxicities in the Preceding Cycle

Toxicity	Grade	Adjusted nab-Paclitaxel Dose as Percentage of Starting Dose
Diarrhea	Grade 4	Discontinue nab-paclitaxel
Oral mucositis/stomatitis	Grade 4	Discontinue nab-paclitaxel
Oral mucositis/stomatitis	Grade 3	1st occurrence: 75%
Diarrhea	Grade 3	2nd occurrence: 50%
Nausea/vomiting	Grade 3 or 4	3rd occurrence: discontinue nab-paclitaxel

Nausea and/or vomiting should be controlled with adequate anti-emetics. If Grade 3 or 4 nausea/vomiting occurs in spite of anti-emetics, the dose should be reduced by 25% for the next course.

5.1.7.3 Neurological Toxicity

Nab-paclitaxel should be withheld for Grade 3–4 peripheral neuropathy and may be resumed at reduced doses (see Table 4) when peripheral neuropathy recovers to Grade 1 or completely resolves.

Table 4 nab-Paclitaxel Permanent Dose Reductions for Neurological Toxicity

Neurological Toxicity	Occurrence	Weekly nab-Paclitaxel Dose Modification
Grade 3 or 4 peripheral neuropathy	First	Withhold treatment until resolves to Grade ≤1, then resume treatment at 75 mg/m^2
	Second	Withhold treatment until peripheral neuropathy resolves to Grade ≤1, then resume treatment at 50 mg/m^2
	Third	Discontinue treatment

5.1.7.4 Hepatic Toxicity

Nab-paclitaxel should be withheld for Grade 3 or 4 hepatic toxicity as specified in Table 5.

Table 5 nab-Paclitaxel Dose Modification for Hepatic Toxicity

Hepatic Toxicity	Nab-Paclitaxel Dose Modification
SGOT (AST) level <10×ULN **and** Bilirubin level >ULN to ≤1.5×ULN	No dose modification; proceed with 100 mg/m^2
SGOT (AST) level <10×ULN **and** Bilirubin level >1.5 to ≤5×ULN	Interrupt treatment until SGOT (AST) level <10×ULN **and** bilirubin level ≤1.5×ULN, then reduce to 75 mg/m^2 [a] If toxicity does not resolve to above criteria within 3 weeks, discontinue treatment.
SGOT (AST) or SGPT (ALT) level >10×ULN **or** Bilirubin level >5×ULN	Discontinue treatment

SGOT=serum glutamic-oxaloacetic transaminase; SGPT= serum glutamic pyruvic transaminase; ULN=upper limit of normal.

[a] A dose increase to 100 mg/m^2 in subsequent courses should be considered if the patient tolerates the reduced dose for two cycles.

The investigator should make all efforts to exclude malignant disease progression as a cause of liver enzyme derangement.

5.1.7.5 Pulmonary events/Pneumonitis: Atezolizumab/Placebo and nab-Paclitaxel

Atezolizumab

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 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 the Atezolizumab Investigator's Brochure.

nab-Paclitaxel

Interstitial pneumonitis has been observed in <1% of patients with nab-paclitaxel monotherapy and 4% with the use of nab-paclitaxel in combination with gemcitabine. Monitor patients closely for signs and symptoms of pneumonitis.

nab-Paclitaxel should be permanently discontinued upon ruling out infectious etiology and making a diagnosis of pneumonitis. Promptly initiate appropriate treatment and supportive measures.

Infections should be ruled out with routine microbiological and/or immunologic methods.

After ruling out an infectious etiology, intravenous high-dose corticosteroid therapy should be instituted without delay, with appropriate premedication and secondary pathogen coverage. Patients with an added immunological component may also require immune modulation with azathioprine or cyclophosphamide.

Table 6 Management Guidelines for Pulmonary Events, including Pneumonitis: Atezolizumab/Placebo and nab-Paclitaxel, or nab-Paclitaxel Alone

Event	Atezolizumab/Placebo	nab-Paclitaxel
Pulmonary event, All Grades	• Refer to Appendix 10	• Permanently discontinue nab-paclitaxel. • After ruling out infection, start high-dose IV corticosteroids with appropriate premedication and secondary pathogen coverage.

IV=intravenous.

5.1.7.6 Other Toxicities

For any Grade 3 or 4 toxicity not mentioned above, nab-paclitaxel should be withheld until the patient recovers completely or to Grade 1 toxicity. Nab-paclitaxel may be resumed at reduced doses (see Table 7) when toxicity recovers to Grade 1 or completely resolves. The treatment should then be resumed at 75% dose (permanent dose reduction) for Grade 3 toxicities and 50% of dose (permanent dose reduction) for Grade 4 toxicities. If recovery to Grade 1 toxicity does not occur within 3 weeks, the patient's chemotherapy will be discontinued. For Grade 1 and 2 toxicities, no dose reduction should be made.

Table 7 nab-Paclitaxel Permanent Dose Reductions for Non-Hematologic, Non-GI, Non-Neurologic, and Non-Hepatic, Toxicity

Adverse Reaction	Occurrence	Weekly nab-Paclitaxel Dose (mg/m^2)
Grade 3 or 4 non-hematologic, non-GI, non-neurologic, non-hepatic toxicity	First	75
	Second	50
	Third	Discontinue treatment

GI=gastrointestinal.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

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

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

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

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

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following conditions which may be suggestive of an autoimmune disorder:

- Pneumonitis
- Grade ≥3 hypoxia or dyspnea
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, or adrenal insufficiency
- Vasculitis
- Hepatitis

- Grade ≥2 transaminitis (AST or ALT >3×ULN and bilirubin >2×ULN or AST/ALT >10×ULN)
- Systemic lupus erythematosus
- Guillain-Barre Syndrome
- Skin reactions: vitiligo, pemphigoid

The following events also require immediate reporting:

- Events suggestive of hypersensitivity, cytokine release, influenza-like illness, systemic inflammatory response syndrome (SIRS), or infusion-reaction syndromes
- 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 5.3.5.6, Abnormal Liver Function Tests)
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4, 5.5, and 5.6.

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until 30 days after the last dose of study drug or until the initiation of another anti-cancer therapy, whichever occurs first. After this period, investigators

should report any serious adverse events and adverse events of special interest that are believed to be related to prior treatment with study drug (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v4.0 will be used for assessing adverse event severity. Table 8 will be used for assessing the severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 8 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

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

Note: Based on the NCI CTCAE (Version 4.0), which can be found at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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

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

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

[d] Must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2. Deaths that are attributed by the investigator solely to progression of mBC should be recorded only on the Study Discontinuation eCRF (see Section 5.3.5.8).

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 related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions

Adverse events that occur during or within 24 hours after study drug administration should be captured as individual signs and symptoms on the Adverse Event eCRF rather than an overall diagnosis (e.g., record dyspnea and hypotension as separate events rather than a diagnosis of infusion-related reaction).

5.3.5.2 Diagnosis versus Signs and Symptoms

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

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

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

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether or not the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF.

If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.5 Abnormal Laboratory Values

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

- Accompanied by clinical symptoms

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

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

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

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

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

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or, if a diagnosis cannot be established, the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2)

and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (see Section 5.4.2).

