# PROTOCOL

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| **TITLE:** | **A PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED STUDY OF IPATASERTIB IN COMBINATION WITH ATEZOLIZUMAB AND PACLITAXEL AS A TREATMENT FOR PATIENTS WITH LOCALLY ADVANCED UNRESECTABLE OR METASTATIC TRIPLE-NEGATIVE BREAST CANCER** |
| **PROTOCOL NUMBER:** | CO41101 |
| **VERSION NUMBER:** | 6 |
| **EUDRACT NUMBER:** | 2019-000810-12 |
| **IND NUMBER:** | 133823 |
| **NCT NUMBER:** | NCT04177108 |
| **TEST PRODUCTS:** | Ipatasertib (RO5532961, GDC0068)<br>Atezolizumab (RO5541267) |
| **MEDICAL MONITOR:** | [redacted], *M.D.* |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |
| **APPROVAL DATE:** | See electronic date stamp below. |

## PROTOCOL AMENDMENT APPROVAL

| Date and Time (UTC) | Title | Approver's Name |
|---|---|---|
| 25-Feb-2022 20:48:14 | Company Signatory | [redacted] |

## PROTOCOL HISTORY

| Protocol | | Associated Country-Specific Protocol | | |
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| **Version** | **Date Final** | **Country** | **Version** | **Date Final** |
| 6 | See electronic date stamp above. | | | |
| 5 | 21 December 2020 | | | |
| 4 | 18 August 2020 | | | |
| 3 | 20 September 2019 | | | |
| 1 | 27 June 2019 | VHP | 2 | 13 September 2019 |

## PROTOCOL AMENDMENT, VERSION 6: RATIONALE

Protocol CO41101 has been amended to primarily align the protocol with the most recent Investigator's Brochures for Ipatasertib (Version 13) and Atezolizumab (Version 17) and to reduce study assessments for long-term follow-up. Changes to the protocol, along with a rationale for each change, are summarized below:

- Language for atezolizumab and accelerated approval in the United States for the treatment of patients with PD-L1–positive locally advanced or metastatic triple-negative breast cancer (mTNBC) has been removed (Section 1.3) due to the withdrawal of the Tecentriq label in PD-L1-positive mTNBC in the United States.
- Benefit-risk assessment and guidance on concomitant administration of severe acute respiratory syndrome coronavirus 2 vaccines with atezolizumab has been added (Sections 1.5 and 4.4.1).
- Text has been added to clarify that long-term follow-up assessments will no longer be collected (Sections 3.1.1, 4.6.1, and Appendix 1).
- The responsibilities of the investigator and the role of the Medical Monitor in determining patient eligibility have been clarified (Sections 4.1.1.2, 4.3.2.3, 4.3.3, 4.4.1, 4.4.2.2, 4.4.2.3, 4.4.3, 4.5.7, 4.5.8, Appendices 1, 4, 13, and 14).
- The Medical Monitor information has been updated (Section 5.4.1).
- The medical term "primary biliary cirrhosis" has been replaced by the term "primary biliary cholangitis" to align with the updated preferred term in MedDRA (Appendix 4).
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 18 (Appendices 13 and 14).

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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| **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 retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

## PROTOCOL SYNOPSIS

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| **TITLE:** | **A PHASE III, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED STUDY OF IPATASERTIB IN COMBINATION WITH ATEZOLIZUMAB AND PACLITAXEL AS A TREATMENT FOR PATIENTS WITH LOCALLY ADVANCED UNRESECTABLE OR METASTATIC TRIPLE-NEGATIVE BREAST CANCER** |
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| **NCT NUMBER:** | NCT04177108 |
| **TEST PRODUCTS:** | Ipatasertib (RO5532961, GDC0068)<br>Atezolizumab (RO5541267) |
| **PHASE:** | Phase III |
| **INDICATION:** | Metastatic triple-negative breast cancer |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

**Objectives and Endpoints**

This study will evaluate the efficacy, safety, and pharmacokinetics of ipatasertib in combination with atezolizumab and paclitaxel in locally advanced unresectable or metastatic triple-negative breast cancer (TNBC) previously untreated in this setting. Patients with programmed death-ligand-1 (PD-L1)–non-positive and PD-L1–positive tumors will be independently enrolled in Cohorts 1 and 2, respectively. The combination of ipatasertib, atezolizumab, and paclitaxel will be evaluated in two independently enrolled cohorts (Cohorts 1 and 2) and the combination of ipatasertib and paclitaxel will be evaluated in Cohort 1.

Specific objectives and corresponding endpoints are outlined in the following sections.

In this protocol, "study treatment" refers to the combination of treatments assigned to any individual patient as part of this study (e.g., ipatasertib/placebo [for ipatasertib], atezolizumab/placebo [for atezolizumab], and paclitaxel).

As of protocol Version 5, the following objectives and the corresponding statistical considerations and analyses will no longer be applicable to the study. Due to the early termination of the enrollment, data from enrolled patients will only be summarized descriptively for endpoints that are deemed appropriate and necessary.

**Efficacy Objectives**

Primary Efficacy Objective

The primary efficacy objective for this study is to independently evaluate the efficacy of the experimental arm treatment compared with control arm treatment in each cohort (i.e., Arm A vs. Arm C and Arm B vs. Arm C in Cohort 1 and Arm A vs. Arm B in Cohort 2), on the basis of the following co-primary endpoints:

- Investigator-assessed progression-free survival (PFS) after randomization, defined as the time from randomization to the first occurrence of disease progression, as determined locally according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), or death from any cause, whichever occurs first
- Overall survival (OS) after randomization, defined as the time from randomization to death from any cause

Exploratory Efficacy Objectives

The exploratory efficacy objectives for this study are as follows:

- To independently evaluate the efficacy of experimental arm treatment compared with control arm treatment in each cohort (i.e., Arm A vs. Arm C in Cohort 1 and Arm B vs. Arm C in Cohort 1 and Arm A vs. Arm B in Cohort 2) on the basis of the following endpoints:
  - Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1
  - Duration of response (DOR), defined as the time from the first occurrence of a documented objective response to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first
  - Clinical benefit rate (CBR), defined as the proportion of patients who have a CR, PR, or stable disease for ≥24 weeks, as determined by the investigator according to RECIST v1.1
- To evaluate patient-reported outcomes (PROs) of function (role, physical), global health status (GHS)/quality of life (QoL) associated with the following:
  - Ipatasertib plus paclitaxel compared with paclitaxel in patients with PD-L1–non-positive tumors (Arm B vs. Arm C in Cohort 1)
  - The addition of atezolizumab to ipatasertib plus paclitaxel compared with ipatasertib plus paclitaxel alone in patients with PD-L1–non-positive tumors (Arm A vs. Arm B in Cohort 1)
  - Ipatasertib plus paclitaxel plus atezolizumab compared with control arm treatments (Arm A vs. Arm C in Cohort 1 and Arm A vs. Arm B in Cohort 2) as measured by the Functional and GHS/QoL scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) on the basis of the following endpoint:
  - Mean and mean changes from baseline score in function (role, physical) and GHS/QoL by assessment timepoint and between treatment arms, as measured using the Functional and the GHS/QoL scales of the EORTC QLQ-C30
- To evaluate the efficacy of atezolizumab when combined with ipatasertib and paclitaxel in patients with PD-L1–non-positive tumors (Arm A vs. Arm B in Cohort 1) on the basis of PFS, OS, and ORR
- To independently evaluate the efficacy of experimental arm treatment compared with control arm treatment in patients with *PIK3CA*/*AKT1*/*PTEN*-altered tumors in each cohort, on the basis of PFS, OS, ORR, DOR, and CBR
- To evaluate PROs of function (cognitive, emotional, social) and disease- and treatment-related symptoms associated with:
  - Ipatasertib plus paclitaxel compared with paclitaxel in patients with PD-L1-non-positive tumors (Arm B vs. Arm C in Cohort 1).
  - The addition of atezolizumab to ipatasertib plus paclitaxel compared with ipatasertib plus paclitaxel alone in patients with PD-L1-non-positive tumors (Arm A vs. Arm B in Cohort 1)

- Ipatasertib plus paclitaxel plus atezolizumab compared with control arm treatments (Arm A vs. Arm C in Cohort 1 and Arm A vs. Arm B in Cohort 2) as measured by the Functional and Symptom scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) on the basis of the following endpoint:

  Mean and mean change from baseline scores in functional (cognitive, emotional, social) and disease- and treatment-related symptoms by cycle and between treatment arms, as assessed using the Functional and Symptom scales of the EORTC QLQ-C30

- To evaluate patients' health utility, as measured by the EuroQol 5-Dimension Questionnaire, 5-Level Version (EQ-5D-5L) to generate utility scores for pharmacoeconomic modeling, on the basis of the following endpoint:

  Utility scores of the EQ-5D-5L Questionnaire

- To independently evaluate the clinical benefit in each cohort, on the basis of the following endpoint:

  PFS2 after randomization, defined as the time from randomization to second occurrence of objective disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause (whichever occurs first)

**Safety Objectives**

The safety objective for this study is to independently evaluate the safety of experimental arm treatment in each cohort, on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined by the investigator according to the NCI Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

The exploratory safety objective for this study is to independently evaluate key patient-reported symptomatic adverse events associated with ipatasertib plus paclitaxel plus atezolizumab compared with control arm treatment in each cohort, on the basis of the following endpoint:

Selected items from the NCI's PRO Version of the CTCAE (PRO-CTCAE) capturing patients' rating of the presence, severity, frequency, and/or activity interference of diarrhea, nausea, vomiting, decreased appetite, fatigue, neuropathy, mouth sores, and rash symptoms, as well as an additional item regarding bother associated with side effects of treatment

**Exploratory Pharmacokinetic Objectives**

The exploratory PK objective for this study are as follows:

- To evaluate the pharmacokinetics of atezolizumab, ipatasertib, and its metabolite (G-0377720) in each cohort, on the basis of the following endpoints:
  - Plasma concentrations of ipatasertib and its metabolite (G-037720) at specified timepoints
  - Serum concentrations of atezolizumab at specified timepoints
- To evaluate potential relationships between ipatasertib and/or atezolizumab exposure, efficacy, and safety of ipatasertib plus paclitaxel plus atezolizumab in each cohort, on the basis of the following endpoints:
  - Relationship between ipatasertib and/or atezolizumab PK and efficacy endpoints, as appropriate based on the data
  - Relationship between ipatasertib and/or atezolizumab PK and safety endpoints, as appropriate based on the data

**Exploratory Immunogenicity Objectives**

The exploratory immunogenicity objectives of this study are as follows:

- To independently evaluate the immune response to atezolizumab in each cohort, on the basis of the following endpoint:
  - Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study
- To evaluate the potential effects of ADAs in each cohort, on the basis of the following endpoint:
  - Relationship between ADA status and efficacy, safety, PK, or biomarker endpoints

**Exploratory Biomarker Objectives**

The exploratory biomarker objectives for this study are as follows:

- To independently evaluate predictive or prognostic biomarkers (plasma or tissue) associated with disease activity status or response to treatment in each cohort, on the basis of the following endpoint:

  Relationship between tissue and blood-based biomarkers and patient clinical features (e.g., baseline features) and outcome (e.g., duration of PFS)
- To identify possible mechanisms of resistance to study treatments through the comparative analysis of potential biomarkers in pretreatment and post-progression biopsy tissue samples and in blood in each cohort, on the basis of the following endpoints:
  - Change in mutation and copy number in oncogenes, tumor suppressors, and/or other genes associated with disease progression by DNA sequencing
  - Change in levels of tumor suppressors, immune checkpoints, mitotic index, apoptotic index, and/or immune-cell infiltration by immunohistochemistry (IHC)

## Study Design

### Description of Study

Overview of Study Design

This study will enroll approximately 1155 patients (approximately 525 patients in Cohort 1 and approximately 630 patients in Cohort 2) with advanced TNBC across up to 350 sites globally. The study will compare the efficacy of the combination of ipatasertib, atezolizumab, and paclitaxel against paclitaxel in patients with PD-L1–non-positive tumors (Cohort 1, Arm A vs. Arm C) and against atezolizumab and paclitaxel in patients with PD-L1–positive tumors (Cohort 2, Arm A vs. Arm B). Cohort 1 will also evaluate the combination of paclitaxel and ipatasertib against paclitaxel in patients with PD-L1–non-positive tumors (Arm B vs. Arm C). In Cohort 1, approximately 525 patients with PD-L1–non-positive tumors will be enrolled and randomized in a 1:1:1 ratio to treatment Arms A, B, and C, respectively. In Cohort 2, approximately 630 patients with PD-L1–positive tumors will be enrolled and randomized in a 1:1 ratio to treatment Arms A and B, respectively. Patients with PD-L1 unknown tumors will be assigned to Cohort 1. It is anticipated that owing to the prevalence of PD-L1 positivity and negativity by the SP142 assay that Cohort 1 will be fully enrolled before Cohort 2.

As of 6 August 2020, further enrollment in Cohort 2 has been terminated; treatment assignments for Cohort 2 were unblinded on 7 August 2020. Patients may continue current study treatment if considered clinically appropriate and if deriving benefit as assessed by the investigator. However, patients in Arm B of Cohort 2 will no longer receive placebo for ipatasertib. No crossover will be permitted for patients in Arm B of Cohort 2. For patients who choose to continue in the study, assessments will proceed as specified in the protocol.

As of 18 September 2020, further enrollment in Cohort 1 has been terminated; treatment assignments for Cohort 1 were unblinded on 21 September 2020. Patients may continue current study treatment if considered clinically appropriate and if deriving benefit as assessed by the investigator. However, patients in Arm B of Cohort 1 will no longer receive placebo for atezolizumab; patients in Arm C of Cohort 1 will no longer receive placebo for ipatasertib nor

placebo for atezolizumab. No crossover will be permitted for patients in Arm B or Arm C of Cohort 1. Assessments will proceed as specified in the protocol.

Ipatasertib or placebo will be administered to patients at a starting dose of 400 mg QD PO for 21 days of each 28-day cycle on Days 1–21 unless held for management of adverse events. Atezolizumab or placebo will be administered to patients by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle. Paclitaxel will be administered to patients at a starting dose of 80 mg/m$^2$ by IV infusion for 3 of 4 weeks on Days 1, 8, and 15 of each 28-day cycle unless deferred to Day 22 because of an adverse event.

Any study treatment may be continued until disease progression, intolerable toxicity, elective withdrawal from the study or study treatment, or study completion or termination.
After treatment discontinuation, patients will be followed every 3 months for survival, PROs, as well as follow-up anti-cancer therapy and related outcomes (therapy and procedures, doses, start and stop dates, best response, most recent tumor assessment date, and progression date). *As of protocol Version 6, these long-term follow-up assessments are no longer required.*

In each cohort, a permuted block randomization scheme will be used to ensure an appropriate allocation of patients to each arm (at an approximately 1:1:1 ratio to Arms A, B, and C in Cohort 1 and approximately a 1:1 ratio to Arms A and B in Cohort 2) with respect to the following stratification factors:

- Geographic region (Asia-Pacific vs. western Europe/North America vs. rest of the world)
- Prior (neo)adjuvant taxane (yes vs. no)
- Prior cancer immunotherapy (CIT) in the (neo)adjuvant setting (yes vs. no)

Assessments and Monitoring

All patients will be closely monitored for adverse events throughout the study, and adverse events will be graded according to the NCI CTCAE v5.0.

Tumor assessments should be performed based on a schedule calculated from Day 1 of Cycle 1, with the first assessment performed at Week 8 and approximately every 8 weeks thereafter, regardless of treatment administration timing or prior early or late tumor assessments. For estimation of PFS, ORR, DOR, and CBR, tumor response will be based on RECIST v1.1. For patients who discontinue treatment without evidence of disease progression per RECIST v1.1, in addition to post-treatment follow-up, patients will be followed every 8 weeks for tumor assessments until documented progression per RECIST v1.1, elective withdrawal from the study, or study completion or termination. Images for tumor assessments for all patients will be prospectively collected to enable retrospective blinded independent central review when needed. As of protocol Version 5, images for tumor assessments will no longer be collected for blinded independent central review.

Patients will also be given the option of providing a tissue biopsy sample obtained at disease progression for exploratory analyses; this decision will not affect overall study eligibility. Such tumor tissue will be collected by biopsy, unless not clinically feasible as assessed and documented by the investigator, at the time of first evidence of radiographic disease progression per RECIST v1.1 (within 40 days after radiographic progression or prior to the start of new anti-cancer treatment, whichever is sooner). These samples will enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of the study treatments.

Safety Data Monitoring

An independent Data Monitoring Committee (iDMC) will evaluate safety data during the study. The analysis supporting iDMC review will be conducted by an independent Data Coordinating Center (iDCC) and provided to the iDMC. Sponsor affiliates will be excluded from iDMC membership. The iDMC will follow a charter that outlines the iDMC roles and responsibilities.

Unblinded safety data will be reviewed by the iDMC on a periodic basis, approximately every 6 months from the time of the first patient's enrollment until the time of the primary analysis of PFS. All summaries and analyses for the iDMC review will be prepared by the iDCC.

After reviewing the data, the iDMC will provide a recommendation to the Sponsor as described in the iDMC Charter. Final decisions will rest with the Sponsor.

Due to the early termination of the enrollment and unblinding of patients, the iDMC's review of the ongoing safety summary data will be discontinued after the unblinding, and the study team will be responsible for the ongoing monitoring of patient safety in the study. As unblinded data will now be available to the study team, aggregate safety data will be reviewed by the study team at the regular frequency interval previously defined by the iDMC Charter (approximately every 6 months). These safety reviews are perfomed in addition to the ongoing assessment of the incidence, nature, and severity of adverse events; serious adverse events; deaths; and laboratory abnormalities.

Any outcomes of these data reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of their respective Institutional Review Boards/Ethics Committees.

**Number of Patients**

This study will enroll approximately 1155 patients (approximately 525 patients in Cohort 1 and approximately 630 patients in Cohort 2) with advanced TNBC across up to 350 sites globally.

As of 6 August 2020, further enrollment in Cohort 2 has been terminated. As of 18 September 2020, further enrollment in Cohort 1 has been terminated.

**Target Population**

Inclusion Criteria

Women or men with locally advanced unresectable or metastatic triple-negative adenocarcinoma of the breast who have not received prior systemic chemotherapy in this setting may be eligible for this study. In patients with *BRCA*-associated tumors, platinum chemotherapy as potentially the preferred treatment option should be taken into consideration when determining whether this study may be appropriate for these patients. Patients may have received prior chemotherapy in the neoadjuvant or adjuvant setting if treatment was completed at least 12 months prior to randomization. Locally advanced unresectable disease must not be amenable to resection with curative intent. Patients must have sufficient tumor tissue and comply with all eligibility criteria to be enrolled.

*General Inclusion Criteria*

Patients must meet the following general criteria for study entry:

- Signed Informed Consent Form(s)
- Women or men, age ≥ 18 years at the time of signing the Informed Consent Form
- Willingness and ability to complete all study-related assessments, including PRO assessments, in the investigator's judgment
- Measurable disease according to RECIST v1.1

  Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
- Adequate hematologic and organ function within 14 days before the first study treatment on Day 1 of Cycle 1, as defined by the following:
  - Neutrophils (ANC ≥ 1500/μL)
  - Hemoglobin ≥ 9 g/dL
  - Platelet count ≥ 100,000/μL
  - Serum albumin ≥ 3 g/dL
  - Total bilirubin ≤ 1.5 × the upper limit of normal (ULN), with the following exception:

    Patients with known Gilbert syndrome who have serum bilirubin ≤ 3 × ULN may be enrolled.
  - AST and ALT ≤ 2.5 × ULN, with the following exception:

    Patients with documented liver or bone metastases may have AST and ALT ≤ 5 × ULN.

- ALP $\leq 2 \times$ ULN, with the following exceptions:

  Patients with known liver involvement may have ALP $\leq 5 \times$ ULN.

  Patients with known bone involvement may have ALP $\leq 7 \times$ ULN.
- PTT (or aPTT) and INR $\leq 1.5 \times$ ULN (except for patients receiving anticoagulation therapy)

  Patients receiving heparin treatment should have a PTT (or aPTT) between $1.5 \times$ and $2.5 \times$ ULN (or a patient's value before starting heparin treatment). Patients receiving coumarin derivatives should have an INR between 2.0 and 3.0 assessed in two consecutive measurements performed 1–4 days apart. Patients should be on a stable anticoagulant regimen.
- Serum creatinine $< 1.5 \times$ ULN or creatinine clearance $\geq 50$ mL/min based on Cockcroft−Gault glomerular filtration rate estimation:

$$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times 0.85 \text{ (if female)}}{72 \times (\text{serum creatinine in mg/dL})}$$
- Fasting total glucose $\leq 150$ mg/dL and hemoglobin $A_{1C} \leq 7.5\%$

- Life expectancy of at least 6 months
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as described below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for at least 28 days after the final dose of ipatasertib/placebo, 5 months after the final dose of atezolizumab/placebo, and 6 months after the final dose of paclitaxel, whichever occurs later, and agreement to refrain from donating eggs during this same period

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq 12$ continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). *Per this definition, a woman with a tubal ligation is considered to be of childbearing potential.* The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year, when used consistently and correctly, include combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, bilateral tubal occlusion, male sterilization, intrauterine hormone-releasing system, copper intrauterine devices, and sexual abstinence.

  Hormonal contraceptive methods may be used in accordance with specific country and local requirements for patients with breast cancer.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for 28 days after the final dose of ipatasertib/placebo, or 6 months after the final dose of paclitaxel, whichever occurs later. Men must refrain from donating sperm during this same period.

With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 28 days after the final dose of ipatasertib/placebo or 6 months after the final dose of paclitaxel, whichever occurs later, to avoid exposing the embryo.

Examples of contraceptive methods with a failure rate of $<1\%$ per year, when used consistently and correctly, include combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, bilateral tubal occlusion, male sterilization, intrauterine hormone-releasing system, copper intrauterine devices, and sexual abstinence.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For any patients enrolled in the extended enrollment phase (i.e., China extension phase): patient is a current resident of mainland China, Hong Kong, or Taiwan, and of Chinese ancestry

*Disease-Specific Inclusion Criteria*

Patients must meet the following disease-specific criteria for study entry:

- Appropriate candidate for paclitaxel monotherapy if tumor PD-L1 status is unknown or non-positive; appropriate candidate for paclitaxel and atezolizumab if tumor PD-L1 status is positive
- Histologically documented triple-negative adenocarcinoma of the breast that is locally advanced or metastatic and is not amenable to resection with curative intent
  - Receptor status at study entry should correspond to the evaluation of the most recent biopsy (i.e., recurrent or metastatic tissue where applicable and if safely accessible, and non–fine-needle aspiration [FNA] sample), as assessed locally (or centrally, if not available locally) according to the American Society of Clinical Oncology/College of American Pathologists 2018 guidelines:

    TNBC is defined as HER2 negative, estrogen receptor (ER) negative, and progesterone receptor (PgR) negative.

    ER or PgR positivity is defined as $\geq 1\%$ of tumor cell nuclei immunoreactive to the respective hormonal receptor.

    HER2 positivity is defined as one of the following: 3+, as assessed on IHC or in situ hybridization positive).
  - Submittal of a formalin-fixed, paraffin-embedded tumor (FFPE) tissue block or a minimum of *10–*15 *slides at least (15 slides preferred) containing* freshly cut unstained, serial tumor slides from the most recently collected tumor tissue (for central analysis of PD-L1 status and for other protocol-mandated secondary and exploratory assessments). Cytologic or FNA samples are not acceptable. Tumor tissue from bone metastases that is subject to decalcification is not acceptable.
  - Tumor tissue must be evaluated centrally for PD-L1 expression prior to enrollment. Patients will be assigned to the appropriate cohort with a centrally determined PD-L1 result.
  - 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 cohort assignment, the PD-L1 score of the patient will be the maximum PD-L1 score among the samples.

    If a more recent specimen is either insufficient or unavailable, a patient may still be eligible if the patient can provide a tissue block (preferred) or a minimum of 15 unstained serial slides from an older archival tumor tissue or undergo an additional pretreatment core or excisional biopsy of a non-target lesion (a non-target lesion is

preferred if it is accessible and the biopsy can be safely obtained). In general, a minimum of three core biopsies is required.

If a patient already has results available from Foundation Medicine, Inc.'s commercial tissue-based next-generation sequencing (NGS) assay known as the FoundationOne CDx™, 10 freshly cut unstained, serial tumor slides from the most recently collected tumor tissue are acceptable for central analysis of PD-L1 status and other protocol-mandated secondary and exploratory assessments.

**Exclusion Criteria**

*General Exclusion Criteria*

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

- Inability to comply with study and follow-up procedures
- History of malabsorption syndrome or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills
- Severe infection within 4 weeks prior to initiation of study treatment (including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia) as well as those who have received treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment are not eligible for the study. Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study. Known HIV infection (there must be a negative HIV test at screening)
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis (e.g., positive for hepatitis B surface antigen [HBsAg] or hepatitis C virus [HCV] antibody at screening), current drug or alcohol abuse, or cirrhosis
  - Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive hepatitis B core antibody [HBcAb] test, accompanied by a negative HBV DNA test) are eligible.
  - Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Current treatment with anti-viral therapy for HBV
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 1 of Cycle 1 or anticipation of need for a major surgical procedure during the study

  Placement of a vascular access device is not considered major surgery.
- Pregnancy or breastfeeding, or intention to become pregnant during the study or within 28 days after the final dose of ipatasertib/placebo, 5 months after the final dose of atezolizumab/placebo, and 6 months after the final dose of paclitaxel whichever occurs later

  Women of childbearing potential (who are not postmenopausal with $\geq$12 months of non–therapy-induced amenorrhea nor surgically sterile) must have a negative serum pregnancy test result either within 96 hours prior to initiation of study drug, or within 7 days of Day 1, Cycle 1 (in this case, confirmed by a negative urine pregnancy test result on Day 1 of Cycle 1 prior to dosing).
- New York Heart Association Class II, III, or IV heart failure, left ventricular ejection fraction $<$50%, or active ventricular arrhythmia requiring medication
- Current unstable angina or history of myocardial infarction within 6 months prior to Day 1 of Cycle 1
- Congenital long QT syndrome or screening QT interval corrected through use Fridericia's formula (QTcF) $>$480 ms
- Current treatment with medications used at doses known to cause clinically relevant prolongation of QT/QTc interval
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion (including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction)

- Requirement for chronic corticosteroid therapy of $>10$ mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressant agents for a chronic disease

  No chronic corticosteroid use is permitted at baseline with rare exceptions. Refer to the Atezolizumab-Specific Exclusion Criteria.
- Treatment with approved or investigational cancer therapy within 14 days prior to Day 1 of Cycle 1
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigator's opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk from treatment complications

*Disease-Specific Exclusion Criteria*

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

- History of or known presence of spinal cord metastases, as determined by computed tomography (CT) or magnetic resonance imaging (MRI) evaluation during screening or prior radiographic assessments
- 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.

    Patients with leptomeningeal carcinomatosis will be excluded.
- Known germline *BRCA1/2* deleterious mutation, unless the patient is not an appropriate candidate for a *PARP*-inhibitor
- Any previous systemic therapy for inoperable locally advanced or metastatic triple-negative adenocarcinoma of the breast

  Patients **may** have received prior neoadjuvant and/or adjuvant chemotherapy, prior neoadjuvant and/or adjuvant CIT, and/or radiotherapy for breast adenocarcinoma, provided all chemotherapy and CIT were completed $\geq 12$ months prior to randomization.

  The 12-month treatment-free minimum interval in these cases begins with the last administration of chemotherapy in the early breast cancer setting and is not meant to encompass HER2-targeted therapy, such as trastuzumab, ado-trastuzumab emtansine, pertuzumab, neratinib, or endocrine therapies.

  Previous systemic therapies for TNBC include, but are not limited to, chemotherapy, immune checkpoint inhibitors, or targeted agents.
- Unresolved, clinically significant toxicity from prior therapy, except for alopecia and Grade 1 peripheral neuropathy

- Patients who have received palliative radiotherapy to peripheral sites (e.g., bone metastases) for pain control and whose last treatment was completed 14 days prior to Day 1 of Cycle 1 may be enrolled in the study if they have recovered from all acute, reversible effects (e.g., to Grade 1 or resolved by enrollment)
- 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 (e.g., to Grade 1 or resolved) from the effects of radiation prior to study enrollment. There is no required minimum recovery period beyond the 14 days required for radiotherapy.
  - 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 (i.e., $>1.5$ mmol/L ionized calcium, $>12$ mg/dL calcium, or corrected serum calcium greater than ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy

  Patients who are receiving bisphosphonate therapy specifically to prevent skeletal events (e.g., bone metastasis, osteoporosis) and who do not have a history of clinically significant hypercalcemia are eligible.
- Malignancies other than breast cancer within 5 years prior to Day 1 of Cycle 1, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer

*Paclitaxel-Specific Exclusion Criteria*

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

- Known hypersensitivity or contraindication to any component of the study treatments, including the paclitaxel excipient, macrogolglycerol ricinoleate
- Grade $\geq 2$ peripheral neuropathy

*Ipatasertib-Specific Exclusion Criteria*

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

- History of Type I or Type II diabetes mellitus requiring insulin

  Patients who are on a stable dose of oral diabetes medication $\geq 2$ weeks prior to initiation of study treatment are eligible for enrollment.
- Grade $\geq 2$ uncontrolled or untreated hypercholesterolemia or hypertriglyceridemia
- History of or active inflammatory bowel disease (e.g., Crohn disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)
- Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, *Aspergillosis*, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia)
- Treatment with strong CYP3A inhibitors or strong CYP3A inducers within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study drug
- Prior treatment with an Akt inhibitor

  Note: Prior treatment with PI3K or mTOR inhibitors is allowed.

*Atezolizumab-Specific Exclusion Criteria*

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

- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis, with the following exceptions:

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

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

  - Rash must cover $<10\%$ of body surface area.
  - Disease is well controlled at baseline and requires only low-potency topical corticosteroids.
  - There $has\ been$ no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.
- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Prior allogeneic stem cell or solid organ transplantation
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during treatment with atezolizumab or within 5 months after the final dose of atezolizumab
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or recombinant human antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin-2) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor-$\alpha$ agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the study, with the following exceptions:

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

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study

**End of Study**

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later.

In addition, the Sponsor may decide to terminate the study at any time.

**Length of Study**

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 2-3 years.

**Investigational Medicinal Products**

**Test Products (Investigational Drugs)**

The investigational medicinal products for this study are ipatasertib, matching ipatasertib placebo, atezolizumab, matching atezolizumab placebo, and paclitaxel.

Ipatasertib and Placebo

Patients will be randomly assigned to a treatment arm through the IxRS. Ipatasertib/placebo will be administered at the starting dosage of 400 mg PO QD, beginning at Cycle 1, on Days 1–21 of each 28-day cycle until the patient experiences disease progression, intolerable toxicity, or withdraws consent. Patients will receive ipatasertib/placebo prior to the IV infusions of paclitaxel and atezolizumab/placebo.

Following unblinding of treatment assignments, placebo for ipatasertib will no longer be administered to patients in Arm B of Cohort 2 and to patients in Arm C of Cohort 1.

Atezolizumab and Placebo

Atezolizumab/placebo will be administered to patients by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle until the patient experiences disease progression, intolerable toxicity orwithdraws consent. Although a ± 1-day window is permitted for atezolizumab/placebo administration, it is discouraged to dose on days other than on Day 1 or 15 because of the risk that atezolizumab doses may fall too close together.

Following unblinding of treatment assignments, placebo for atezolizumab will no longer be administered to patients in Arm B and Arm C of Cohort 1.

Paclitaxel

The dose of paclitaxel in this study is 80 mg/m$^2$ administered to patients by IV infusion on Days 1, 8, and 15 of each 28-day cycle.

**Non-Investigational Medicinal Products**

Because of the known potential for allergic reactions to paclitaxel and/or the Cremophor® vehicle, precautions must be taken to decrease the risk of anaphylaxis. Patients must be premedicated prior to paclitaxel with dexamethasone, diphenhydramine, and an H2-receptor blocker (i.e., ranitidine or famotidine) or per institutional practice. Ranitidine and famotidine are recommended H2-receptor blockers for prophylactic treatment of paclitaxel infusion-related reactions. However, in cases when ranitidine and famotidine are not available, cimetidine may be used with caution. Cimetidine is a moderate CYP3A inhibitor, which can increase the exposure of ipatasertib up to approximately 2-fold. It can take up to 3 days for ipatasertib concentration to return to typical steady state levels.

Only applicable while the patient is receiving ipatasertib:

- For visits without PK sample collection, intravenous cimetidine can be administered irrespective of timing with the oral dose of ipatasertib. For visits that include PK sample collection, intravenous cimetidine can be administered after ipatasertib sampling is complete or 2 hours after ipatasertib dosing, whichever is later.
- For sites needing use of oral cimetidine, cimetidine should be administered at least 2 hours after ipatasertib or after completion of PK sampling, whichever is later.