5.3.5.7 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:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator's judgment

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF (see Section 5.3.5.4), unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.8 Deaths

All deaths occurring during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of mBC should be recorded only on the Study Completion/Early Discontinuation eCRF. All other deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

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. The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. 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.

During survival follow-up, deaths attributed to progression of mBC should be recorded only on the Survival eCRF, while the date of death should be captured on the Study Discontinuation eCRF.

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Breast Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only.

In most cases, the expected pattern of progression will be based on RECIST. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or to perform an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that both 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 (including symptoms)

The following hospitalization scenario is not considered to be a serious adverse event but should be reported as an adverse event instead:

- Hospitalization for outpatient care outside of normal clinic operating hours that is required per protocol or per local standard of care

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

Study drug overdose is the accidental or intentional use of the drug(s) in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event but it may result in an adverse event.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF and reported as a protocol deviation.

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No safety data related to overdosing of atezolizumab are available.

5.3.5.13 Patient-Reported Outcome Data

PRO measures to be collected in the study are described in Section 3.3.8. The methods for collecting and analyzing PRO data are different from those for the ascertainment of observed or volunteered adverse events. Because of these differences, PRO data will not be reported as adverse events; no attempt will be made to resolve any noticeable discrepancies between PRO data and observed or volunteered adverse events and no safety analyses will be performed using PRO data. The PRO data will be presented in tables, figures, and data listings separate from the adverse event data, and will be included in the appropriate section of the final study report.

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; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.4.2 for further details)

- Non-serious adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

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

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor: [redacted], M.D. (primary)
Telephone No.: [redacted]
Mobile Telephone No.:

Medical Monitor: [redacted], *M.D.* (secondary)
Telephone No.: [redacted]
Mobile Telephone No.:

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor contact information, will be distributed to all investigators.

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

5.4.2.1 Events that Occur Prior to Study Drug Initiation

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

5.4.2.2 Events that Occur After Study Drug Initiation

After initiation of study drug, serious adverse events and non-serious adverse events of special interest will be reported until 30 days after the last dose of study drug or until initiation of another anti-cancer therapy, whichever occurs first. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

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

Instructions for reporting post-study adverse events 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 last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancies should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until the conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will update the Pregnancy Report eCRF when updated information on the course and outcome of the pregnancy becomes available.

In the event that the EDC system is unavailable, a Clinical Trial Pregnancy Reporting Form and Fax Coversheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), with use of the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within

6 months after the last dose of nab-paclitaxel. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus to support an informed decision in cooperation with the treating physician and/or obstetrician.

In the event that the EDC system is unavailable, follow reporting instructions provided in Section 5.4.3.1.

5.4.3.3 Abortions

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

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

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better or is assessed as stable by the investigator or until the patient is lost to follow-up or withdraws consent. Every effort should be made to follow all serious adverse

events considered related to study drug or study-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious 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 POST-TREATMENT ADVERSE EVENTS

At the treatment discontinuation visit, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

Investigators should notify the Sponsor of any serious adverse events and adverse events of special interest that are believed to be related to prior drug treatment or study procedures that occur at any time after a patient has discontinued treatment. The Sponsor should also be notified if the investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient who participated in this study.

The investigator should report these events to Roche Safety Risk Management on the Adverse Event eCRF. If the Adverse Event eCRF is no longer 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 with use of the fax number or email address provided to investigators.

During survival follow-up, deaths attributed to progression of mBC should be recorded only on the Survival eCRF.

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

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

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

- *A*tezolizumab Investigator's Brochure
- *EU Summary of Product Characteristics* for nab-paclitaxel.

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

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

An iDMC will monitor the incidence of these expected events 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

This is a randomized, Phase III, double-blind, placebo-controlled study designed to evaluate the safety and efficacy of atezolizumab+nab-paclitaxel as compared with placebo+nab-paclitaxel.

The analysis populations are defined as follows:

- The ITT population is defined as all randomized patients, whether or not the assigned study treatment was received.
- The PD-L1–selected subpopulation is defined as patients in the ITT population whose PD-L1 status is IC1/2/3 at the time of randomization.
- The ORR-evaluable population is defined as patients in the ITT population with measurable disease at baseline.
- The DOR-evaluable population is defined as patients with an objective response.
- The PRO-evaluable population is defined as patients in the ITT population with baseline PRO assessment.

- The safety-evaluable population is defined as patients who received any amount of any study drug.

For all efficacy analyses, patients will be grouped according to the treatment assigned at randomization.

For safety analyses, patients will be grouped according to whether any amount of atezolizumab was received, including cases in which atezolizumab was received in error.

6.1 DETERMINATION OF SAMPLE SIZE

Up to 900 patients in total will be randomized into the study.

6.1.1 Type I Error Control

The Type I error (α) for this study is 0.05 (two-sided). Type I error will be controlled for the following efficacy endpoints:

- Co-primary efficacy endpoint of investigator-assessed PFS by RECIST v1.1 (as defined for United States registrational purposes; see Section 6.4.1; ITT and PD-L1–selected subgroups)
- Co-primary efficacy endpoint of OS (ITT and PD-L1–selected subgroups)
- Secondary efficacy endpoint: Investigator-assessed ORR by RECIST v1.1 (measurable disease population)

Type I error will be controlled by comparing these endpoints between treatment arms according to the following testing procedure (Figure 2).

At the time of the analysis of PFS, the co-primary endpoints of PFS and OS and the secondary endpoint of ORR are tested in the ITT population and in the PD-L1–selected subpopulation, as follows:

1. α (0.05) will be allocated between PFS (0.01) and OS (0.04). The allocated type I error for PFS is further allocated to PFS in the ITT (0.005) and PFS in the PD-L1–selected subgroup (0.005).

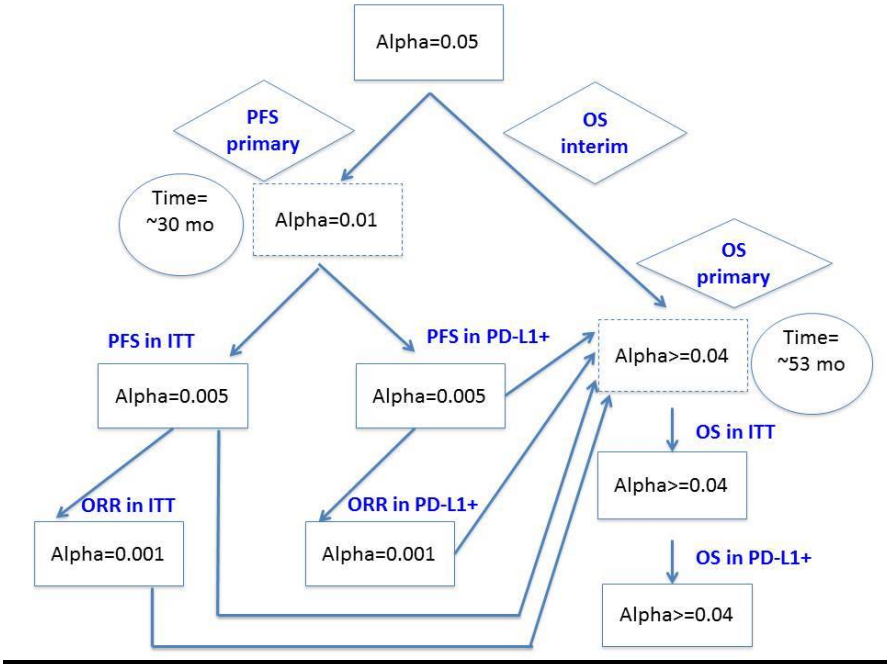
Testing of PFS and ORR

2. Test the null hypothesis of no difference in PFS between the two arms using the stratified log-rank test in the ITT population and the PD-L1–selected subgroup with the allocated type I error.
3. If one or both of the null hypotheses from the step above is rejected, ORR will subsequently be compared between the two arms in the corresponding populations (one or both) using the stratified Cochran-Mantel-Haenszel test using a Type I error of 0.001 for each correspondingly.