Diarrhea is a common adverse event associated with ipatasertib and/or paclitaxel treatment. In this study, to improve diarrhea management and patient burden, loperamide (racecadotril as used in Europe) will be administered to patients daily as prophylaxis for diarrhea. Prophylactic use is mandated in the first cycle (if allowed by local guidance), and as clinically indicated in subsequent cycles to prevent diarrhea. Patients who experience diarrhea should be on treatment doses of loperamide per the management guidelines. *The Medical Monitor is available to advise as needed.*

Patients should be educated/reminded to be cognizant of the onset, duration, severity, and frequency of symptoms and the medications administered. If side effects of loperamide are not

tolerated, doses may be reduced (or if necessary, discontinued) at any time. Investigators are encouraged to continue prophylactic- and/or treatment-dose loperamide for the remainder of the study at their discretion based on clinical judgment.

Owing to the risk of rash in Cycle 1, patients should receive the following prophylaxis during the first cycle when all three study treatments will be given:

- Unless contraindicated, daily PO antihistamine prophylaxis should be used for at least the first cycle. It is suggested that a non-sedating longer-acting oral antihistamine be used (such as 10 mg of cetirizine PO QD or comparable dose of other antihistamines, e.g., loratadine, fexofenadine). The daily oral antihistamine used for rash prophylaxis may be held on the days of paclitaxel infusion if the paclitaxel premedication already includes an antihistamine.
- On days when patients will receive atezolizumab/placebo (typically, Days 1 and 15), patients should receive at least 10 mg/day of prednisone (or equivalent dosing of other steroids e.g., methylprednisolone, prednisolone) as premedication prior to atezolizumab, followed by a fixed dose of 10 mg/day prednisone (or equivalent) for 2–4 consecutive days thereafter, unless contraindicated. If institutional practice prior to paclitaxel is to give at least 10 mg of prednisone on the day of paclitaxel, then the additional 10 mg of prophylactic prednisone should not be given on that day to prevent rash. If the investigator determines that administration of the steroid immediately prior to paclitaxel, rather than prior to atezolizumab/placebo, is more appropriate, this is acceptable.

As of protocol Versions 4 and 5, rash and antidiarrheal prophylaxis is no longer applicable to patients in Arm C of Cohort 1 and Arm B of Cohort 2.

**Statistical Methods**

As of protocol Versions 4 and 5, statistical considerations and the analyses outlined in Section 6 are no longer applicable to the study as indicated in the respective sections. Due to the early termination of the enrollment, data from enrolled patients will only be summarized descriptively for endpoints that are deemed appropriate and necessary (e.g., demographics, disposition, and adverse events).

Efficacy analyses will be performed independently for each cohort. All efficacy analyses will be based on the intent-to-treat population within each cohort according to the treatment arm to which patients are allocated. The analysis of DOR will include all patients with an objective response.

All primary and exploratory endpoints based on tumor burden will be based on radiological (or photographic, if applicable) assessments by the local radiologist or investigator, unless otherwise specified.

**Primary Analysis**

The co-primary efficacy endpoints are investigator-assessed PFS and OS.

Investigator-assessed PFS, defined as the time from randomization to the first occurrence of disease progression, as determined locally by the investigator using RECIST v1.1, or death from any cause, whichever occurs first. Data for patients without the occurrence of disease progression or death as of the clinical data cutoff date will be censored at the time of the last tumor assessment (or at the time of randomization plus 1 day if no tumor assessment was performed after the baseline visit).

OS is defined as the time from randomization to death from any cause. Data for patients who have not died as of the clinical data cutoff date will be censored at the last date they are known to be alive. Data for patients who do not have postbaseline information will be censored at the randomization plus 1 day.

Both PFS and OS will be compared between treatment arms using the stratified log-rank test. The hazard ratio will be estimated using a stratified Cox proportional hazards model. The 95% CI for the hazard ratio will be provided. The stratification factors to be used will be the same as the randomization stratification factors. Results from an unstratified analysis will also be provided. For each treatment arm, Kaplan-Meier methodology will be used to estimate the median PFS and OS, and the Brookmeyer-Crowley method will be used to construct the 95% CI

for the median PFS and OS (Brookmeyer and Crowley 1982). Kaplan-Meier curves will be produced as well.

**Determination of Sample Size**

Type I Error Control

Cohort 1 (patients with PD-L1−non-positive tumors) and Cohort 2 (patients with PD-L1 positive tumors) are two independent cohorts and will be analyzed separately for all endpoints unless otherwise specified. Each cohort will be tested independently with an overall 5% type I error control.

For Cohort 1, the overall type I error ($\alpha$) is 0.05 (two sided) and is split among the co-primary efficacy endpoints 0.01 for PFS for Arm A versus Arm C, 0.01 for PFS for Arm B versus Arm C, and 0.03 for OS. PFS for Arm A versus Arm C and Arm B versus Arm C will be tested independently, whereas OS will be tested in a hierarchical sequence of Arm A versus Arm C followed by Arm B versus Arm C. The PFS data will mature earlier and PFS will be firstly tested with $\alpha$ of 0.01 for Arm A versus Arm C and 0.01 for Arm B versus Arm C. When a PFS test is passed at an $\alpha$ level of 0.01, that 0.01 $\alpha$ assigned will be recycled to OS (i.e., OS will be tested at the significance level of 0.05 [if both PFS tests are passed] or 0.04 [if only one PFS test is passed]; otherwise, OS will be tested at the significance level of 0. 03[when neither PFS tests is passed] to control the overall type I error at 0.05).

For Cohort 2, the overall type I error ($\alpha$) is 0.05 (two sided) and is split between the two co-primary efficacy endpoints PFS and OS. The PFS data will mature earlier and PFS will be firstly tested with $\alpha$ of 0.01. If the PFS test is passed at the significance level of 0.01, the 0.01 $\alpha$ assigned to PFS will be recycled to OS (i.e., OS will be tested at the significance level of 0.05; otherwise, OS will be tested at the significance level of 0.04 to control the overall type I error at 0.05).

Sample Size Consideration for Cohort 1

The following statistical considerations were applicable prior to the termination of enrollment on 18 September 2020 and subsequent unblinding of Cohort 1 on 21 September 2020. At that time, a total of 127 patients had been enrolled in Cohort 1.

Approximately 525 patients will be enrolled and randomized in a 1:1:1 ratio to Arm A (ipatasertib plus atezolizumab plus paclitaxel), Arm B (ipatasertib plus paclitaxel plus placebo) and Arm C (paclitaxel plus placebo plus placebo). The sample size is determined by the co-primary endpoints: PFS comparing Arm A versus Arm C, PFS comparing Arm B versus Arm C, and OS comparing Arm A versus Arm C.

The primary analysis of PFS will be conducted when approximately 239 PFS events from all three arms (including approximately 171 PFS events for the comparison of Arm B versus Arm C and approximately 166 PFS events for the comparison of Arm A vs. Arm C) are observed or when the last patient has been randomized, whichever occurs later.

With 172 PFS events for the comparison of Arm B versus Arm C, this allows for 80% power to detect an improvement in median PFS from 5.6 months to approximately 9.4 months (hazard ratio=0.593) at the 1% level of significance (two sided). The largest hazard ratio deemed to be statistically significant at the 1% level will be approximately 0.675 (with median improvement in PFS from 5.6 to 8.3 months). With 166 PFS events for the comparison of Arm A vs. C, this allows for 94% power to detect an improvement in median PFS from 5.6 months to approximately 10.6 months (hazard ratio=0.528) at the 1% level of significance (two sided). The largest hazard ratio deemed to be statistically significant at the 1% level will be approximately 0.670 (with median improvement in PFS from 5.6 to 8.4 months).

If the 0.02 $\alpha$ assigned to PFS is recycled, the co-primary endpoint, OS, will be tested at the 5% level of significance (two sided). The final OS analysis will be conducted when approximately 216 OS events for the comparison of Arm A vs. Arm C) are observed. With $\alpha$ spending to the interim analyses of OS, at the OS final analysis, 216 OS events for the comparison of Arm A vs. Arm C will allow for 80% power to detect an improvement in median OS from 18.4 to 27.1 months (hazard ratio=0.680) at the 5% level of significance (two sided). The largest OS hazard ratio deemed to be statistically significant will be approximately 0.759 (with median OS improvement from 18.4 to 24.2 months).

If the 0.02 $\alpha$ assigned to PFS is not recycled or only 0.01 $\alpha$ is recycled, the co-primary endpoint, OS, will be tested at the 3% or 4% level of significance (two sided), respectively. The final OS

analysis timing and the require number of OS events will be adjusted accordingly to allow 80% power to detect an improvement in median OS from 18.4 to 27.1 months (hazard ratio = 0.680) at the 3% or 4% level of significance (two sided). Further details will be provided in the Statistical Analysis Plan.

The enrollment duration is projected to be approximately 22 months (from the first patient randomized). For all three arms, an annual loss to follow-up rate of 5% and 2% are assumed for PFS and OS, respectively. Based on these, it is projected that the primary PFS analysis will occur when the last patient is randomized, and the final OS analysis is projected to occur approximately 49 months after the first patient is enrolled, if the 0.02 $\alpha$ assigned to PFS is recycled for OS.

Sample Size Consideration for Cohort 2

The following statistical considerations were applicable prior to the termination of enrollment on 6 August 2020 and subsequent unblinding of Cohort 2 on 7 August 2020. At that time, a total of 115 patients had been enrolled in Cohort 2.

Approximately 630 patients will be enrolled and randomized in a 1:1 ratio to Arm A (ipatasertib plus atezolizumab plus paclitaxel) and Arm B (atezolizumab plus paclitaxel plus placebo).

The primary analysis of PFS will be conducted when approximately 228 PFS events are observed or when the last patient has been randomized, whichever occurs later. Based on the enrollment assumption, it is most likely driven by the last patient's randomization.

With 228 PFS events, this allows for 80% power to detect an improvement in median PFS from 7.5 to approximately 11.8 months (hazard ratio=0.636) at the 1% level of significance (two sided). The largest hazard ratio deemed to be statistically significant at the 1% level will be approximately 0.711 (with median improvement in PFS from 7.5 to 10.5 months).

If the 0.01 α assigned to PFS is recycled, the co-primary endpoint, OS, will be tested at the 5% level of significance (two sided). The final OS analysis will be conducted when approximately 417 OS events are observed. With $\alpha$ spending to the interim analyses of OS (see details in Section 6.9.2.2), at the OS final analysis, it will allow for 80% power to detect a hazard ratio of 0.758 (median OS improvement from 25 to 33 months) at the 5% level of significance (two sided). The largest OS hazard ratio deemed to be statistically significant will be approximately 0.820 (with median OS improvement from 25 to 30.5 months).

If the 0.01 $\alpha$ assigned to PFS is not recycled, the co-primary endpoint, OS, will be tested at the 4% level of significance (two sided). The final OS analysis will be conducted when approximately 444 OS events are observed. With $\alpha$ spending to the interim analyses of OS, at the OS final analysis, it will allow for 80% power to detect a hazard ratio of 0.758 (median OS improvement from 25 to 33 months) at the 4% level of significance (two sided). The largest OS hazard ratio deemed to be statistically significant will be approximately 0.818 (with median OS improvement from 25 to 30.6 months).

The enrollment duration is projected to be approximately 36 months (from the first patient randomized). For both arms, an annual loss to follow-up rate of 5% and 2% are assumed for PFS and OS, respectively. Based on these, it is projected that the primary PFS analysis will occur when the last patient is randomized, and it is predicted that there will be approximately 372 PFS events. With 372 PFS events, the largest hazard ratio deemed to be statistically significant at the 1% level will be approximately 0.766 (with median PFS improvement from 7.5 to 9.8 months). The final OS analysis is projected to occur approximately 70 months after the first patient is enrolled, if the 0.01 $\alpha$ assigned to PFS is recycled for OS.

**Interim Analyses**

Planned Interim Safety Analysis

An external iDMC will be formed to evaluate safety data in Cohorts 1 and 2 on a periodic basis, approximately every 6 months from the time of the first patient's enrollment until the time of the primary analysis of PFS for both cohorts are complete. All summaries/analyses by treatment arm for the iDMC's review will be prepared by an external iDCC for each cohort. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the IRB/EC. A detailed plan will be included in the iDMC Charter.

In the absence of extenuating circumstances, accrual will not be halted while the interim safety analysis is conducted. The iDMC will review the available data to make a recommendation as to the following: to continue without changes to the protocol, to modify the safety monitoring and/or eligibility criteria, to add additional safety reviews to address emerging safety issues, or to terminate the study. The final decision will rest with the Sponsor. In addition, the Sponsor may request ad-hoc meetings of the iDMC at any time during the study to review ongoing safety summary data.

Due to the early termination of enrollment and unblinding of patients, the iDMC's review of the ongoing safety summary data will be terminated after the unblinding. The study team will be responsible for the ongoing monitoring of patient safety in the study.

Planned Interim OS Analysis for Cohort 1

The following statistical considerations were applicable prior to the early termination of enrollment on 18 September 2020 and subsequent unblinding of Cohort 1 on 21 September 2020, and they are not appliacable as of protocol V5.

There are two planned OS interim analyses for the comparisons across the three treatment arms. The first OS interim analysis will be performed at the time of PFS analysis. The second OS interim analysis will be performed when around 80% of the OS events required for the final OS analysis for the comparison of Arm A versus Arm C is reached. OS will be tested in a hierarchical testing sequence of Arm A versus Arm C followed by Arm B versus Arm C, and the Lan-DeMets $\alpha$-spending function with an O'Brien-Fleming boundary will be used to control the type I error accounting for the interim and final analyses of OS. The comparison of Arm A versus Arm B will be conducted for descriptive purposes only with no type I error control.

If the 0.02 $\alpha$ assigned to PFS is recycled, the final OS will be analyzed when 216 OS events for the comparison of Arm A vs. Arm C occur at approximately 49 months after the first patient has been enrolled. It is estimated that there will be approximately (76, 176, 216) OS events at the first interim, the second interim, and the final OS analyses for the comparison of Arm A versus Arm C, with corresponding p-value boundaries of (0.0003, 0.0259, 0.0424) and hazard ratio boundaries of (0.438, 0.715, 0.759) at the first interim, the second interim, and the final OS analysis for the comparison of Arm A versus Arm C, respectively. The actual boundaries will be adjusted according to the actual information fractions at the interim analyses using the Lan-DeMets $\alpha$–spending function with an O'Brien-Fleming boundary.

If the 0.02 α assigned to PFS is not recycled or only 0.01 $\alpha$ is recycled, the final OS analysis for timing, the required number of OS events, the p-value, and the hazard ratio boundaries for the interim and final analyses will be adjusted accordingly. The detailed analyses will be outlined in the Statistical Analysis Plan (SAP). The analyses specified in the SAP supersede those specified in the protocol for regulatory filing purposes.

At the time of each OS analysis, OS test comparing Arm B versus Arm C will be formally performed only if the OS test comparing Arm A versus Arm C is passed with statistical significance; otherwise, OS test for Arm B versus C will be descriptive only. When comparison of Arm B versus Arm C is formally tested, the same p-value and hazard ratio boundaries used by Arm A versus Arm C comparison will be used, so that the overall type I error of 5% is controlled. The OS test for Arm A versus Arm B will be performed descriptively only. Further details will be provided in the Statistical Analysis Plan.

Planned Interim OS Analysis for Cohort 2

The following statistical considerations were applicable prior to the termination of enrollment on 6 August 2020 and subsequent unblinding of Cohort 2 on 7 August 2020, and they are not applicable as of protocol Version 4.

There are two planned OS interim analyses for the comparisons between the two treatment arms. The first OS interim analysis will be performed at the time of PFS analysis. The second OS interim analysis will be performed when 80% of the OS events required for the final OS analysis is reached. The Lan-DeMets $\alpha$-spending function with an O'Brien-Fleming boundary will be used to control the type I error accounting for the interim and final analyses of OS.

If the 0.01 $\alpha$ assigned to PFS is recycled, the final OS will be analyzed when 417 OS events occur at approximately 70 months after the first patient has been enrolled. It is estimated that there will be approximately (184, 334, 417) OS events at the first interim, the second interim and the final OS analyses, with corresponding p-value boundaries of (0.0015, 0.0204, 0.0427) and

corresponding hazard ratio boundaries of (0.626, 0.781, 0.820) at the first interim, the second interim, and the final OS analysis, respectively. The actual boundaries will be adjusted according to the actual information fractions at the interim analyses using the Lan-DeMets α-spending function with an O'Brien-Fleming boundary.

If the 0.01 $\alpha$ assigned to PFS is not recycled, the final OS will be analyzed when 444 OS events occur at approximately 76 months after the last patient has been enrolled. It is estimated that there will be approximately (184, 355, 444) OS events at the first interim, the second interim and the final OS analysis, with corresponding p-value boundaries of (0.0006, 0.0183, 0.0345) and corresponding hazard ratio boundaries of (0.603, 0.779, 0.818) at the first interim, the second interim, and the final OS analysis, respectively.

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ADA | anti-drug antibody |
| ASCO | American Society of Clinical Oncology |
| CAP | College of American Pathologists |
| CBR | clinical benefit rate |
| CI | confidence interval |
| CIT | cancer immunotherapy |
| CLIA | Clinical Laboratory Improvement Amendments |
| *COVID-19* | *coronavirus 2019* |
| CR | complete response |
| *CRS* | *cytokine release syndrome* |
| CT | computed tomography |
| ctDNA | circulating-tumor DNA |
| CYP | cytochrome P |
| DOR | duration of response |
| EC | Ethics Committee |
| eCRF | electronic Case Report Form |
| *ECOG* | *Eastern Cooperative Oncology Group* |
| EDC | electronic data capture |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 |
| EQ-5D-5L | EuroQol 5 Dimension Questionnaire, 5-Level Version |
| ER | estrogen receptor |
| Fc | fragment crystallizable |
| FDA | (U.S.) Food and Drug Administration |
| FFPE | formalin-fixed, paraffin-embedded |
| FMI | Foundation Medicine, Inc. |
| FNA | fine-needle aspiration |
| GHS | global health status |
| $HbA_{1C}$ | hemoglobin $A_{1C}$ |
| HBcAb | hepatitis B core antibody |
| 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 |

| Abbreviation | Definition |
|---|---|
| HR | hormone receptor |
| HRQoL | health-related quality of life |
| ICH | International Council for Harmonisation |
| iDCC | independent Data Coordinating Center |
| iDMC | independent Data Monitoring Committee |
| *IFN* | *interferon* |
| *IL* | *interleukin* |
| *IRR* | *infusion-related reaction* |
| IMP | investigational medicinal product |
| IND | Investigational New Drug (Application) |
| IRB | Institutional Review Board |
| ITT | intent to treat |
| IxRS | interactive voice or web-based response system |
| LPLV | last patient, last visit |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | magnetic resonance imaging |
| *NCCN* | *National Comprehensive Cancer Network* |
| NCI | National Cancer Institute |
| NCI CTCAE, v5 | National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5 |
| NGS | next-generation sequencing |
| NMPA | National Medical Products Administration |
| ORR | objective response rate |
| OS | overall survival |
| PCR | polymerase chain reaction |
| PD-1 | programmed death receptor–1 |
| PD-L1 | programmed death-ligand–1 |
| PFS | progression-free survival |
| PgR | progesterone receptor |
| *PIK3CA* | phosphatidylinositol-4, 5–bisphosphate 3-kinase, catalytic subunit, alpha |
| PK | pharmacokinetic |
| PR | partial response |
| PRO | patient-reported outcome |
| PRO-CTCAE | Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events |
| *PTEN* | phosphatase and tensin homolog |
| Q2W | every 2 weeks |

| Abbreviation | Definition |
|---|---|
| Q3W | every 3 weeks |
| QoL | quality of life |
| QW | once a week |
| QLQ-C30 | Quality of Life Questionnaire for Cancer |
| RBR | Research Biosample Repository |
| QTcF | QT interval corrected through use of Fridericia's formula |
| RECIST *v1.1* | Response Evaluation Criteria in Solid Tumors, *Version 1.1* |
| *SARS-CoV-2* | *severe acute respiratory syndrome coronavirus 2* |
| *SITC* | *Society for Immunotherapy of Cancer* |
| TNF-α | tumor necrosis factor–α |
| WES | whole exome sequencing |
| WGS | whole genome sequencing |
| ULN | upper limit of normal |

# 1. BACKGROUND

## 1.1 BACKGROUND ON TRIPLE-NEGATIVE 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 approximately 15% (Jemal et al. 2011; Ferlay et al. 2015).

Triple-negative breast cancer (TNBC) accounts for approximately 20% of all breast cancers and is defined by the absence of immunostaining (<1%) for estrogen receptor (ER), progesterone receptor (PgR), and non-amplified HER2 expression per the American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) guidelines (ASCO/CAP 2010, 2013, 2018). Patients with metastatic TNBC exhibit a particularly poor clinical outcome, generally with rapid progression and a median overall survival (OS) of approximately 16 months in a diagnostically unselected population (Rodler et al. 2010; Miles et al. 2013) and up to approximately 25 months in patients with tumors expressing PD-L1 (Schmid et al. 2018b). The TNBC phenotype has been associated with black race, younger age, and more advanced tumor stage at presentation (Millikan et al. 2008; Lund et al. 2009; Trivers et al. 2009; Lin et al. 2012; Danforth 2013). Although TNBC may respond to chemotherapy, including taxanes, there are no approved first-line regimens or targeted therapies for an all-comer population. Because of an increase in toxicity and little survival benefit with combination chemotherapy, treatment with sequential single agents is generally preferred (Cardoso et al. 2017; National Comprehensive Cancer Network 2017). Paclitaxel is considered an appropriate first-line regimen, with a median progression-free survival (PFS) of approximately 6 months in patients with TNBC (Miles et al. 2013, 2017). There is a pressing need for clinically active agents for the treatment of triple-negative subtype of metastatic breast cancer.

### The PI3K/Akt Pathway in Breast Cancer

The phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway is more frequently activated by genomic aberrations than any other signaling pathway in cancer (LoRusso 2016). The most common genetic alterations in this pathway are activating mutations of phosphatidylinositol-4, 5–bisphosphate 3-kinase, catalytic subunit, alpha (*PIK3CA*), loss-of-function alterations of the tumor suppressor phosphatase and tensin homolog (*PTEN*), deregulation of receptor tyrosine kinase signaling, and amplification and mutations of receptor tyrosine kinases (Cancer Genome Atlas Network 2012; Millis et al. 2015). Alterations in Akt itself, including amplification and overexpression of individual Akt isoforms, as well as activating mutations in Akt, have been identified in a subset of human cancers (Bellacosa et al. 2005; Brugge et al. 2007; Tokunaga et al. 2008). All of these mechanisms of pathway activation ultimately funnel through Akt as the central node that drives cell survival, growth, proliferation, angiogenesis, metabolism, and migration (Manning and Cantley 2007).

Large-scale comprehensive genomic analyses have characterized the heterogeneous nature of TNBC, including a subgroup of patients with a PI3K/Akt pathway activation signature characterized by *PIK3CA*- or *AKT1*-activating mutations and *PTEN* alterations (Cancer Genome Atlas Network 2012). Overall, *PIK3CA*/*AKT1*/*PTEN*-altered tumors are frequently observed in breast cancer and are reported in approximately 35% of patients with TNBC and in approximately 50% of hormone receptor (HR)-positive and HER2-negative breast cancers (Cancer Genome Atlas Network 2012).

To date, the relationship between PI3K/Akt pathway activation and prognosis in early breast cancer is mixed, with some data demonstrating association with favorable outcomes, some data indicating poor prognosis, and a number of studies showing insignificant results (Yang et al. 2016). Information demonstrating significant differences in the prevalence of these gene alterations between primary and metastatic tumor tissues is limited, while enrichment in metastatic patients is probable (Millis et al. 2015).

## 1.2 BACKGROUND ON IPATASERTIB

Ipatasertib is a potent, highly selective small molecule inhibitor of all three isoforms of the serine/threonine kinase Akt. Ipatasertib binds to the activated conformation of Akt and is ATP competitive. Ipatasertib binding inhibits the kinase activity of Akt and suppresses the phosphorylation of its direct substrates, including PRAS40, and additional downstream targets, such as S6 ribosomal protein, resulting in $G_1$ arrest and/or apoptosis in human cancer cells (Lin et al. 2012). In clinical tumor samples, robust Akt pathway inhibition by ipatasertib can be achieved at clinically relevant doses (Yan et al. 2013).

Upregulation of Akt signaling (whether intrinsic or induced following chemotherapy) represents a potentially important survival pathway in response to genotoxic and mitotic stress (Xu et al. 2012). Activation of Akt signaling following chemotherapy (including taxanes) may promote cell survival and chemoresistance across several cancer models, including breast cancer (Clark et al. 2002). Conversely, inhibition of the PI3K/Akt pathway in diverse cancers leads to radiosensitization and/or chemosensitization (Brognard et al. 2001; Solit et al. 2003; Wallin et al. 2010).

In nonclinical models with high levels of phosphorylated Akt or PI3K/Akt pathway activity (i.e., *PIK3CA* mutation, *PTEN* alterations), sensitivity to ipatasertib has been observed across different tumor models, including breast cancers (Lin et al. 2013). Additionally, ipatasertib plus microtubule inhibitors or DNA-damaging chemotherapeutic agents showed a clear advantage over respective single-agent treatment in preclinical models (refer to the Ipatasertib Investigator's Brochure for further information).

Based on the scientific rationale that PI3K/Akt blockade attenuates survival signals associated with mitotic stress from treatment with microtubule inhibitors and the high prevalence of PI3K/Akt pathway activation signatures in TNBC and in HR-positive and HER2-negative tumors (Cancer Genome Atlas Network 2012), clinical trials evaluating

the preliminary safety and efficacy of the combination of ipatasertib and paclitaxel in patients with breast cancer have been conducted. These trials include a Phase Ib study (PAM4983g; Arm C), with an expansion cohort of patients with HER2-negative breast cancer, and a Phase II randomized study (GO29227; LOTUS) comparing ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line treatment for patients with inoperable locally advanced or metastatic TNBC.

In the Phase Ib study PAM4983g, 3 of the 15 patients (20%) with breast cancer remained progression free for $>6$ months (HR-positive patients/HER2-negative patients: $n=2$; TNBC: $n=1$), and 4 partial responses included patients who had prior exposure to paclitaxel or investigational PI3K inhibitors (HR-positive patients/HER2-negative patients: $n=2$; TNBC: $n=2$).

Results of the Phase II randomized study GO29227 demonstrated that adding ipatasertib to paclitaxel as first-line therapy for inoperable locally advanced or metastatic TNBC improves PFS in the intent-to-treat (ITT) and in *PTEN*-low populations; the PFS improvement was more pronounced in patients with *PIK3CA/AKT1/PTEN*-altered tumors identified with the FoundationOne next-generation sequencing (NGS) assay (representing approximately 40% of the randomized patients in this setting). The use of *PIK3CA/AKT1/PTEN* alteration status as a predictive biomarker for response to the combination of ipatasertib and paclitaxel in metastatic TNBC is further supported by the pronounced PFS improvement over the complementary population of patients with *PIK3CA/AKT1/PTEN*–non-altered tumors. This study showed improvement in median PFS in the ITT population (hazard ratio: 0.60; 6.2 months in the ipatasertib arm compared with 4.9 months in the control arm), and in the prespecified patient population with *PIK3CA/AKT1/PTEN*-altered tumors (hazard ratio: 0.44; 9 vs. 4.9 months).

The ongoing Phase III, randomized, double-blind, placebo-controlled study CO40016 (IPATunity130) uses an identical treatment assignment for first-line therapy for patients with inoperable locally advanced or metastatic TNBC with *PIK3CA/AKT1/PTEN*-altered tumors and was designed to confirm the results seen in the preplanned efficacy analysis in the GO29227 study population with *PIK3CA/AKT1/PTEN*-altered tumors. The primary endpoint for Cohort A of the IPATunity130 study was not met: ipatasertib in combination with paclitaxel did not significantly reduce the risk of investigator-assessed PFS events compared with paclitaxel alone in patients with mTNBC who have PIK3CA/AKT/PTEN alterations. The primary analysis results for Cohort A show that the safety profile of ipatasertib in combination with paclitaxel was consistent with the known risks of each individual study drug and no new safety signal was identified.

In addition, the clinical safety profile of ipatasertib has been evaluated in multiple clinical trials as a single agent in the Phase Ia study (PAM4743g) and in combination with paclitaxel in the Phase Ib (PAM4983g) and Phase II (GO29227) studies. As a single agent, ipatasertib has a predictable pharmacokinetic (PK) profile, with a half-life of

approximately 48 hours, and significantly downregulates the PI3K/Akt pathway at doses ≥200 mg.

In Study GO29227, the adverse effects of ipatasertib plus paclitaxel in metastatic TNBC were consistent with previous experience of ipatasertib and of paclitaxel, most notably ipatasertib-related gastrointestinal toxicities that are manageable and reversible. Common adverse events with a ≥10% higher incidence in the ipatasertib arm than in the placebo arm were diarrhea, nausea, asthenia, and peripheral sensory neuropathy. Common Grade ≥3 adverse events included diarrhea, neutropenia, decreased neutrophil count, and fatigue. When grouping the adverse event preferred terms with similar medical concepts, asthenia/fatigue and peripheral neuropathy were not significantly different between the two arms (refer to the Ipatasertib Investigator's Brochure and Section 3.3.3 for detailed safety information). In Study GO29227, diarrhea was more common in the ipatasertib arm compared with the placebo arm (93% vs. 19%); however, the majority of cases were low-grade events. The onset of diarrhea was most common during the first cycle of treatment; late-onset diarrhea was rare, and no cases of colitis were reported. Diarrhea generally responded to loperamide treatment and to ipatasertib dose holds and dose reductions when resuming treatment; limited (3%) discontinuation of ipatasertib treatment because of diarrhea was reported. Despite the high frequency of diarrhea in the ipatasertib arm, the median relative dose intensity of both ipatasertib and paclitaxel approached 100% and was comparable in the ipatasertib and placebo arms.

Because of the high incidence of diarrhea seen in Study GO29227, loperamide prophylaxis has been implemented in the Phase III study CO40016. The primary analysis results for Cohort A of study CO40016, show that the safety profile of ipatasertib in combination with paclitaxel was consistent with the known risks of each individual study drug and no new safety signal was identified.

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

## 1.3 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to fragment crystallizable (Fc) receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies.

Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy (CIT).

The safety findings of single-agent atezolizumab across multiple tumor types in the clinical development program are consistent with the known mechanism of action of atezolizumab and the underlying disease. Currently, no maximum tolerated dose, no dose-limiting toxicities, and no clear dose-related trends related to the incidence of adverse events have been observed.

Atezolizumab is approved *in numerous countries* for the treatment of *several types of solid tumors, including* urothelial carcinoma, non–small cell lung cancer, small-cell lung cancer, and PD-L1–positive TNBC. .

The Phase III IMpassion130 (WO29522) study met its co-primary endpoint, PFS, as assessed by investigator in the ITT population (hazard ratio for progression or death, 0.80; 95% CI: 0.69% to 0.92%; $p=0.002$) and PD-L1–selected population (hazard ratio: 0.62; 95% CI: 0.49 to 0.78; $p<0.001$). In the ITT analysis, median PFS was 7.2 months with atezolizumab plus nab-paclitaxel compared with 5.5 months with placebo plus nab-paclitaxel; among patients with PD-L1–positive tumors, the median PFS was 7.5 months and 5.0 months, respectively. Clinically meaningful OS benefit was seen at interim OS analysis in PD-L1–positive patients. In the ITT analysis, median OS was 21.3 months with atezolizumab plus nab-paclitaxel and 17.6 months with placebo plus nab-paclitaxel (hazard ratio for death: 0.84; 95% CI: 0.69 to 1.02; $p=0.08$); among patients with PD-L1–positive tumors, median OS was 25.0 months and 15.5 months, respectively (hazard ratio: 0.62; 95% CI: 0.45 to 0.86) (Schmid et al. 2018a).