Testing of OS

4. At the time of the analysis of PFS, an interim analysis of OS in the ITT (OS [ITT]) will be performed. The interim analysis of OS (ITT) will be performed regardless of the results of the analyses of PFS and ORR. The interim analysis boundary for statistical significance will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming use function according to the Type I error allocated to the comparison of OS (ITT). Allocation of the type I error to the comparison of OS (ITT) will depend on the outcome of the testing of PFS and ORR outlined in the Steps 1–3 above. Details for the different Type I error allocations to the OS (ITT) testing are provided in Appendix 9.
5. If hypothesis of no difference in OS in the ITT population can be rejected, OS in the PD-L1–selected subgroup will be compared by recycling the Type I error used for OS (ITT) testing.

Figure 2 Overview of the Type I Error Control



ITT=intent to treat; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PD-L1=programmed death-ligand 1.

6.1.2 Co-Primary Endpoint: Progression-Free Survival

The definitive analysis of the co-primary endpoint of PFS will take place when approximately 600 PFS events (67% of 900; see Section 6.4.1), have occurred in the ITT population on the basis of the following assumptions:

- Two-sided, stratified log-rank test at the 0.005 significance level (two-sided) in the ITT population
- Approximately 95% power for PFS in ITT population

- Median PFS for of 6 months in the placebo+nab-paclitaxel arm and 10 months in the atezolizumab+nab-paclitaxel arm (corresponding to an HR of 0.6) in the ITT population
- 2-month initial delay in the onset of the treatment effect
- 5% annual loss to follow-up for PFS
- No interim analysis for PFS in the ITT population

Accrual is projected to occur over 26 months. On the basis of these assumptions, the required number of PFS events in the ITT population is projected to occur at Month 30. Also on the basis of these assumptions, it is projected that an observed HR of 0.72 or better will result in a statistically significant difference between the treatment arms (i.e., HR=0.72 will be the minimally detectable difference for the analysis; this corresponds to an improvement of 2.3 months in median PFS from 6 months in the placebo+nab-paclitaxel arm to 8.3 months in the atezolizumab+nab-paclitaxel arm).

At this timepoint, a definitive analysis of PFS in the PD-L1–selected subgroup and an interim analysis on OS are conducted in addition (see Section 6.1.1). Assuming a PD-L1–selected rate of 40% and assuming a median PFS of 6 months in the placebo + nab-paclitaxel arm and 12 months in the atezolizumab+nab-paclitaxel arm (corresponding to a HR of 0.5) in the PD-L1–selected subgroup, it is predicted that there will be about 215 PFS events (59.8% of 360 PFS events). This corresponds to a power of about 75% and a minimally detectable difference of HR=0.57 (corresponding to an increase of about 4.5 months from 6 months to 10.5 months).

6.1.3 Co-Primary Endpoint: Overall Survival

The timing and the two interim analyses and the final analysis for OS depends on the results of the definitive analysis of the co-primary endpoint PFS as well as the secondary endpoint ORR as described in Appendix 9, where the pre-specified boundaries for the different scenarios are also presented.

The final analysis will take place around 53 months after FPI, when approximately the pre-planned number of deaths will have been observed (see Section 3.2 for details on the end of the study), based on the following assumptions:

- Two-sided, stratified log-rank test at the 0.005 significance level (two-sided) in the ITT population
- Approximately 88% power for OS in ITT population
- Median OS of 16 months in the placebo+nab-paclitaxel arm and 20.5 months in the atezolizumab+nab-paclitaxel arm (corresponding to an HR of 0.78) in the ITT population
- Assumption of proportionality
- 5% annual loss to follow-up for OS

- Two interim analyses, at approximately 50% and 80% of the information fraction (see Appendix 9 for details)

Accrual is projected to occur over 26 months. On the basis of these assumptions, the required number of OS events in the ITT population is projected to occur in Month 53 (α=0.05; Month 58 if α=0.04).

If the null hypothesis of no difference of OS in the ITT population can be rejected, OS in the PD-L1–selected subgroup will be tested with the same α as OS in the ITT population. Again assuming a PD-L1–selected rate of 40% and assuming a median OS of 16 months in the placebo+nab-paclitaxel arm and 22.5 months in the atezolizumab+nab-paclitaxel arm (corresponding to a HR of 0.71) in the PD-L1–selected subgroup, it is predicted that there will be about 253 (α=0.05; 269 if α=0.04) OS events in this subgroup. This corresponds to a power of about 76%.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, major protocol violations including major deviations of inclusion/exclusion criteria, and 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 (in particular, 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 study treatment.

6.4 EFFICACY ANALYSES

Efficacy analyses will be performed separately for the ITT population and the PD-L1–selected subpopulation.

6.4.1 Co-Primary Efficacy Endpoints

6.4.1.1 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 (see Appendix 3), or death from any cause, whichever occurs first. PFS is simultaneously assessed in the ITT and PD-L1–selected subgroup (see Section 6.1.1).

For United States registration purposes, the co-primary efficacy endpoint of PFS will be defined as described above with an additional censoring rule for missed visits. Data for patients with a PFS event who missed two or more scheduled assessments immediately

prior to the PFS event will be censored at the last tumor assessment prior to the missed visits. Type I error control (see Section 6.1.1) will be applied to this analysis of PFS.

The following analyses will be performed for both PFS endpoints described above. PFS will be compared between treatment arms with use of the stratified log-rank test. The HR for disease progression or death will be estimated using a stratified Cox proportional hazards model. The 95% CI for the HR will be provided. The stratification factors will be the same as the randomization stratification factors: presence of liver metastases (yes vs. no), prior taxane treatment (yes vs. no), and tumor PD-L1 status (IC0 vs. IC1/2/3). Results from an unstratified analysis will also be provided. Kaplan-Meier methodology will be used to estimate the median PFS for each treatment arm, and Kaplan-Meier curves will be produced. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS for each treatment arm (Brookmeyer and Crowley 1982).

6.4.1.2 Overall Survival

OS is defined as the time from the date of randomization to the date of death from any cause. Testing of OS is outlined in Section 6.1.1 and analysis of OS is performed analogously to PFS.

OS will be analyzed in a similar manner as PFS.

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- ORR by investigator assessment (ORR-evaluable population; RECIST v1.1 [see Appendix 3])
- DOR by investigator assessment (DOR-evaluable population; RECIST v1.1)
- TTD in Items 29 and 30 of the EORTC QLQ-C30

6.4.2.1 Objective Response Rate

An objective response is defined for patients with measurable disease at baseline as either a partial response (PR) or a complete response (CR) using RECIST v1.1. Confirmation of PR or CR is not required. Patients not meeting this criterion, including patients without any post-baseline tumor assessment, will be considered as non-responders. ORR is defined as the proportion of patients who have an objective response.

An estimate of ORR will be calculated for each treatment arm, and its 95% CI will be calculated using the Clopper-Pearson method.

ORR will be compared between treatment arms using the stratified Cochran-Mantel-Haenszel test. The stratification factors will be the same as those described for the analysis of the primary endpoint of PFS. The difference in ORR

between treatment arms will be calculated, and its 95% CI will be calculated using the normal approximation to the binomial distribution.

6.4.2.2 Duration of Objective Response

DOR is defined for patients who had an objective response as the time from the first occurrence of a documented unconfirmed response (CR or PR) to the date of disease progression per RECIST v1.1 or death from any cause, whichever occurs first. Data for patients who have not experienced disease progression or death will be censored at the last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of CR or PR, data for DOR will be censored at the date of the first occurrence of CR or PR+1 day.

The analysis of DOR is based on a non-randomized subset of patients (those who achieved an unconfirmed response); therefore, formal hypothesis testing will not be performed for this endpoint. Comparisons between treatment arms will be made for descriptive purposes only. The methodologies described for the analysis of PFS will be used for the analysis of DOR except that the analysis will not be stratified.

6.4.2.3 Time to Deterioration in Global Health Status

See Section 6.7 for a description of the endpoint and corresponding analysis.

6.4.3 Handling of Missing Data

For PFS, patients without a date of disease progression will be analyzed as censored observations on the date of last tumor assessment. If no post-baseline tumor assessment is available, PFS will be censored at the date of randomization+1 day. In the analysis of PFS for United States registrational purposes, data for patients with a PFS event who missed two or more scheduled assessments immediately prior to the PFS event will be censored at the last tumor assessment prior to the missed visits (see Section 6.4.1).

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

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

6.5 SAFETY ANALYSES

Safety analyses will include all patients who received at least one dose of study treatment, with patients grouped according to the treatment actually received.

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

Verbatim descriptions of adverse events will be mapped to MedDRA terms. Treatment-emergent events (defined as events occurring on or after the first dose of study treatment and within 30 days prior to the last dose of study treatment) will be summarized by MedDRA term, appropriate MedDRA levels, and NCI CTCAE v4.0 grade, regardless of relationship to 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 leading to withdrawal of study drug, adverse events leading to dose reduction or interruption, Grade ≥3 adverse events, Grade 5 adverse events, serious adverse events, and adverse events of special interest.

All deaths and causes of death will be summarized.

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

ATA results will be summarized and listed by patient and cycle.

6.6 PHARMACOKINETIC ANALYSES

Atezolizumab serum concentration data (C_{min} and C_{max}) will be tabulated and summarized. Descriptive statistics will include means, medians, ranges, and SDs, as appropriate.

Plasma concentrations of nab-paclitaxel (reported as total paclitaxel) will be measured where applicable (see Appendix 2). The concentration data will be summarized with use of descriptive statistics as stated above.

Additional PK and PD analyses will be conducted as appropriate.

6.7 PATIENT-REPORTED OUTCOME ANALYSES

6.7.1 Analysis of Time to Deterioration in Global Heath Status

The primary patient-reported endpoint is the TTD in Global Health Status/HRQoL. Deterioration in global health status/HRQoL (Items 29, 30 of the EORTC QLQ C30) is defined as a ≥10-point decrease from the baseline scale score. A 10-point change is defined as the minimally important difference (MID) (Osoba et al. 1998). Data for patients who do not achieve a 10-point decrease will be censored at the last time PRO data are available. Only patients with baseline global health status/HRQoL scores will be included in the analysis. Data for patients without at least one post-baseline assessment will be censored at the date of randomization +1 day.

TTD in global health status/HRQoL will be compared between the treatment groups using the same method as the primary endpoint of PFS.

6.7.2 Exploratory Patient-Reported Outcomes Analyses

Summary statistics (mean, standard deviation, median, and range) of absolute scores and mean changes from baseline will be calculated for all items and subscales of the EORTC QLQ-C30 and QLQ-BR23 at each assessment timepoint for each arm while on treatment. The mean (and 95% CI) and median of the absolute scores and the changes from baseline will be reported for interval and continuous variables. Previously published minimally important differences will be used to identify meaningful change from baseline within each treatment group on the functional and disease/treatment-related symptoms scales (Osoba et al. 1998; Cocks et al. 2011).

A time-to-event analysis to investigate the time to clinically meaningful deterioration in the functional (physical, role, and cognitive) subscales of the EORTC QLQ-C30 will be conducted to assess the time from baseline to worsening in patient function. Deterioration in function will be assessed using the published corresponding MIDs by Cocks et al. (2011). Patients who do not achieve an MID on the basis of published thresholds will be censored at the last time PRO data are available and only patients with baseline scores will be included. Patients without at least one post-baseline assessment will be censored at the date of randomization +1 day. A stratified log-rank test will be used to test the differences between treatment arms.

A longitudinal analysis will be conducted to estimate the effect difference on PRO repeated responses over a selected period of time and between the treatment arms, and mixed models on a set of covariates (baseline domain score, patient demographic, and clinical variables) will be conducted. Change from baseline at subsequent cycles will be presented by treatment arm and will include least squares mean (LS Mean), difference in LS Mean between two treatment arms, and 95% confidence intervals for the differences. The standard error (SE) will also be calculated for each LS Mean.

The EORTC QLQ-C30 and QLQ-BR23 data will be scored according to the EORTC scoring manual (Fayers et al. 2001). In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a pro-rated score will be computed consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed, the subscale will be considered as missing. PRO completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm.

6.7.2.1 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 analysis will be reported separately from the clinical study report.

6.8 EXPLORATORY ANALYSES

6.8.1 Subgroup Analyses

To assess the consistency of study results in subgroups defined by demographic and baseline characteristics, PFS, OS, and ORR in these subgroups will be examined.

6.8.2 Exploratory Biomarker Analysis

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

6.9 INTERIM ANALYSES

6.9.1 Progression-Free Survival

There are no planned interim analyses of the co-primary endpoint of PFS.

6.9.2 Overall Survival

A total of three analyses of OS will be performed (two interim analyses and one final analysis). The timing and the two interim analyses and the final analysis for OS depends on the results of the definitive analysis of the co-primary endpoint PFS as well as the secondary endpoint ORR as described in Appendix 9, where the pre-specified boundaries for OS of all different scenarios are also presented (see Section 6.1.3).

The boundary for statistical significance at each interim analysis and the final analysis will be determined based on the Lan-DeMets implementation of the O'Brien-Fleming use function (DeMets and Lan 1994).

6.9.3 Safety Monitoring

The iDMC will convene to review interim safety analysis results. See Section 3.1.1 for additional details regarding the iDMC.