No new safety signals were identified. The most common adverse events (occurring in $\geq$20% of patients) in the atezolizumab arm were alopecia, fatigue, nausea, diarrhea, anemia, constipation, cough, headache, peripheral neuropathy, neutropenia, and decreased appetite. Serious adverse events occurred in 22.8% of patients in the experimental arm compared with 18.3% in the control arm. Fatal adverse events occurred in 1.3% of patients in the experimental arm and 0.7% in the control arm. Grade 3 or 4 adverse events occurred in 48.7% of patients in the experimental arm relative to 42.2% in the control arm. All-grade adverse events that occurred with $\geq$5% higher incidence in the experimental arm included nausea, cough, neutropenia, pyrexia, and hypothyroidism and the only Grade 3 or 4 adverse event with $\geq$2% higher incidence in the experimental arm was peripheral neuropathy. Adverse events of special interest (predefined to detect adverse events suggestive of a potential immune-mediated cause) occurred in 57.3% of patients in the experimental arm and 41.8% in the control arm. Grade 3 or 4 adverse events of special interest occurred in 7.5% of patients in the experimental arm versus 4.3% in the control arm. Adverse events led to discontinuation of (any) study treatment in 15.9% of patients in the experimental arm relative to 8.2% of patients in the control arm (Schmid et al. 2018a).

Also in metastatic TNBC, the Phase III IMpassion131 (MO39196) study (clinical cutoff date of 15 November 2019; data as of 29 July 2020) did not meet its primary endpoint of investigator-assessed PFS in the PD-L1–positive population. At the primary analysis, atezolizumab plus paclitaxel did not significantly reduce the risk of investigator-assessed PFS events compared with placebo plus paclitaxel in this population. Safety of atezolizumab in combination with paclitaxel appeared consistent with the known safety profiles of the individual medicines. The combination was generally well-tolerated and toxicities were manageable. No new safety signal was identified.

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

## 1.4 BACKGROUND ON STUDIES IN TNBC COMBINING IPATASERTIB AND ATEZOLIZUMAB

There are at present four ongoing Roche-sponsored studies with study treatments that include combinations of ipatasertib and atezolizumab in advanced breast cancer.

Studies CO40115 and CO39611 are studies within a Phase Ib/II, open-label, multicenter, randomized umbrella study, evaluating the safety and efficacy of immunotherapy-based treatment combinations in patients with unresectable locally advanced or metastatic TNBC and HR-positive and HER2-negative breast cancer, respectively. Both studies have an experimental arm with ipatasertib in combination with atezolizumab at the same dose and schedule used in this study, without chemotherapy. Study CO40115 has enrolled 22 patients in the second-line setting in unresectable locally advanced or metastatic TNBC. Study CO39611 has enrolled 15 patients in the second- and third-line settings for HR-positive and HER2-negative unresectable locally advanced or metastatic breast cancer, after progression with CDK4/6 inhibitors. Internal and external safety monitoring are being performed for this study, and to date, safety evaluations have been conducted for 6 patients in each study. Based on a safety analysis of data from the 6 patients in each study, no new safety signals were identified.

The Phase Ib study CO40151 is evaluating the safety and efficacy of the combination of ipatasertib and atezolizumab with either paclitaxel or nab-paclitaxel in a population of patients with diagnostically unselected (all-comer) advanced TNBC in the first-line setting. As of the clinical cutoff date of 5 January 2019, a safety and efficacy analysis had been completed of the data from the first 26 patients enrolled after a median 6.1 months in the study (18 patients treated with paclitaxel + ipatasertib + atezolizumab; 8 patients treated with nab-paclitaxel + ipatasertib + atezolizumab) in Cohort 1 and enrollment is ongoing. To date, more than 100 patients have been treated in this study, and more than 200 patients are anticipated to have been treated by the completion of the study. The preliminary but promising response rate of > 70% (Schmid et al. 2019) does not seem to be dependent on tumor *PIK3CA*/*AKT1*/*PTEN* alterations or PD-L1 expression. In the safety analysis, no Grade 4 or 5 adverse events were reported and Grade 3 events occurred in 53.8% of patients. Serious adverse events occurred in

46.2% of patients. In all, 19.2% of patients discontinued any of the three individual study drugs because of an adverse event, but no patient discontinued study treatment altogether because of an adverse event. The preliminary efficacy and tolerability of the combination suggest that this is a promising treatment regimen for further development (Schmid et al. 2019).

Study CO40016 is a Phase III study for patients with *PIK3CA*/*AKT1*/*PTEN*-altered positive locally advanced or metastatic TNBC or HR-positive HER2-negative breast cancer, with the primary objective of evaluating the efficacy of the combination of ipatasertib and paclitaxel compared with paclitaxel. One open-label single-treatment assignment cohort in this study will evaluate the combination of ipatasertib with atezolizumab and paclitaxel in up to approximately 100 patients with *PIK3CA*/*AKT1*/*PTEN*-altered negative locally advanced or metastatic TNBC.

Across these studies, more than 200 patients have been treated to date with ipatasertib and atezolizumab in combination, with no new safety signals reported.

## 1.5 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Metastatic breast cancer remains an incurable disease. For patients with locally advanced unresectable and metastatic TNBC, clinical outcome for some patients has improved with the incorporation of atezolizumab (Schmid et al. 2018a), although the prospect for long-term survival remains disappointingly low. As the biomarker-based segmentation of patient populations becomes more common, there are expected to be increasing challenges of appropriate treatment selection. Identification of an effective therapeutic approach that is broadly applicable is desirable. Study CO41101 continues the work of multiple Phase Ib–III clinical trials that have taken the approach of building on a taxane backbone with ipatasertib, atezolizumab, or the combination of the two.

CIT has demonstrated significant survival benefits over standard treatment observed across multiple advanced malignancies. Currently, the prevailing CIT approach is to circumvent immune evasion mechanisms and reinvigorate anti-tumor responses by identifying and targeting T-cell co-inhibitory surface receptors, such as cytotoxic T lymphocyte–associated protein 4 (CTLA-4) and PD-L1/PD-1. Although CIT has resulted in remarkable clinical therapeutic success for various cancer indications, ongoing research indicates a series of stepwise events necessary for the generation of a continuous anti-tumor immune response (Chen and Mellman 2013). Each event is critical for an effective response, and each is also susceptible to several tumor immune evasion mechanisms. Thus, the need to identify and circumvent the various factors involved in tumor immune evasion will be critical for propagating the anti-tumor immune response and advancing the field of CIT, most likely through combined targeted therapy regimens.

Recently, nonclinical and clinical data have indicated a correlation between *PTEN* loss and impaired anti-tumor immune responses, including reduced CD8 T-cell infiltration and

reduced efficacy of anti–PD-1 therapy in patients with melanoma. Furthermore, nonclinical studies reveal synergistic anti-tumor responses when combining PI3K-Akt pathway inhibition and PD-L1/PD-1 axis blockade (Peng et al. 2016). In addition, Akt inhibitors may restore and enhance physiological functionalities of T cells in the tumor microenvironment and enhance expansion of tumor-specific lymphocytes with memory cell phenotype (Crompton et al. 2015). Concurrent treatment with ipatasertib may enhance checkpoint inhibitor efficacy by driving development of memory T cells over effector T cells, thereby enabling a long-term response in patients (Gubser et al. 2013; Xue et al. 2015). On the basis of these results, as well as the tolerability and limited overlapping toxicity of atezolizumab, ipatasertib, and paclitaxel, combination treatment with these agents appears to have promising therapeutic potential in solid tumors such as TNBC.

As noted previously, the Phase III IMpassion130 (WO29522) study met its co-primary endpoint investigator-assessed PFS in the ITT population and PD-L1–positive population. The co-primary endpoint, OS, did not cross the interim boundary in ITT population. However, the magnitude of OS benefit in PD-L1–positive population is clinically meaningful.

Multiple ongoing open-label studies are evaluating the combination of ipatasertib with atezolizumab showing no new safety concerns. In particular, the ongoing Phase Ib study CO40151, evaluating ipatasertib in combination with atezolizumab and either paclitaxel or nab-paclitaxel, shows promising preliminary clinical efficacy with generally tolerable safety profile of the triplet treatment regimen in first-line locally advanced or metastatic TNBC. Because of the high incidence of rash and diarrhea observed in Study CO40151, the current study will take a preventative approach to the most common adverse events affecting patient experience, as outlined in Section 5.1.

On the basis of the data available to date, the benefit–risk assessment for administration of ipatasertib in combination with atezolizumab and paclitaxel is considered positive in patients with locally advanced unresectable or metastatic TNBC.

This Study CO41101 is designed to evaluate the efficacy of ipatasertib plus atezolizumab plus paclitaxel against an appropriate control arm treatment in two independent PD-L1 status-driven cohorts (Cohort 1, PD-L1 non–positive and Cohort 2 PD-L1–positive; see Section Section 3.1.1). Based on results from the primary analysis of the Phase III IMpassion131 (MO39196) study (see Section 1.3), the control arm for Cohort 2 of this study (atezolizumab plus paclitaxel plus placebo for ipatasertib) is no longer considered appropriate. As of 6 August 2020, further enrollment in Cohort 2 has been suspended and all patients in Cohort 2 have been unblinded to their treatment assignment to allow the patients to make informed decisions in consultation with their investigators regarding their treatment options.

Based on results from the primary analysis of the Phase III IPATunity130 (CO40016) study (see Section 1.2 ), Arm B for Cohort 1 of this study (ipatsertib plus paclitaxel plus placebo for atezolizumab) is no longer considered appropriate. As of 18 September 2020, further enrollment in Cohort 1 has been terminated, and all patients in Cohort 1 have been unblinded to their treatment assignment on 21 September 2020 to allow the patients to make informed decisions in consultation with their investigators regarding their treatment options.

### *Covid-19 Benefit–Risk Assessment*

*In the setting of the coronavirus disease 2019 (COVID-19) pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, it is unclear whether or how systemic cancer therapies, such as chemotherapy, targeted therapy, or immunotherapy, impact the incidence or severity of SARS-CoV-2 infection.*

*A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13) (Frebel et al. 2012). However, there are insufficient and inconsistent clinical data to assess if outcome from SARS-CoV-2 infection is altered by cancer immunotherapy.*

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

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

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

*Given the mechanism of action for ipatasertib, atezolizumab and paclitaxel, immune-mediated adverse events are potential overlapping toxicities associated with combination use of these agents.There are limited data concerning the possible interactions between cancer immunotherapy treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune-modifying therapies may positively or negatively impact the efficacy and safety of COVID-19 vaccination (Society for Immunotherapy of Cancer [SITC] 2020).*

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

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

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

## 2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of ipatasertib in combination with atezolizumab and paclitaxel in locally advanced unresectable or metastatic TNBC previously untreated in this setting. Patients with PD-L1–non-positive and PD-L1–positive tumors will be independently enrolled in Cohorts 1 and 2, respectively. The combination of ipatasertib, atezolizumab, and paclitaxel will be evaluated in two independently enrolled cohorts (Cohorts 1 and 2) and the combination of ipatasertib and paclitaxel will be evaluated in Cohort 1.

Specific objectives and corresponding endpoints are outlined in the following sections.

In this protocol, "study treatment" refers to the combination of treatments assigned to any individual patient as part of this study (e.g., ipatasertib/placebo [for ipatasertib], atezolizumab/placebo [for atezolizumab], and paclitaxel).

As of protocol Version 5, the following objectives and the corresponding statistical considerations and analyses will no longer be applicable to the study. Due to the early termination of the enrollment, data from enrolled patients will only be summarized descriptively for endpoints that are deemed appropriate and necessary (see Section 6 for details).

## 2.1 EFFICACY OBJECTIVES

### 2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to independently evaluate the efficacy of the experimental arm treatment compared with control arm treatment in each cohort (i.e., Arm A vs. Arm C and Arm B vs. Arm C in Cohort 1 and Arm A vs. Arm B in Cohort 2; for a description of each arm see Figure 1 and Section 3.1.1), on the basis of the following co-primary endpoints:

- Investigator-assessed progression-free survival (PFS) after randomization, defined as the time from randomization to the first occurrence of disease progression, as determined locally according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), or death from any cause, whichever occurs first
- Overall survival (OS) after randomization, defined as the time from randomization to death from any cause

### 2.1.2 Exploratory Efficacy Objectives

The exploratory efficacy objectives for this study are as follows:

- To independently evaluate the efficacy of experimental arm treatment compared with control arm treatment in each cohort (i.e., Arm A vs. Arm C and Arm B vs. Arm C in Cohort 1 and Arm A vs. Arm B in Cohort 2), on the basis of the following endpoints:
  - Objective response rate (ORR), defined as the proportion of patients with a complete response (CR) or partial response (PR) on two consecutive occasions $\geq$4 weeks apart, as determined by the investigator according to RECIST v1.1
  - Duration of response (DOR), defined as the time from the first occurrence of a documented objective response to the first occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first
  - Clinical benefit rate (CBR), defined as the proportion of patients who have a CR, PR, or stable disease for $\geq$24 weeks, as determined by the investigator according to RECIST v1.1

- To evaluate patient-reported outcomes (PROs) of function (role, physical), global health status (GHS)/quality of life (QoL) associated with the following:
  - Ipatasertib plus paclitaxel compared with paclitaxel in patients with PD-L1–non-positive tumors (Arm B vs. Arm C in Cohort 1)
  - The addition of atezolizumab to ipatasertib plus paclitaxel compared with ipatasertib plus paclitaxel alone in patients with PD-L1–non-positive tumors (Arm A vs. Arm B in Cohort 1)
  - Ipatasertib plus paclitaxel plus atezolizumab compared with control arm treatments (Arm A vs. Arm C in Cohort 1 and Arm A vs. Arm B in Cohort 2) as measured by the Functional and GHS/QoL scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) on the basis of the following endpoint:

    Mean and mean changes from baseline score in function (role, physical) and GHS/QoL by assessment timepoint and between treatment arms, as measured using the Functional and the GHS/QoL scales of the EORTC QLQ-C30
- To evaluate the efficacy of atezolizumab when combined with ipatasertib and paclitaxel in patients with PD-L1–non-positive tumors (Arm A vs. Arm B in Cohort 1) on the basis of PFS, OS, and ORR
- To independently evaluate the efficacy of experimental arm treatment compared with control arm treatment in patients with PIK3CA/AKT1/PTEN-altered tumors in each cohort, on the basis of PFS, OS, ORR, DOR, and CBR
- To evaluate PROs of function (cognitive, emotional, social) and disease- and treatment-related symptoms associated with:
  - Ipatasertib plus paclitaxel compared with paclitaxel in patients with PD-L1-non-positive tumors (Arm B vs. Arm C in Cohort 1)
  - The addition of atezolizumab to ipatasertib plus paclitaxel compared with ipatasertib plus paclitaxel alone in patients with PD-L1-non-positive tumors (Arm A vs. Arm B in Cohort 1)
  - Ipatasertib plus paclitaxel plus atezolizumab compared with control arm treatments (Arm A vs. Arm C in Cohort 1 and Arm A vs. Arm B in Cohort 2) as measured by the Functional and Symptom scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) on the basis of the following endpoint:

    Mean and mean change from baseline scores in functional (cognitive, emotional, social) and disease- and treatment-related symptoms by cycle and between treatment arms, as assessed using the Functional and Symptom scales of the EORTC QLQ-C30
- To evaluate patients' health utility, as measured by the EuroQol 5-Dimension Questionnaire, 5-Level Version (EQ-5D-5L) to generate utility scores for pharmacoeconomic modeling, on the basis of the following endpoint:

  Utility scores of the EQ-5D-5L Questionnaire

- To independently evaluate the clinical benefit in each cohort, on the basis of the following endpoint:

  PFS2 after randomization, defined as the time from randomization to second occurrence of objective disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause (whichever occurs first)

## 2.2 SAFETY OBJECTIVES

The safety objective for this study is to independently evaluate the safety of experimental arm treatment in each cohort, on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined by the investigator according to the NCI Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)
- Change from baseline in targeted vital signs
- Change from baseline in targeted clinical laboratory test results

**Exploratory Safety Objective**

The exploratory safety objective for this study is to independently evaluate key patient-reported symptomatic adverse events associated with ipatasertib plus paclitaxel plus atezolizumab compared with control arm treatment in each cohort, on the basis of the following endpoint:

Selected items from the NCI's PRO Version of the CTCAE (PRO-CTCAE) capturing patients' rating of the presence, severity, frequency, and/or activity interference of diarrhea, nausea, vomiting, decreased appetite, fatigue, neuropathy, mouth sores, and rash symptoms, as well as an additional item regarding bother associated with side effects of treatment.