6.9.4 Optional Interim Analysis

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one additional interim efficacy analysis for OS. The specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed are outlined below.

The Sponsor will remain blinded. The interim analysis will be conducted by an external statistical group and reviewed by the independent Data Monitoring Committee (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 Statistical Analysis Plan

(SAP), and the SAP will be submitted to relevant health authorities at least 2 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., stop the study for positive efficacy, stop the study for futility), and the iDMC charter will also be made available to relevant health authorities.

If there is a potential for the study to be stopped for positive efficacy as a result of the interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained.

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 using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by

relevant national or local health authorities, whichever is longer. After that period of time the documents may be destroyed, subject to local regulations.

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and *applicable* regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug application (IND) will comply with FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) 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 Informed Consent Form (and ancillary sample Informed Consent Forms such as a Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Informed Consent Form will contain a separate section that addresses the collection of optional samples and the use of remaining mandatory samples (plasma, serum, whole blood, and tissue) for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told 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 allow the collection of optional samples and to use any remaining specimens for exploratory research. Patients who decline to participate will not provide a separate signature.

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

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

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

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

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for 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 Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

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

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports

or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This study will be sponsored and managed by F. Hoffmann-La Roche Ltd. Approximately 257 sites globally will participate in the study and up to 900 patients will be randomized.

Randomization will occur through the IxRS. 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; 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 to the public, both at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study, and redacted clinical study reports and other summary reports will be provided upon request (see Section 8.4 for more details)*, provided the requirements of Roche's global policy on data sharing have been met*. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

http://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 involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical study results within 6 months after the availability of the respective clinical study report. In addition, for all clinical studies in patients involving an IMP for which a marketing authorization application has been filed

or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Assessments

Assessment Window (Days)	Screening	All Cycles		Treatment Discontinuation [d]		
	Days – 28 to –1	1 [b]	8 (+3) [b,c]	15 (+3) [b]	≤30 Days after Last Dose	Follow-Up
Signed Informed Consent Form(s) [a]	x					
Review of eligibility criteria	x					
Medical, surgical, and cancer histories, including demographic information [e]	x					
HIV, HBV, HCV serology [f]	x					
Concomitant medications [g]	x	x	x	x	x	
Tumor assessment [h]	x	See footnote (h)			x	x
Head CT or MRI	x					
Patient-reported outcomes [i]		x			x	x[j]
Complete physical examination [k]	x				x	
Limited physical examination [k]		x [l]				
ECOG performance status	x	x [l]			x	
Vital signs [m]	x	x	x	x	x	
12-lead electrocardiogram [n]	x	Perform as clinically indicated				
Weight	x	x			x	
Height	x					
Hematology [o]	x	x [l]	x	x	x	

Appendix 1
Schedule of Assessments (cont.)

Assessment Window (Days)	Screening	All Cycles		Treatment Discontinuation [d]		
	Days – 28 to –1	1 [b]	8 (+3) [b,c]	15 (+3) [b]	≤30 Days after Last Dose	Follow-Up
Serum chemistry [p]	x	x [l]	x	x	x	
Coagulation panel (aPTT, INR)	x				x	
C-reactive protein testing	x	x [l]				
Urinalysis [q,r]	x	Perform as clinically indicated				
Pregnancy test (women of childbearing potential only)	x [s]	x [t]			x [t]	
TSH, free T3, free T4	x	C1D1 & every 2nd cycle [l]			x	
Auto-antibody testing [u]		x				
Serum sample for ATA assessment [v]		x			x	x
Serum sample for atezolizumab PK sampling [v]		x			x	x
Plasma samples for nab-paclitaxel [v]		x				
Blood samples for PD biomarkers [v]		x			x	
Optional whole blood sample for RCR DNA [w]		x				
Adverse events [x]		x	x	x	x	
Atezolizumab/placebo infusion [y]		x		x		
Nab-paclitaxel administration		x	x	x		
Archival/fresh screening FFPE tumor tissue block or 20 unstained slides [z]	x					
Optional fresh biopsy		Cycle 2 [aa]				
Mandatory FFPE tumor tissue specimen at disease progression [bb]					x	
Survival and anti-cancer therapy follow-up [cc]						x

Appendix 1
Schedule of Assessments (cont.)

anti-HBc=antibody to hepatitis B core antigen; anti-HBs=antibody to hepatitis B surface antigen ATA=anti-therapeutic antibody; CT=computerized tomography; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organisation for Research and Treatment of Cancer; ePRO=electronic patient-reported outcome; EQ-5D (5L)=European Quality of Life 5 Dimensions, 5 level; FFPE=formalin fixed paraffin embedded; HBV=hepatitis B virus; HCV=hepatitis C virus; MRI=magnetic resonance imaging; PD-L1 = programmed death-ligand 1; PK=pharmacokinetic; q8w=every 8 weeks; QLQ-BR23=Quality-of-life Questionnaire Breast Cancer Module; QLQ-C30=Quality-of-life Questionnaire Core 30; RCR=Roche Clinical Repository; RECIST=Response Evaluation Criteria in Solid Tumors; TSH=thyroid-stimulating hormone; v=version.

Note: Assessments scheduled on the days of study treatment infusions should be performed before the infusion unless otherwise noted.

[a] Written informed consent is required before performing any study-specific tests or procedures. Signing of the Informed Consent Form can occur outside the 28-day screening period. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to randomization (except where otherwise specified) may be used for screening assessments rather than repeating such tests. 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.

[b] Assessment window of ±3 days for Day 1 of Cycles ≥2. Doses of nab-paclitaxel should not be administered more frequently than every 7 days. If scheduled dosing is precluded because of a holiday, then dosing may be postponed to the soonest following date, with subsequent dosing continuing on the specified schedule. After five cycles, one of three cycles may be delayed by 1 week to allow for vacations. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment infusion unless otherwise noted.

[c] Day 8 visits are not required for patients who have discontinued nab-paclitaxel and are continuing treatment with atezolizumab/placebo alone.

[d] Patients will be asked to return to the clinic not more than 30 days after the decision to discontinue treatment for a treatment discontinuation visit. The visit at which the decision is made to discontinue treatment (e.g., disease progression is determined or confirmed) may be used as the treatment discontinuation visit.

[e] Cancer history includes stage, date of diagnosis, and prior anti-tumor treatment. Demographic information includes age and self-reported race/ethnicity. Reproductive status and smoking history should also be captured.

[f] All patients will be tested for HIV locally prior to the inclusion into the study; HIV-positive patients will be excluded from the clinical study. Hepatitis B surface antigen, anti-HBc, and anti-HBs should be collected during screening and tested locally. HBV DNA must be collected prior to randomization in patients who have negative serology for hepatitis B surface antigen and positive serology for anti-HBc.

Appendix 1
Schedule of Assessments (cont.)