## 2.3 EXPLORATORY PHARMACOKINETIC OBJECTIVES

The exploratory PK objectives for this study are as follows:

- To evaluate the pharmacokinetics of atezolizumab, ipatasertib, and its metabolite (G-0377720) in each cohort, on the basis of the following endpoints:
  - Plasma concentrations of ipatasertib and its metabolite (G-037720) at specified timepoints
  - Serum concentrations of atezolizumab at specified timepoints
- To evaluate potential relationships between ipatasertib and/or atezolizumab exposure, efficacy, and safety of ipatasertib plus paclitaxel plus atezolizumab in each cohort, on the basis of the following endpoints:
  - Relationship between ipatasertib and/or atezolizumab PK and efficacy endpoints, as appropriate based on the data
  - Relationship between ipatasertib and/or atezolizumab PK and safety endpoints, as appropriate based on the data

## 2.4 EXPLORATORY IMMUNOGENICITY OBJECTIVES

The exploratory immunogenicity objectives for this study are as follows:

- To independently evaluate the immune response to atezolizumab in each cohort, on the basis of the following endpoint:
  - Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study
- To evaluate the potential effects of ADAs in each cohort, on the basis of the following endpoint:
  - Relationship between ADA status and efficacy, safety, PK, or biomarker endpoints

## 2.5 EXPLORATORY BIOMARKER OBJECTIVES

The exploratory biomarker objectives for this study are as follows:

- To independently evaluate predictive or prognostic biomarkers (plasma or tissue) associated with disease activity status or response to treatment in each cohort, on the basis of the following endpoint:

  Relationship between tissue and blood-based biomarkers and patient clinical features (e.g., baseline features) and outcome (e.g., duration of PFS)
- To identify possible mechanisms of resistance to study treatments through the comparative analysis of potential biomarkers in pretreatment and post-progression biopsy tissue samples and in blood in each cohort, on the basis of the following endpoints:
  - Change in mutation and copy number in oncogenes, tumor suppressors, and/or other genes associated with disease progression by DNA sequencing
  - Change in levels of tumor suppressors, immune checkpoints, mitotic index, apoptotic index, and/or immune-cell infiltration by immunohistochemistry (IHC)

# 3. STUDY DESIGN

## 3.1 DESCRIPTION OF THE STUDY

### 3.1.1 Overview of Study Design

This study will enroll approximately 1155 patients (approximately 525 patients in Cohort 1, and approximately 630 patients in Cohort 2) with advanced TNBC across up to 350 sites globally. The study will compare the efficacy of the combination of ipatasertib, atezolizumab, and paclitaxel against paclitaxel in patients with PD-L1–non-positive tumors (Cohort 1, Arm A vs. Arm C) and against atezolizumab and paclitaxel in patients with PD-L1–positive tumors (Cohort 2, Arm A vs. Arm B). Cohort 1 will also evaluate the combination of paclitaxel and ipatasertib against paclitaxel in patients with PD-L1–non-positive tumors (Arm B vs. Arm C). In Cohort 1, approximately 525 patients with PD-L1–non-positive tumors will be enrolled and randomized in a 1:1:1 ratio to treatment Arms A, B, and C, respectively. In Cohort 2, approximately 630 patients with PD-L1–positive tumors will be enrolled and randomized in a 1:1 ratio to treatment

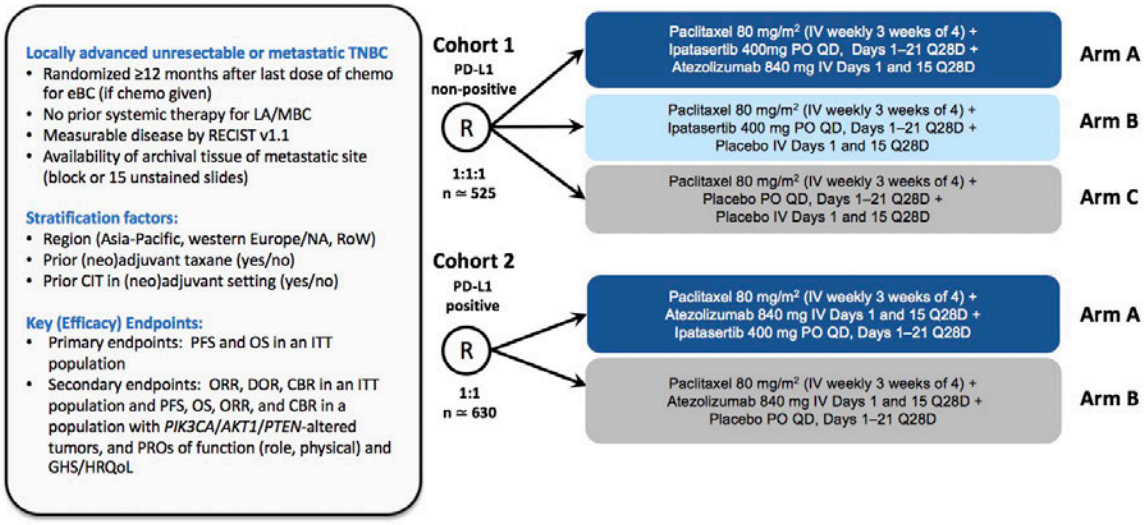
Arms A and B, respectively. Patients with PD-L1 unknown tumors will be assigned to Cohort 1. It is anticipated that owing to the prevalence of PD-L1 positivity and negativity by the SP142 assay that Cohort 1 will be fully enrolled before Cohort 2.

As of 6 August 2020, further enrollment in Cohort 2 has been terminated; treatment assignments for Cohort 2 were unblinded on 7 August 2020. Patients may continue current study treatment if considered clinically appropriate and if deriving benefit as assessed by the investigator. However, patients in Arm B of Cohort 2 will no longer receive placebo for ipatasertib. No crossover will be permitted for patients in Arm B of Cohort 2. For patients who choose to continue in the study, assessments will proceed as specified in the protocol (see Appendix 1 and Appendix 2).

As of 18 September 2020, further enrollment in Cohort 1 has been terminated; treatment assignments for Cohort 1 were unblinded on 21 September 2020. Patients may continue current study treatment if considered clinically appropriate and if deriving benefit as assessed by the investigator. However, patients in Arm B of Cohort 1 will no longer receive placebo for atezolizumab; patients in Arm C of Cohort 1 will no longer receive placebo for ipatasertib nor placebo for atezolizumab. No crossover will be permitted for patients in Arm B or Arm C of Cohort 1. Assessments will proceed as specified in the protocol (see Appendix 1 and Appendix 2).

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1. The PK and immunogenicity sampling schedule is presented in Appendix 2.

**Figure 1 Study Schema**




CBR = clinical benefit rate; CIT = cancer immunotherapy; DOR = duration of response; eBC = early breast cancer; FMI = Foundation Medicine, Inc.; GHS = global health status; HRQoL = health-related quality of life; ITT = intent to treat; LA = locally advanced; MBC = metastatic breast cancer; NA = North America; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death-ligand–1; PFS = progression-free survival; PO = orally; PROs=patient-reported outcomes; Q28D = every 28 days; QD = once a day; R = randomization; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; RoW = rest of world.

Note: Following unblinding of treatment assignments, patients in Arm B of Cohort 2 will no longer receive placebo for ipatasertib, patients in Arm B of Cohort 1 will no longer receive placebo for atezolizumab, and patients in Arm C of Cohort 1 will no longer receive placebo for ipatasertib nor placebo for atezolizumab.

Ipatasertib or placebo will be administered to patients at a starting dose of 400 mg QD PO for 21 days of each 28-day cycle on Days 1–21 unless held for management of adverse events. Atezolizumab or placebo will be administered to patients by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle. Paclitaxel will be administered to patients at a starting dose of 80 mg/m$^2$ by IV infusion for 3 of 4 weeks on Days 1, 8, and 15 of each 28-day cycle unless deferred to Day 22 because of an adverse event.

Any study treatment may be continued until disease progression, intolerable toxicity, elective withdrawal from the study or study treatment, or study completion or termination. After treatment discontinuation, patients will be followed every 3 months for survival, PROs (see Section 4.5.10), as well as follow-up anti-cancer therapy and related outcomes (therapy and procedures, doses, start and stop dates, best response, most recent tumor assessment date, and progression date). *As of protocol Version 6, these long-term follow-up assessments are no longer required.*

In each cohort, a permuted block randomization scheme will be used to ensure an appropriate allocation of patients to each arm (at an approximately 1:1:1 ratio to Arms A,

B, and C in Cohort 1 and approximately a 1:1 ratio to Arms A and B in Cohort 2) with respect to the following stratification factors:

- Geographic region (Asia-Pacific vs. western Europe/North America vs. rest of the world)
- Prior (neo)adjuvant taxane (yes vs. no)
- Prior CIT in the (neo)adjuvant setting (yes vs. no)

### 3.1.2 Assessments and Monitoring

All patients will be closely monitored for adverse events throughout the study, and adverse events will be graded according to the NCI CTCAE v5.0.

Tumor assessments should be performed based on a schedule calculated from Day 1 of Cycle 1, with the first assessment performed at Week 8 and approximately every 8 weeks thereafter, regardless of treatment administration timing or prior early or late tumor assessments (see Appendix 6). For estimation of PFS, ORR, DOR, and CBR, tumor response will be based on RECIST v1.1 (see Appendix 5). For patients who discontinue treatment without evidence of disease progression per RECIST v1.1, in addition to post-treatment follow-up, patients will be followed every 8 weeks for tumor assessments until documented progression per RECIST v1.1, elective withdrawal from the study, or study completion or termination. Images for tumor assessments for all patients will be prospectively collected to enable retrospective blinded independent central review when needed. As of protocol Version 5, images for tumor assessments will no longer be collected for blinded independent central review.

Patients will also be given the option of providing a tissue biopsy sample obtained at disease progression for exploratory analyses; this decision will not affect overall study eligibility. Such tumor tissue will be collected by biopsy, unless not clinically feasible as assessed and documented by the investigator, at the time of first evidence of radiographic disease progression per RECIST v1.1 (within 40 days after radiographic progression or prior to the start of new anti-cancer treatment, whichever is sooner). These samples will enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of the study treatments.

For additional details regarding tumor assessments, refer to Section 4.5.7.

### 3.1.3 Safety Data Monitoring

An iDMC will evaluate safety data during the study. The analysis supporting iDMC review will be conducted by an independent Data Coordinating Center (iDCC) and provided to the iDMC. Sponsor affiliates will be excluded from iDMC membership. The iDMC will follow a charter that outlines the iDMC roles and responsibilities.

Unblinded safety data will be reviewed by the iDMC on a periodic basis, approximately every 6 months from the time of the first patient's enrollment until the time of the primary

analysis of PFS. All summaries and analyses for the iDMC review will be prepared by the iDCC.

After reviewing the data, the iDMC will provide a recommendation to the Sponsor as described in the iDMC Charter. Final decisions will rest with the Sponsor.

Due to the early termination of the enrollment and unblinding of patients, the iDMC's review of the ongoing safety summary data will be discontinued after the unblinding, and the study team will be responsible for the ongoing monitoring of patient safety in the study. As unblinded data will now be available to the study team, aggregate safety data will be reviewed by the study teama regularly when appropriate. These safety reviews are perfomed in addition to the ongoing assessment of the incidence, nature, and severity of adverse events; serious adverse events; deaths; and laboratory abnormalities.

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

## 3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last patient, whichever occurs later.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 2–3 years.

## 3.3 RATIONALE FOR STUDY DESIGN

### 3.3.1 Rationale for Ipatasertib Dose and Schedule

For ipatasertib, the starting dose of 400 mg QD on Days 1–21 of each 28-day cycle was selected on the basis of safety and PK data from Arm C of Study PAM4983g (a Phase Ib trial of ipatasertib combined with paclitaxel; refer to the Ipatasertib Investigator's Brochure for details). The pharmacokinetics of paclitaxel and ipatasertib following co-administration showed no evidence of drug–drug interaction (see Section 3.3.8), and 400 mg of ipatasertib was better tolerated than 600 mg of ipatasertib in this combination.

In the Phase II, randomized, placebo-controlled study (GO29227) in patients with locally advanced or metastatic TNBC, the combination 400 mg of ipatasertib administered QD on Days 1–21 of each 28-day cycle with 80 mg/m$^2$ of paclitaxel administered QW on Days 1, 8, and 15 of each 28-day cycle was generally well tolerated and showed an improvement in PFS (refer to Section 1.2); the sparse sampling exposure results in this

study were also consistent with the known PK profiles of ipatasertib (and its metabolite G-037720).

In addition, the totality of pharmacodynamic data from the Phase I study PAM4743g (PK/pharmacodynamic analysis) and safety and efficacy data (including exploratory exposure–response analyses; data on file) from Phase II randomized studies (GO29227 and GO27983) of ipatasertib support the selected starting dose of 400 mg of ipatasertib for sufficient pathway inhibition and efficacy with a generally acceptable safety profile (refer to the Ipatasertib Investigator's Brochure for details). In the ipatasertib plus paclitaxel arm of Study GO29227, despite dose reduction of ipatasertib that occurred in 21.3% of patients because of adverse events, discontinuation of ipatasertib for any adverse event was 6.1% and the median cumulative dose intensity of both ipatasertib and paclitaxel was maintained at 99.0% (ipatasertib) and 100% (paclitaxel).

A relative bioavailability and food-effect study (GO29868) was conducted in healthy volunteers. The study confirmed that the Phase III tablet formulation of ipatasertib to be used in this study is anticipated to provide exposure similar to the exposure of ipatasertib powder-in-capsule and Phase II tablet formulations used in the Phase I (PAM4743g and PAM4983g) and Phase II (GO29227) studies, respectively.

### 3.3.2 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered to patients at a fixed dose of 840 mg Q2W (840 mg on Days 1 and 15 of each 28-day cycle). This is an approved dosage for atezolizumab (Tecentriq U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical PK efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details). The 840-mg Q2W dosage in the present study is the same atezolizumab dose and schedule used in the Phase Ib study CO40151 and the WO29522 (IMpassion130) study.

### 3.3.3 Rationale for Paclitaxel Dose and Schedule

Taxanes, in particular, paclitaxel or docetaxel, are increasingly used for adjuvant treatment of HER2-negative breast cancers worldwide. Many patients are expected to have received adjuvant chemotherapy, including taxanes, leading to a concern regarding re-challenge with taxane treatment at recurrence when patients first relapse in the advanced setting. Although there has been no specific prospective trial to evaluate the efficacy of re-challenge with paclitaxel in the metastatic setting after prior adjuvant taxane exposure, guidelines support the retreatment with a taxane in the metastatic setting, particularly if there has been at least 1 year of disease-free survival since its use in the adjuvant setting (Cardoso et al. 2017). In this study, patients who have relapsed

within 12 months of completing neoadjuvant or adjuvant chemotherapy treatment (including a taxane) will be excluded, thus selecting for patients who are likely to retain sensitivity to paclitaxel in the metastatic setting.

The TNT study demonstrated superiority of carboplatin over docetaxel for the treatment of patients with *BRCA* mutation–positive breast cancer (Tutt et al. 2015). Thus, in patients with *BRCA*-associated TNBC, a platinum regimen may be a preferred option, if not previously administered (Cardoso et al. 2017). The efficacy of ipatasertib in combination with paclitaxel for patients with homologous recombination repair deficiency (e.g., patients who are *BRCA1/2* germline mutation positive) is unknown. More recently, the Phase III OlympIAD trial led to the first approval of a *PARP*-inhibitor (olaparib) for patients with deleterious or suspected deleterious germline *BRCA*-mutated (*gBRCAm*), HER2-negative metastatic breast cancer. In this study patients previously exposed to chemotherapy were treated in the advanced setting with olaparib or the physician's choice of one of three chemotherapeutic agents. The study met its primary endpoint of PFS by blinded independent central review (Robson et al. 2017). There was no statistically significant improvement in OS based on the final OS analysis (Robson et al. 2019).

Although dosing in the package insert for paclitaxel is 220 mg/m$^2$ Q3W, the current study uses the equivalent of 240 mg/m$^2$ every 4 weeks. Clinical studies in metastatic breast cancer suggest that paclitaxel given QW may have a better efficacy than paclitaxel given Q3W (Green et al. 2005; Gonzalez-Angulo and Hortobagyi 2008; Seidman et al. 2008; Lu et al. 2014). In addition, a model-based meta-analysis of 29 monotherapy paclitaxel trials showed that a paclitaxel regimen of 65–80 mg/m$^2$ QW may have improved efficacy (based on results from breast cancer trials) and a lower incidence of neutropenia (based on results from breast cancer and mixed-patient population trials) than a 175-mg/m$^2$ paclitaxel Q3W regimen. A lower dose and more frequent administration pattern of paclitaxel are also observed in clinical practice. A recent analysis (Roche unpublished data) of Flatiron Health electronic medical records of 95 patients with metastatic TNBC treated with paclitaxel monotherapy in the first-line setting (2011–2018) in the United States suggested that two-thirds of the patient sample reported receiving a first administration dose of 80 mg/m$^2$; furthermore, the most frequent unique administration pattern at the start of therapy was QW 3 of 4 weeks, which was seen in just over one-third of the patient population.