[g] Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has used within the 7 days prior to the screening visit should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

[h] Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of Cycle 1, Day 1 may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the screening visit. Radiologic imaging performed during the screening period should consist of 1) CT and/or MRI of the chest/abdomen/pelvis, 2) bone scan or PET scan, and 3) any other imaging studies (CT neck, plain films, etc.) as clinically indicated by the treating physician. The same radiographic procedures and technique must be used throughout the study for each patient (e.g., if the patient had CT chest/abdomen/pelvis performed during screening, then she should subsequently undergo CT performed using the same radiologic protocol throughout the remainder of the study). Results must be reviewed by the investigator before dosing at the next cycle. Tumor assessments will be performed at baseline, every 8 weeks (±1 week) for the first 12 months following randomization, and every 12 weeks (±1 week) thereafter, with additional scans as clinically indicated. All known sites of disease documented at screening should be re-assessed at each subsequent tumor evaluation. Tumor assessments performed after the screening period should consist of 1) CT and/or MRI of the chest/abdomen/pelvis, 2) bone scan or PET scan if there were osseous sites of disease identified on these studies during the screening period or if these studies are felt to be clinically indicated by the treating physician, and 3) any other imaging studies felt to be clinically indicated by the treating physician. Tumor response will be evaluated using RECIST v1.1 (Appendix 3). In the absence of disease progression, tumor assessments should continue regardless of whether patients discontinue study treatment, unless they withdraw consent or the study is terminated by the Sponsor, whichever occurs first.

[i] The EORTC QLQ-C30, QLQ-BR23, and EQ-5D-5L questionnaires will be completed in order by the patient on an ePRO tablet at the site at baseline (Cycle 1, Day 1), and then Day 1 of each subsequent cycle thereafter, at the treatment discontinuation visit, and during survival follow-up. All PRO questionnaires scheduled for administration during a clinic visit are required to be completed by the patient at the investigational site at the start of the clinic visit and before discussion of the patient's health state, lab results, or health record, before administration of study treatment, and/or prior to any other study assessments that could bias patients' responses to ensure that the validity of the instrument is not compromised and that data quality meets regulatory requirements. Interview assessment by a member of the clinical staff will be allowed if the patient is not able to complete the measure on their own. Study personnel should review the ePRO device to ensure measures have been completed and saved before the patient leaves the investigational site. All patients will also complete the three PRO questionnaires every 28 days for 1 year after treatment discontinuation, regardless of whether the patient is receiving subsequent anti-cancer therapy. Questionnaires will be completed after treatment discontinuation by the patient at home on an ePRO handheld device provisioned to the patient at the treatment discontinuation visit. Male patients will not complete the QLQ-BR23, as this measure has not been validated in men.

[j] Collect every 28 days (±3 days) for 1 year during survival follow-up.

Appendix 1
Schedule of Assessments (cont.)

[k] Complete and limited physical examinations are defined in Section 4.5.2.2.

[l] ECOG performance status, limited physical examination, local laboratory assessments, and C-reactive protein assessment may be obtained ≤96 hours before Day 1 of each cycle.

[m] Vital signs include heart rate, respiratory rate, blood pressure, and temperature. On days of study treatment administration (atezolizumab, placebo, or nab-paclitaxel), the patient's vital signs should be determined up to 60 minutes before all infusions. Vital signs will also be collected during and after every infusion of atezolizumab or placebo if clinically indicated.

[n] Patients should be resting and in a supine position for at least 10 minutes prior to each ECG collection.

[o] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, and other cells), and platelet count. A manual differential can be done if clinically indicated. Local laboratory assessment must be reviewed prior to every study treatment administration. Refer to Section 4.1.1 for a list of laboratory results obtained within 14 days prior to the first study treatment.

[p] Serum chemistry includes BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate, calcium, phosphorus, glucose, total bilirubin, ALT, AST, alkaline phosphatase, total protein, and albumin. Magnesium and phosphorus must be tested during screening; during treatment, magnesium and phosphorus should be tested as clinically indicated. Local laboratory assessments must be reviewed prior to every study treatment administration. Refer to Section 4.1.1 for a list of laboratory results obtained within 14 days prior to the first study treatment.

[q] Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood).

[r] As clinically indicated during treatment.

[s] Serum pregnancy test within 14 days before Cycle 1, Day 1.

[t] Urine pregnancy test; if a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[u] Baseline sample to be collected on Cycle 1, Day 1 prior to the first dose of study treatment. For patients who show evidence of immune-mediated toxicity, additional samples will be collected, and all samples will be analyzed centrally. Includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[v] See Appendix 2 for detailed schedule.

[w] Whole blood for DNA isolation will be collected from patients who have consented to optional RCR sampling at baseline. If, however, the RCR 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.

Appendix 1
Schedule of Assessments (cont.)

[x] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. After this period, investigators should report any serious adverse events and adverse events of special interest that are believed to be related to prior treatment with study drug. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or study-related procedures until a final outcome can be reported.

[y] Patients should receive their first dose of study drug on the day of randomization if possible. If this is not possible, the first dose should occur no later than 3 days after randomization. For atezolizumab/placebo, the initial dose will be administered over 60 (±10) minutes. If the first infusion is well tolerated, all subsequent infusions may be administered over 30 (± 10) minutes. For nab-paclitaxel, study drug will be administered according to the local prescribing information.

[z] Tumor tissue should be of good quality based on 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, and lavage samples are not acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation. Retrieval of archival tumor sample can occur outside the 28-day screening period.

[aa] For patients who have provided consent on the Consent for Optional Biopsy; optional tumor biopsy samples may be collected by core needle or excisional/punch biopsy at Cycle 2 Day 1 per investigator discretion.

[bb] Preferably, samples collected at the time of radiographic progression should be collected from growing lesions.

[cc] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months after the treatment discontinuation visit (±21 days) until death, loss to follow-up, or until study termination by the Sponsor. All patients will be followed for survival and new anti-cancer therapy (including targeted therapy and immunotherapy) information unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Appendix 2
Anti-Therapeutic Antibody, Pharmacodynamic, and Pharmacokinetic Sampling Schedule

Study Visit	Timepoint	Sample
Cycle 1, Day 1	Predose	ATA Atezolizumab PK Nab-paclitaxel PK Pharmacodynamics [b]
	30 (±10) minutes after end of atezolizumab infusion	Atezolizumab PK
Cycle 2, Day 1	Predose	ATA Atezolizumab PK [a] Pharmacodynamics [b]
Cycle 3, Day 1	Predose	ATA Atezolizumab PK [a] Nab-paclitaxel PK [a]
	5–10 minutes before the end of nab-paclitaxel infusion	Nab-paclitaxel PK [a]
	1 hour after the end of nab-paclitaxel infusion	Nab-paclitaxel PK [a]
Cycle 4, Day 1	Predose	ATA Atezolizumab PK [a]
Cycles 8 and 16 and every eight cycles thereafter, Day 1	Predose	ATA Atezolizumab PK [a]
At time of radiographic progression		Pharmacodynamics [c]
Treatment discontinuation visit	At visit	ATA Atezolizumab PK [a]
120 (±30) days after last dose of atezolizumab/placebo	At visit	ATA Atezolizumab PK [a]

ATA = anti-therapeutic antibody; PK=pharmacokinetic.

[a] Sample collection for both atezolizumab and nab-paclitaxel PK is required as long as patients are receiving both atezolizumab or placebo and nab-paclitaxel. For patients who discontinue atezolizumab or placebo and continue on nab-paclitaxel alone, the scheduled collection for atezolizumab PK at the treatment discontinuation visit and 120 (±30) days after the last dose of atezolizumab or placebo is still required.

[b] Whole blood, serum, plasma.

[c] Plasma.

Appendix 3
Response Evaluation Criteria in Solid Tumors: 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:

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

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

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 masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

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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.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

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 noncystic 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

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.

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.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

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

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

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

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast due to allergy or renal insufficiency, the decision as to whether a noncontrast 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 noncontrast CT or MRI (enhanced or nonenhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward.</u> Care must be taken in measurement of target lesions on a different modality and interpretation of nontarget 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 the 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 3
Response Evaluation Criteria in Solid Tumors: 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 NONTARGET 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-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but 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 nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and should not be recorded or followed.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

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 nontarget 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 nontarget 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

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 nontarget) 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

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 the CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and below measurable limit (BML) should be ticked. (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.

Evaluation of Nontarget Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of nontarget lesions. While some nontarget 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 nontarget lesions and (if applicable) normalization of tumor marker level)

  All lymph nodes must be non-pathological in size (<10 mm short axis).

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

- **Non-CR/Non-PD**: persistence of one or more nontarget lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- **PD**: unequivocal progression of existing nontarget lesions

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

Special Notes on Assessment of Progression of Nontarget Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget 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 nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget 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 nontarget disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique,

change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show partial or complete response. 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

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 nontarget) disease only, Table 2 is to be used.

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

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

Target Lesions	Nontarget 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 Nontarget Lesions Only

Nontarget 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 nontarget 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.

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 nontarget lesions are not assessed, the response for nontarget 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 nontarget 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 3
Response Evaluation Criteria in Solid Tumors: 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.

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

Appendix 3
Response Evaluation Criteria in Solid Tumors: Modified Excerpt from Original Publication (cont.)

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 nontarget disease as shown in Table 1, Table 2, and Table 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.

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 nontarget lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or nontarget lesion.

Appendix 4
Patient-Reported Outcome Instruments

ENGLISH

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):

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

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

Please go on to the next page

Appendix 4
Patient-Reported Outcome Instruments (cont.)

ENGLISH

EORTC QLQ - BR23

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 a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

Appendix 4
Patient-Reported Outcome Instruments (cont.)

ENGLISH

During the past week:		Not at All	A Little	Quite a Bit	Very Much
47	Did you have any pain in your arm or shoulder?	1	2	3	4
48	Did you have a swollen arm or hand?	1	2	3	4
49	Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50	Have you had any pain in the area of your affected breast?	1	2	3	4
51	Was the area of your affected breast swollen?	1	2	3	4
52	Was the area of your affected breast oversensitive?	1	2	3	4
53	Have you had skin problems on or in the area of your affected breast (e g , itchy, dry, flaky)?	1	2	3	4

Appendix 4
Patient-Reported Outcome Instruments (cont.)

Health Questionna

English v sio K

Appendix 4
Patient-Reported Outcome Instruments (cont.)

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

MOBILITY

I have no problems in walking about ❑
I have slight problems in wa king 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, hou work family or leisure activities)*

I have no problems doing my usual activitie
I have slight problems doing activ ❑
I have moderate problems d al ❑
I have severe problems doi ❑
I am unable to do my usual ctivities ❑

PAIN / DISCOMFORT

I have no pain or discomfor ❑
I have slight pain o isc ❑
I hav oderat dis com ❑
I hav se con ❑
I have e pai om ❑

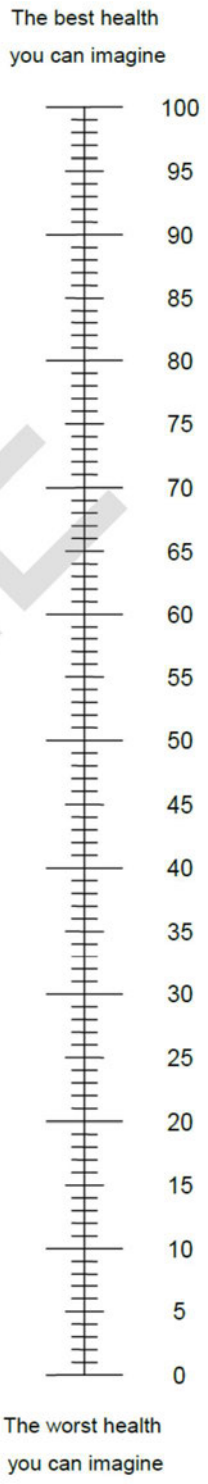
ANX ON

I am sed ❑
I am ~~slightly anxious or~~ depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Appendix 4
Patient-Reported Outcome Instruments (cont.)

- 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 5
Preexisting Autoimmune Diseases

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-mediated hypothyroidism on a stable dose of thyroid replacement hormone may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Please contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

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

Appendix 6
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study drug infusion, the following procedures should be performed:

6. Stop the study drug infusion.
7. Maintain an adequate airway.
8. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
9. Continue to observe the patient and document observations.

Appendix 7
Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix 8
Patient Eligibility per Archival and Fresh Tumor Tissue Quantity and Histology

Archival Sample		Fresh Sample			
Status	Quantity	Status	Quantity [a]	Eligible?	Reason
TNBC [b]	Adequate [c]	TNBC	Any	Yes	
TNBC [b]	Adequate	Unknown/ not analyzed [d]	Any	Yes	
TNBC [b]	Adequate	Not clinically feasible		Yes	
TNBC [b]	< Adequate	TNBC	< Adequate	No	TNBC specimen amount inadequate
TNBC [b]	< Adequate	Unknown/ not analyzed [d]	Any	No	TNBC specimen amount inadequate
TNBC [b]	< Adequate	Not clinically feasible		No	TNBC specimen amount inadequate
Non-TNBC	Any	TNBC	< Adequate	No	TNBC specimen amount inadequate
Non-TNBC	Any	Unknown/ not analyzed [d]	Any	No	No specimen demonstrating TNBC
Any	Any	2 specimens: 1 TNBC/ 1 non-TNBC	Adequate	No	Recurrent disease status uncertain
Any	Any	non-TNBC	Any	No	Most recent specimen is not TNBC
Any	Any	TNBC	Adequate	Yes	

ASCO=American Society of Clinical Oncology; CAP=College of American Pathologists; TNBC=triple negative breast cancer.

[a] A minimum of three cores is strongly recommended for the fresh specimen. However, if an adequate archival specimen has also been submitted, any number of cores will be accepted. On the other hand, if an archival specimen demonstrating TNBC status is <u>not</u> available, fresh tissue in the amount of at least 20 unstained slides (or a paraffin block) will have to be submitted.

[b] Triple-negative status will be determined by ASCO/CAP criteria (Wolff et al. 2013).

[c] 'Adequate' is defined as a block or ≥20 unstained slides. Patients with fewer than 20 unstained slides available at baseline (but no fewer than 12) may be eligible upon discussion with the Medical Monitor.

[d] ASCO/CAP guidelines recommend that the status of recurrent disease is confirmed. Under some conditions (e.g., fine-needle aspirate having been used initially to confirm recurrence), core needle or other specimens obtained subsequently may be submitted without an associated pathology report.