### 3.3.4 Rationale for Patient Population

Tumor-cell killing by cytotoxic chemotherapy may expose the immune system to high levels of tumor antigens. Boosting tumor-specific T-cell immunity in this setting by blocking the PD-L1 pathway may result in deeper and more durable responses than those observed with standard chemotherapy alone (Merritt et al. 2003; Apetoh et al. 2007), and this may reasonably occur in tumors regardless of PD-L1 expression.

Both Studies GO29227 (LOTUS; paclitaxel, with or without ipatasertib) and WO29522 (IMpassion130; nab-paclitaxel, with or without atezolizumab) demonstrated statistically significant PFS improvement at the primary PFS analysis for a first-line locally advanced or metastatic TNBC population. In light of the encouraging data for TNBC seen in both combinations of ipatasertib with paclitaxel and atezolizumab with nab-paclitaxel, as well as the preliminary clinical activity and tolerability profile for the combination of ipatasertib, atezolizumab, and taxane chemotherapy in Study CO40151, this study further evaluates the combination of ipatasertib with atezolizumab and paclitaxel in the first-line locally advanced or metastatic TNBC population.

### 3.3.5 Rationale for Control Group

Data from the WO29522 (IMpassion130) study suggested that patients with PD-L1–positive tumors may significantly benefit from the addition of atezolizumab to taxane chemotherapy. Hence this study is designed with two distinct cohorts, in which patients with PD-L1–non-positive tumors will receive at least paclitaxel alone as standard-of-care treatment and patients with PD-L1–positive tumors will receive at least paclitaxel with atezolizumab. The combination of paclitaxel, ipatasertib, and atezolizumab and the combination of ipatasertib and paclitaxel are expected to have significant benefit over paclitaxel alone in patients with PD-L1–non-positive tumors. The combination of paclitaxel, ipatasertib, and atezolizumab is expected to have significant benefit over paclitaxel plus atezolizumab in patients with PD-L1–positive tumors.

As noted in Section 1.5, the control arm for Cohort 2 of this study (atezolizumab plus paclitaxel plus placebo for ipatasertib) is no longer considered appropriate, based on results from the primary analysis of the Phase III IMpassion131 (MO39196) study. Disposition of patients in Cohort 2 will proceed as outlined in Section 3.1.1.

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

In this study, the co-primary efficacy endpoints will be investigator-assessed PFS and OS. This study will test the hypothesis that treatment regimens in the experimental arms will prolong PFS and OS compared with treatments in the control arms.

PFS as an endpoint can reflect tumor growth and can be assessed before the determination of a survival benefit; additionally, its determination is not generally confounded by subsequent therapies. Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the benefit–risk profile of the new treatment compared with available therapies (U.S. Food and Drug Administration [FDA] 2007; European Medicines Agency 2012).

Improvement in OS is generally accepted as the best measure of clinical benefit for patients with advanced TNBC, but it may be confounded by therapies that follow the end of study treatment. However, recent data from studies of other solid tumors suggest that OS may be a more appropriate endpoint for CIT than PFS. For example, in a Phase II

randomized study (GO28753), patients with advanced non–small cell lung cancer in the ITT population had a significant improvement in OS when treated with atezolizumab compared with docetaxel, with a stratified hazard ratio of 0.73 (95% CI: 0.53% to 0.99%) while PFS was similar between the two arms: hazard ratio=0.94 (95% CI: 0.72% to 1.23%) (Fehrenbacher et al. 2016).

### 3.3.7 Rationale for Biomarker Assessments

Published results suggest that the expression of PD-L1 in tumors correlates with response to anti–PD-1 and anti–PD-L1 therapy (Topalian et al. 2012; Herbst et al. 2014, 2016; Borghaei et al. 2015; Fehrenbacher et al. 2016; Rosenberg et al. 2016, Schmid et al. 2018a). In the current study, archival or baseline tumor specimens will be collected from patients and tested for PD-L1 expression by a central laboratory during the screening period. In addition to the assessment of PD-L1 status, *PIK3CA*/*AKT1*/*PTEN*-altered status and other exploratory biomarkers, such as potential predictive and prognostic biomarkers related to the clinical benefit of ipatasertib and/or atezolizumab, tumor immunobiology, mechanisms of resistance, or tumor type, may be analyzed.

Archival or fresh tumor tissue will be collected at baseline. In order to obtain the most accurate reflection of a patient's current disease while minimizing burden, a specimen from the most recently obtained tumor tissue is requested. Tumor tissue collected by biopsy will also be requested at the time of first evidence of radiographic disease progression per RECIST v1.1, if deemed clinically feasible by the investigator, to enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of ipatasertib, atezolizumab, and/or paclitaxel. This biopsy at progression is optional but strongly encouraged.

Circulating-tumor DNA (ctDNA) can be detected in the blood of patients with epithelial cancers and may have diagnostic and therapeutic significance (Schwarzenbach et al. 2011). For example, the mutational status of tumor cells may be obtained through the isolation of ctDNA (Maheswaran et al. 2008), and ctDNA has been used to monitor treatment effectiveness in melanoma (Shinozaki et al. 2007). In the current study, blood samples will be collected at screening, at time of first tumor assessment, and at the study completion or early termination visit to evaluate oncogenic genetic alterations at baseline and to assess for the possible emergence of new alteration after treatment with ipatasertib, atezolizumab, and/or paclitaxel. Genetic alterations will be evaluated in relevant genes in the PI3K/Akt pathway, including, but not limited to, *PIK3CA* and *AKT1*. Identifying potential discordances in the *PIK3CA* and *AKT1* status between tumor samples and ctDNA may help clarify the prognostic and predictive significance of *PIK3CA* and *AKT1* mutations in patients with breast cancer treated with ipatasertib and paclitaxel.

Blood samples will be collected at baseline and during the study to evaluate changes in surrogate biomarkers. Changes in biomarkers (such as ctDNA, cytokines associated

with T-cell activation, and lymphocyte subpopulations) may provide evidence of biologic activity of ipatasertib and/or atezolizumab in humans. Correlations between these biomarkers and safety and efficacy endpoints will be explored to identify blood-based biomarkers that might be predictive of which patients are more likely to benefit from ipatasertib and/or atezolizumab.

Genetic variants of drug-metabolizing enzymes and transporters can alter the pharmacokinetics of drugs, affecting their safety and efficacy. For example, patients who carry defective alleles of the gene encoding uridine diphosphate glucuronosyltransferase 1A1 (*UGT1A1*), which facilitates the metabolism and excretion of SN-38 (the active metabolite of irinotecan), are at higher risk for adverse events associated with the use of standard doses of irinotecan (O'Dwyer and Catalano 2006). Preliminary results from in vitro metabolism studies suggest that ipatasertib is primarily metabolized by the cytochrome P (CYP) 450 enzyme CYP3A, with a minor contribution by CYP2D6. Although in vitro studies can help elucidate the roles of enzymes in the metabolism of the drug, these results are not always predictive of in vivo metabolism for a number of reasons, including differences in drug concentrations that the enzymes encounter in vitro and in vivo. For this reason, a blood sample for DNA isolation will be collected from all patients in this study for potential pharmacogenetic analysis of genes or biomarkers that may affect the pharmacokinetics of ipatasertib in combination with paclitaxel. The decision to analyze the samples will be based on a review of the PK data. For example, if a patient in a given treatment arm has substantially higher ipatasertib plasma levels than other patients in that treatment arm, he or she may carry a defective allele of a gene important in the metabolism or transport of ipatasertib. The genotyping efforts would be guided by results from in vitro metabolism studies and by results from ongoing clinical studies with ipatasertib.

The pharmacogenetic analysis, if needed, will be performed on identifiable (referring to the blinded clinical trial number assigned to the patient at the time of randomization and not to the actual name or other protected health information of the patient) DNA samples, because it is necessary to link a patient's PK data with genotype. This analysis will be restricted to the evaluation of genes that may be involved in the pharmacokinetics of ipatasertib (e.g., drug metabolism, disposition, or elimination genes, or genes influencing these processes).

In addition, tumor DNA can contain both reported and unreported chromosomal alterations resulting from the tumorigenesis process. To help control for sequencing calls in previously unreported genomic alterations, the WGS blood sample will help determine whether an observed alteration identified in the tumor tissue is somatic throughout the evaluation of the DNA isolated in peripheral blood.

### 3.3.8 Rationale for the Pharmacokinetic Evaluation Schedule

As of protocol Version 5, blood samples for PK and ADA analyses will no longer be collected.

A sparse sampling strategy will be applied in this study. Samples for PK characterization of ipatasertib and its metabolite G-037720 will be collected as outlined in Section 4.5.9. Samples will be collected on Days 1 and 15 of Cycle 1 and on Day 15 of Cycle 3 for ipatasertib and G-037720 analysis. Samples will be collected on Days 1 and 15 of Cycle 1, and on Day 1 of Cycles 2, 3, 4, 8, 12, and 16 for atezolizumab exposure and ADA analyses. The sampling schedule is designed to enable characterization of ipatasertib and atezolizumab using population-PK methodology for characterization.

Paclitaxel is metabolized by CYP2C8 and CYP3A4. In vivo, paclitaxel was not a sensitive substrate of CYP3A4, and exposure did not markedly change in combination with the potent CYP3A4 inhibitor, ketoconazole (Jamis-Dow et al. 1997; Woo et al. 2003). Given that ipatasertib is a mild to moderate inhibitor of CYP3A4 (Study PAM4743g; see the Ipatasertib Investigator's Brochure for details) and is not an inhibitor of CYP2C8, ipatasertib is not expected to alter paclitaxel exposure. The PK results of paclitaxel and ipatasertib in Study PAM4983g were comparable with their respective single-agent data, providing evidence that ipatasertib does not alter paclitaxel exposure. Therefore, paclitaxel pharmacokinetics will not be evaluated in this study.

In general, monoclonal antibodies do not affect the hepatic, renal, or biliary elimination of small molecules, and there is low risk of drug–drug interactions between monoclonal antibodies and small molecules given their distinct routes of elimination (Zhou and Mascelli 2011). Atezolizumab is a monoclonal antibody and is not anticipated to have any CYP-mediated drug–drug interactions with ipatasertib. Also, ipatasertib is not expected to change the clearance of atezolizumab. Sparse sampling of atezolizumab and ipatasertib will also allow for comparison with single-agent data from other trials.

Any remaining PK samples after evaluation of ipatasertib and its metabolite may be used for exploratory evaluation of other analytes related to the administered drugs or biomarkers affecting their disposition.

### 3.3.9 Rationale for Collection of DNA (Blood) for Exploratory Whole Genome Sequencing

PK plasma samples will be collected for DNA extraction to enable WGS or whole exome sequencing (WES) to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or

develop adverse events. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

This sample for WGS will be collected if approved locally.

### 3.3.10 Rationale for Patient-Reported Outcome Assessments

As of protocol Version 5, PRO assessments will no longer be collected.

As metastatic breast cancer 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 provide an understanding of the impact a treatment has on a patient. The EORTC QLQ-C30 is a validated instrument that has been widely used in assessing HRQoL in patients with cancer (Anderson et al. 1993). The core instrument assesses GHS/QoL, functioning (physical, role, emotional, cognitive, and social), and general cancer symptoms, and, side effects of systemic chemotherapy (see Appendix 10).

Cancer treatments, particularly combination therapies, can produce significant symptomatic adverse events. Recent research has shown that clinicians may underreport the incidence and severity of symptoms experienced by patients receiving treatment for cancer (Fromme et al. 2004; Trotti et al. 2007; Pakhomov et al. 2008; Basch 2010; Quinten et al. 2011; Atkinson et al. 2012; Basch et al. 2014). Collecting adverse event information directly from patients can provide a better understanding of treatment characteristics and their effects. In order to evaluate the tolerability of ipatasertib in combination with atezolizumab and paclitaxel, patients will be asked to report on their experience of breast cancer treatment–related symptoms selected from the validated PRO-CTCAE item bank (Basch et al. 2014) (see Appendix 12). These symptoms were identified as being salient to patients' experience with ipatasertib in combination with atezolizumab and paclitaxel on the basis of preliminary safety data from the ongoing studies containing this triplet, as well as side effects pertinent to the individual drug classes.

The EORTC QLQ-C30 will be administered to patients to assess disease- and treatment-related symptoms, functioning, and HRQoL (see Section 4.5.10). In addition, selected items from the PRO-CTCAE and an additional item regarding bother owing to side effects will be collected to assess treatment-related symptoms and overall treatment burden. The EQ-5D-5L (see Appendix 11) will be used to derive health states for use in economic models and therefore will not be included in the Clinical Study Report.

The EORTC QLQ-C30, selected items from the PRO-CTCAE, and EQ-5D-5L will be assessed in this order (EORTC QLQ-C30 first, followed by the PRO-CTCAE second, and the EQ-5D-5L last), at baseline (Day 1 of Cycle 1), on Day 15 of Cycles 1 and 2, on

Day 1 of each subsequent cycle, and at the treatment discontinuation visit (see Appendix 1). After treatment discontinuation to minimize burden on patients, only selected scales of the EORTC QLQ-C30 as well as the EQ-5D-5L measure will be administered over the telephone to patients or completed at the site during follow-up calls (or visits) and recorded on paper approximately every 3 months until death (see Appendix 1). The selected scales of the EORTC QLQ-C30 are as follows: the GHS/QoL (which consists of Questions 29 and 30), Physical Function (Questions 1–5), Role Function (Questions 6 and 7), Pain (Questions 9 and 19), Fatigue (Questions 10, 12, and 18), and Dyspnea (Question 8).

# 4. MATERIALS AND METHODS

## 4.1 PATIENTS

Approximately 1155 patients with locally advanced unresectable or metastatic TNBC with no prior systemic therapy for TNBC in the advanced setting will be enrolled during the global enrollment phase of this study. After completion of the global enrollment phase, additional patients from mainland China may be enrolled during an extended China enrollment phase.

### 4.1.1 Inclusion Criteria

Women or men with locally advanced unresectable or metastatic triple-negative adenocarcinoma of the breast who have not received prior systemic chemotherapy in this setting may be eligible for this study. In patients with *BRCA*-associated tumors, platinum chemotherapy (Cardoso et al. 2017) or olaparib (Robson et al. 2019) as potentially the preferred treatment option should be taken into consideration when determining whether this study may be appropriate for these patients. Patients may have received prior chemotherapy in the neoadjuvant or adjuvant setting if treatment was completed at least 12 months prior to randomization. Locally advanced unresectable disease must not be amenable to resection with curative intent. Patients must have sufficient tumor tissue and comply with all eligibility criteria to be enrolled.

#### 4.1.1.1 General Inclusion Criteria

Patients must meet the following general criteria for study entry:

- Signed Informed Consent Form(s)
- Women or men, age ≥ 18 years at the time of signing the Informed Consent Form
- Willingness and ability to complete all study-related assessments, including PRO assessments, in the investigator's judgment
- Measurable disease according to RECIST v1.1 (see Appendix 5)

  Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (see Appendix 3)
- Adequate hematologic and organ function within 14 days before the first study treatment on Day 1 of Cycle 1, as defined by the following:
  - Neutrophils (ANC ≥ 1500/μL)
  - Hemoglobin ≥ 9 g/dL
  - Platelet count ≥ 100,000/μL
  - Serum albumin ≥ 3 g/dL
  - Total bilirubin ≤ 1.5 × the upper limit of normal (ULN), with the following exception:

    Patients with known Gilbert syndrome who have serum bilirubin ≤ 3 × ULN may be enrolled.
  - AST and ALT ≤ 2.5 × ULN, with the following exception:

    Patients with documented liver or bone metastases may have AST and ALT ≤ 5 × ULN.
  - ALP ≤ 2 × ULN, with the following exceptions:

    Patients with known liver involvement may have ALP ≤ 5 × ULN.

    Patients with known bone involvement may have ALP ≤ 7 × ULN.
  - PTT (or aPTT) and INR ≤ 1.5 × ULN (except for patients receiving anticoagulation therapy)

    Patients receiving heparin treatment should have a PTT (or aPTT) between 1.5 × and 2.5 × ULN (or a patient's value before starting heparin treatment). Patients receiving coumarin derivatives should have an INR between 2.0 and 3.0 assessed in two consecutive measurements performed 1–4 days apart. Patients should be on a stable anticoagulant regimen.