Appendix 9
Interim and Final Analyses for Overall Survival

Different Scenarios of PFS and ORR Testing	Alpha Level	Analysis Timing	Time from 1st Patient Enrolled (months)	Information Fraction	No. of Events	Stopping Boundary in HR	Stopping Boundary in p-Value
Both PFS and ORR are statistically significant in both IC1/2/3 and ITT	0.05	First interim	30	53%	IC1/2/3: 134 AC: 345	IC1/2/3: HR≤0.609 AC: HR≤0.734	p-value≤0.0042
		Second interim	41	80%	IC1/2/3: 202 AC: 520	IC1/2/3: HR≤0.726 AC: HR≤0.819	p-value≤0.0231
		Final	53	100%	IC1/2/3: 253 AC: 650	IC1/2/3: HR≤0.775 AC: HR≤0.853	p-value≤0.0425
PFS is statistically significant in both IC1/2/3 and ITT; ORR is statistically significant in either IC1/2/3 or ITT, but not both	0.049	First interim	30	53%	IC1/2/3: 134 AC: 346	IC1/2/3: HR≤0.609 AC: HR≤0.734	p-value≤0.004
		Second interim	41	80%	IC1/2/3: 204 AC: 523	IC1/2/3: HR≤0.726 AC: HR≤0.819	p-value≤0.0226
		Final	53	100%	IC1/2/3: 254 AC: 654	IC1/2/3: HR≤0.775 AC: HR≤0.853	p-value≤0.0417
PFS is statistically significant in both IC1/2/3 and ITT; ORR is not statistically significant in either IC1/2/3 or ITT	0.048	First interim	30	53%	IC1/2/3: 135 AC: 348	IC1/2/3: HR≤0.609 AC: HR≤0.734	p-value≤0.0039
		Second interim	41	80%	IC1/2/3: 205 AC: 526	IC1/2/3: HR≤0.726 AC: HR≤0.819	p-value≤0.022
		Final	54	100%	IC1/2/3: 256 AC: 657	IC1/2/3: HR≤0.774 AC: HR≤0.853	p-value≤0.0409
PFS is statistically significant in either IC1/2/3 or ITT, but not both, and the subsequent ORR is statistically significant	0.045	First interim	30	52%	IC1/2/3: 135 AC: 347	IC1/2/3: HR≤0.602 AC: HR≤0.728	p-value≤0.0031
		Second interim	42	80%	IC1/2/3: 209 AC: 534	IC1/2/3: HR≤0.725 AC: HR≤0.818	p-value≤0.0205
		Final	55	100%	IC1/2/3: 260 AC: 668	IC1/2/3: HR≤0.774 AC: HR≤0.852	p-value≤0.0384

Appendix 9
Interim and Final Analyses for Overall Survival (cont.)

Different Scenarios of PFS and ORR Testing	Alpha Level	Analysis Timing	Time from 1st Patient Enrolled (months)	Information Fraction	No. of Events	Stopping Boundary in HR	Stopping Boundary in p-Value
PFS is statistically significant in either IC1/2/3 or ITT, but not both ; ORR is not statistically significant	0.044	First interim	30	52%	IC1/2/3: 136 AC: 349	IC1/2/3: HR≤0.602 AC: HR≤0.728	p-value≤0.003
		Second interim	42	80%	IC1/2/3: 210 AC: 538	IC1/2/3: HR≤0.725 AC: HR≤0.818	p-value≤0.0199
		Final	56	100%	IC1/2/3: 262 AC: 672	IC1/2/3: HR≤0.774 AC: HR≤0.852	p-value≤0.0376
PFS is not statistically significant in either IC1/2/3 or ITT	0.04	First interim	30	50%	IC1/2/3: 134 AC: 344	IC1/2/3: HR≤0.587 AC: HR≤0.717	p-value≤0.002
		Second interim	42	78%	IC1/2/3: 210 AC: 536	IC1/2/3: HR≤0.717 AC: HR≤0.813	p-value≤0.0162
		Final	58	100%	IC1/2/3: 269 AC: 688	IC1/2/3: HR≤0.773 AC: HR≤0.851	p-value≤0.0348

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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.

Although most *immune-mediated* adverse events observed with immunomodulatory agents have been mild and self-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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (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.
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 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, 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 1–2 mg/kg/day oral prednisone or equivalent. • 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 agreed upon by the investigator and the Medical Monitor.

[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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (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.

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 2: Management Guidelines for Hepatic Events	
Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits.
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 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]
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 1–2 mg/kg/day oral prednisone or equivalent. • 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 tests.

[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 agreed upon by the investigator and the Medical Monitor.

[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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

GASTROINTESTINAL EVENTS

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

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (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 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to1–2 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]
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 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.

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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 agreed upon by the investigator and the Medical Monitor.

[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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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 (TSH) and 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 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4: Management Guidelines for Endocrine Events	
Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • 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. **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
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]
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 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 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]

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 4: Management Guidelines for Endocrine Events (cont.)	
Event	Management
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
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 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.

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

MRI=magnetic resonance imaging; TSH=thyroid-stimulating hormone.

[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 agreed upon by the investigator and the Medical Monitor.

[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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

OCULAR EVENTS

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

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 agreed upon by the investigator and the Medical Monitor.

[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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (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. *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 gastrointestinal 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 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 6: Management Guidelines for *Immune-Mediated* Myocarditis

Event	Management
Immune-mediated myocarditis, Grade 1	• Refer patient to cardiologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider 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 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 myocarditis, Grade 3-4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • 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.

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

[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 agreed upon by the investigator and the Medical Monitor.

[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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

INFUSION-RELATED REACTIONS

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

Guidelines for medical management of IRRs during Cycle 1 are provided in Table 7. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Table 7: Management Guidelines for Infusion-Related Reactions

Event	Management
IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR, Grade 2	• Interrupt atezolizumab infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs.
IRR, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Permanently discontinue atezolizumab and contact Medical Monitor.[a]

IRR=infusion-related reaction; *IV=intravenous*.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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.

Table 8: Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	• Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
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]
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 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 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]

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 8: Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist. • 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.

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 agreed upon by the investigator and the Medical Monitor.

[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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

DERMATOLOGIC EVENTS

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self limited, with or without pruritus. 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.

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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.
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]

[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 agreed upon by the investigator and the Medical Monitor.

[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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (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. • 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] • 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 agreed upon by the investigator and the Medical Monitor.

[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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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.

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

RENAL EVENTS

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. *R*enal 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.

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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, 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 agreed upon by the investigator and the Medical Monitor.

[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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

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 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]

[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 agreed upon by the investigator and the Medical Monitor.*

[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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 13 Management Guidelines for Immune-Mediated 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.*

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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[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 agreed upon by the investigator and the Medical Monitor.*

[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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.*

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).

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 ≥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 <100×10^9/L (100,000/μL)*
  - *ANC <1.0×10^9/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)*

Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

- *Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥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 and/or an immunosuppressive agent.* • *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.*

HLH=hemophagocytic lymphohistiocytosis; MAS=macrophage activation syndrome.

REFERENCES

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Appendix 10
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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