- Serum creatinine $< 1.5 \times$ ULN or creatinine clearance $\geq 50$ mL/min based on Cockcroft−Gault glomerular filtration rate estimation:

$$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times 0.85 \text{ (if female)}}{72 \times (\text{serum creatinine in mg/dL})}$$

- Fasting total glucose $\leq 150$ mg/dL and hemoglobin $A_{1C}$ ($HbA_{1C}$) $\leq 7.5\%$

- Life expectancy of at least 6 months
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as described below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for at least 28 days after the final dose of ipatasertib/placebo, 5 months after the final dose of atezolizumab/placebo, and 6 months after the final dose of paclitaxel, whichever occurs later, and agreement to refrain from donating eggs during this same period

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq 12$ continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). *Per this definition, a woman with a tubal ligation is considered to be of childbearing potential.* The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year, when used consistently and correctly, include combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, bilateral tubal occlusion, male sterilization, intrauterine hormone-releasing system, copper intrauterine devices, and sexual abstinence.

  Hormonal contraceptive methods may be used in accordance with specific country and local requirements for patients with breast cancer.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

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

With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year during the treatment period and for 28 days after the final dose of ipatasertib/placebo, or 6 months after the final dose of paclitaxel, whichever occurs later. Men must refrain from donating sperm during this same period.

With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 28 days after the final dose of ipatasertib/placebo or 6 months after the final dose of paclitaxel, whichever occurs later, to avoid exposing the embryo.

Examples of contraceptive methods with a failure rate of $<1\%$ per year, when used consistently and correctly, include combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, bilateral tubal occlusion, male sterilization, intrauterine hormone-releasing system, copper intrauterine devices, and sexual abstinence.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For any patients enrolled in the extended enrollment phase (i.e., China extension phase): patient is a current resident of mainland China, Hong Kong, or Taiwan, and of Chinese ancestry

#### 4.1.1.2 Disease-Specific Inclusion Criteria

Patients must meet the following disease-specific criteria for study entry:

- Appropriate candidate for paclitaxel monotherapy if tumor PD-L1 status is unknown or non-positive; appropriate candidate for paclitaxel and atezolizumab if tumor PD-L1 status is positive
- Histologically documented triple-negative adenocarcinoma of the breast that is locally advanced or metastatic and is not amenable to resection with curative intent
  - Receptor status at study entry should correspond to the evaluation of the most recent biopsy (i.e., recurrent or metastatic tissue where applicable and if safely accessible, and non–fine-needle aspiration [FNA] sample), as assessed locally (or centrally, if not available locally) according to the ASCO/CAP 2018 guidelines (ASCO/CAP 2018; and Woolf et al. 2018 for HER2 testing update):

TNBC is defined as HER2 negative, ER negative, and PgR negative.

ER or PgR positivity is defined as ≥ 1% of tumor cell nuclei immunoreactive to the respective hormonal receptor (see Appendix 8).

HER2 positivity is defined as one of the following: 3+, as assessed on IHC or in situ hybridization positive (see Appendix 9).

- Submittal of a formalin-fixed, paraffin-embedded tumor (FFPE) tissue block or a minimum of *10–15 slides at least (*15 *slides preferred) containing* freshly cut unstained, serial tumor slides from the most recently collected tumor tissue (for central analysis of PD-L1 status and for other protocol-mandated secondary and exploratory assessments). Cytologic or FNA samples are not acceptable. Tumor tissue from bone metastases that is subject to decalcification is not acceptable.
- Tumor tissue must be evaluated centrally for PD-L1 expression prior to enrollment. Patients will be assigned to the appropriate cohort with a centrally determined PD-L1 result.
- 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 cohort assignment, the PD-L1 score of the patient will be the maximum PD-L1 score among the samples.
- If a more recent specimen is either insufficient or unavailable, a patient may still be eligible if the patient can provide a tissue block (preferred) or a minimum of 15 unstained serial slides from an older archival tumor tissue or undergo an additional pretreatment core or excisional biopsy of a non-target lesion (a non-target lesion is preferred if it is accessible and the biopsy can be safely obtained). In general, a minimum of three core biopsies is required.

  If a patient already has results available from Foundation Medicine, Inc.'s (FMI's) commercial tissue-based NGS assay known as the FoundationOne CDx™, 10 freshly cut unstained, serial tumor slides from the most recently collected tumor tissue is acceptable for central analysis of PD-L1 status and other protocol-mandated secondary and exploratory assessments.

### 4.1.2 Exclusion Criteria

#### 4.1.2.1 General Exclusion Criteria

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

- Inability to comply with study and follow-up procedures
- History of malabsorption syndrome or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills
- Severe infection within 4 weeks prior to initiation of study treatment (including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia) as well as those who have received treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment are not eligible for the study. Patients receiving prophylactic antibiotics (e.g., for prevention of

a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.

- Known HIV infection (there must be a negative HIV test at screening)
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis (e.g., positive for hepatitis B surface antigen [HBsAg] or hepatitis C virus [HCV] antibody at screening), current drug or alcohol abuse, or cirrhosis
  - Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive hepatitis B core antibody [HBcAb] test, accompanied by a negative HBV DNA test) are eligible.
  - Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Current treatment with anti-viral therapy for HBV
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 1 of Cycle 1 or anticipation of need for a major surgical procedure during the study

  Placement of a vascular access device is not considered major surgery.

- Pregnancy or breastfeeding, or intention to become pregnant during the study or within 28 days after the final dose of ipatasertib/placebo, 5 months after the final dose of atezolizumab/placebo, and 6 months after the final dose of paclitaxel whichever occurs later

  Women of childbearing potential (who are not postmenopausal with $\geq$12 months of non–therapy-induced amenorrhea nor surgically sterile) must have a negative serum pregnancy test result either within 96 hours prior to initiation of study drug, or within 7 days of Day 1, Cycle 1 (in this case, confirmed by a negative urine pregnancy test result on Day 1 of Cycle 1 prior to dosing).
- New York Heart Association Class II, III, or IV heart failure, left ventricular ejection fraction $<$50%, or active ventricular arrhythmia requiring medication
- Current unstable angina or history of myocardial infarction within 6 months prior to Day 1 of Cycle 1
- Congenital long QT syndrome or screening QT interval corrected through use Fridericia's formula (QTcF) $>$480 ms
- Current treatment with medications used at doses known to cause clinically relevant prolongation of QT/QTc interval (see list in Appendix 15)
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion (including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction)

- Requirement for chronic corticosteroid therapy of > 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressant agents for a chronic disease

  No chronic corticosteroid use is permitted at baseline with rare exceptions. Refer to Section 4.1.2.5, Atezolizumab-Specific Exclusion Criteria.

- Treatment with approved or investigational cancer therapy within 14 days prior to Day 1 of Cycle 1
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that, in the investigator's opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or renders the patient at high risk from treatment complications

#### 4.1.2.2 Disease-Specific Exclusion Criteria

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

- History of or known presence of spinal cord metastases, as determined by computed tomography (CT) or magnetic resonance imaging (MRI) evaluation during screening or prior radiographic assessments
- 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.

    Patients with leptomeningeal carcinomatosis will be excluded.
- Known germline *BRCA*1/2 deleterious mutation, unless the patient is not an appropriate candidate for a *PARP*-inhibitor
- Any previous systemic therapy for inoperable locally advanced or metastatic triple-negative adenocarcinoma of the breast

  Patients **may** have received prior neoadjuvant and/or adjuvant chemotherapy, prior neoadjuvant and/or adjuvant CIT, and/or radiotherapy for breast

adenocarcinoma, provided all chemotherapy and CIT were completed ≥12 months prior to randomization.

The 12-month treatment-free minimum interval in these cases begins with the last administration of chemotherapy in the early breast cancer setting and is not meant to encompass HER2-targeted therapy, such as trastuzumab, ado-trastuzumab emtansine, pertuzumab, neratinib, or endocrine therapies.

Previous systemic therapies for TNBC include, but are not limited to, chemotherapy, immune checkpoint inhibitors, or targeted agents.

- Unresolved, clinically significant toxicity from prior therapy, except for alopecia and Grade 1 peripheral neuropathy
- Patients who have received palliative radiotherapy to peripheral sites (e.g., bone metastases) for pain control and whose last treatment was completed 14 days prior to Day 1 of Cycle 1 may be enrolled in the study if they have recovered from all acute, reversible effects (e.g., to Grade 1 or resolved by enrollment)
- 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 (e.g., to Grade 1 or resolved) from the effects of radiation prior to study enrollment. There is no required minimum recovery period beyond the 14 days required for radiotherapy.
  - 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 (i.e., >1.5 mmol/L ionized calcium, >12 mg/dL calcium, or corrected serum calcium greater than ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy
  - Patients who are receiving bisphosphonate therapy specifically to prevent skeletal events (e.g., bone metastasis, osteoporosis) and who do not have a history of clinically significant hypercalcemia are eligible.
- Malignancies other than breast cancer within 5 years prior to Day 1 of Cycle 1, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, or Stage I uterine cancer

#### 4.1.2.3 Paclitaxel-Specific Exclusion Criteria

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

- Known hypersensitivity or contraindication to any component of the study treatments, including the paclitaxel excipient, macrogolglycerol ricinoleate
- Grade ≥2 peripheral neuropathy

#### 4.1.2.4 Ipatasertib-Specific Exclusion Criteria

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

- History of Type I or Type II diabetes mellitus requiring insulin

  Patients who are on a stable dose of oral diabetes medication ≥ 2 weeks prior to initiation of study treatment are eligible for enrollment.
- Grade ≥2 uncontrolled or untreated hypercholesterolemia or hypertriglyceridemia
- History of or active inflammatory bowel disease (e.g., Crohn disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)
- Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, *Aspergillosis*, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia)
- Treatment with strong CYP3A inhibitors or strong CYP3A inducers within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study drug
- Prior treatment with an Akt inhibitor

  Note: Prior treatment with PI3K or mTOR inhibitors is allowed.

#### 4.1.2.5 Atezolizumab-Specific Exclusion Criteria

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

- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 4 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

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

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

- Rash must cover $<10\%$ of body surface area.
- Disease is well controlled at baseline and requires only low-potency topical corticosteroids.
- There $has\ been$ no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months.

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Prior allogeneic stem cell or solid organ transplantation
- Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during treatment with atezolizumab or within 5 months after the final dose of atezolizumab
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or recombinant human antibodies
- Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin-2) within 4 weeks or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–tumor necrosis factor-$\alpha$ [TNF-$\alpha$] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the study, with the following exceptions:

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

  Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study

## 4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

### 4.2.1 Treatment Assignment

In this Phase III, randomized, double-blind, placebo-controlled study, patients will be randomized between treatment arms as follows. In Cohort 1, patients will be

randomized in a 1:1:1 ratio to Arms A, B, and C, respectively. In Cohort 2, patients will be randomized in a 1:1 ratio to Arms A and B.

As of 6 August 2020, further enrollment in Cohort 2 has been terminated.

There is no planned crossover in this trial.

Patients will be allocated to each of the treatment arms through the use of a permuted-block randomization to ensure within-stratum balance of patient characteristics between treatment arms. Randomization will be stratified according to the following criteria:

- Geographic region (Asia-Pacific vs. western Europe/North America vs. rest of the world)
- Prior (neo)adjuvant taxane (yes vs. no)
- Prior CIT in the (neo)adjuvant setting (yes vs. no)

The various stratification factors may correlate with different prognoses and differential responses to checkpoint inhibition, or they may reflect different regional clinical practices.

To further protect the integrity of the study, the results of any patient-specific plasma concentration data for ipatasertib and atezolizumab will not be made known to either investigators or the contract research organizations, and any interim analyses done by iDCC and reviewed by iDMC will not be made known to the investigators or the Sponsor. Baseline NGS data from tumor samples will not be disclosed to the investigators or patients unless the report is already available in a Clinical Laboratory Improvement Amendments (CLIA)-certified format. NGS data from post-progression tumor samples will be made available in a CLIA-certified report if and when available. The NGS research report, when released, upon request by the investigator, is not intended for treatment decisions.

### 4.2.2 Blinding

Study site personnel, including the investigator, and patients will be blinded to treatment assignment during the study. The Sponsor and its agents will also be blinded to treatment assignment, with the exception of individuals who require access to patient treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, Sponsor-independent PK bioanalytical personnel, interactive voice or web-based response system (IxRS) service provider, iDMC members, and the iDCC.

As of 7 August 2020 and 21 September 2020, treatment assignments for patients in Cohort 2 and Cohort 1 have been unblinded to the Sponsor and study site personnel,

respectively, to allow the patients to make informed decisions in consultation with their investigators regarding their treatment options.

While PK and immunogenicity samples must be collected from patients assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for these patients are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to patient treatment assignments to identify appropriate samples for analysis. PK samples from patients assigned to the comparator arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline immunogenicity samples will be analyzed for all patients. Postbaseline immunogenicity samples from patients assigned to the comparator arm will not be analyzed for ADAs except by request.

To optimize timelines for delivery of PK-related analyses, unblinded PK and ADA data may be released to selected and appropriately documented clinical pharmacology or designated personnel at the clinical cutoff date prior to study unblinding.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

Non-emergency unblinding may be permitted by the Sponsor in the scenario where there is an approval (relevant to the patient's country) of an in-class molecule in the same disease setting. Non-emergency unblinding may be permitted by the Sponsor if knowledge of the treatment assignment is necessary to confirm eligibility for a clinical trial. If the Medical Monitor agrees to patient unblinding, the investigator will be able to break the treatment code by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The patient may continue to receive treatment, and the investigator, patient, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to patient treatment assignments to fulfill their roles (as defined above) will remain blinded to treatment assignment.

Unless otherwise indicated, Sponsor blinding to the treatment assignment will remain in place until the primary analysis (see Section 6.4.1). Except for the conditions stated above permitting individual treatment unblinding, the investigators and patients will be blinded to treatment assignments until the final analysis of all efficacy endpoints.

## 4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are ipatasertib, matching ipatasertib placebo, atezolizumab, matching atezolizumab placebo, and paclitaxel.

Loperamide (or racecadotril, which may be more commonly used in Europe), prophylactic steroids and prophylactic antihistamines (see Section 4.3.3), are non-IMPs in this study.

### 4.3.1 Study Treatment Formulation, Packaging, and Handling

#### 4.3.1.1 Ipatasertib and Placebo

Ipatasertib is intended for oral administration and will be supplied by the Sponsor as 100- and 200-mg tablets.

The ipatasertib placebo tablets have been manufactured to match the size, shape, and color of the ipatasertib active tablets (100 and 200 mg) and are indistinguishable in appearance from the active ipatasertib tablets. Tablet bottles and drug kits for placebo will also be identical to those for ipatasertib, except for the unique kit numbers on the kit boxes. For information on the formulation and handling of ipatasertib/placebo, see the Ipatasertib Investigator's Brochure.

The period between re-dispensing and the last tablet consumed should not exceed 1 month. The investigational product is for investigational use only and is to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for patient use or returned to the Sponsor.

#### 4.3.1.2 Atezolizumab and Placebo

The 840-mg atezolizumab drug product will be supplied by the Sponsor in a single-use, 15-mL USP/Ph. Eur. Type 1 glass vial with 20-mm stoppers. The vial is designed to deliver 14 mL (840 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 14-mL volume.

Placebo will consist of the vehicle without the antibody. Placebo will be supplied in a single-use, 15-mL USP/Ph. Eur. Type 1 glass vial with 20-mm stoppers intended for IV administration. The vial contains approximately 14 mL of solution. The formulation contains 20 mM histidine acetate, 120 mM sucrose, and 0.04% polysorbate 20, pH 5.8.

Vials are filled to enable delivery of 14 mL of solution containing histidine acetate, sucrose, and polysorbate 20.

For information on the formulation and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

#### 4.3.1.3 Paclitaxel

For information on the formulation, packaging, and handling of paclitaxel, see the local prescribing information for paclitaxel.

### 4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.1. The sequence of drug administration is ipatasertib/placebo, then atezolizumab/placebo, and then paclitaxel. On non-atezolizumab administration days, the sequence of drug administration is ipatasertib/placebo and then paclitaxel.

Refer to the pharmacy manual, supplemented by the Investigator's Brochures (for ipatasertib and atezolizumab) and local prescribing information (for paclitaxel) for detailed instructions on drug preparation, storage, and administration.

Any dose modification should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Appendix 14.

#### 4.3.2.1 Ipatasertib and Placebo

Patients will be randomly assigned to a treatment arm through the IxRS. Ipatasertib/placebo will be administered at the starting dosage of 400 mg PO QD, beginning at Cycle 1, on Days 1–21 of each 28-day cycle until the patient experiences disease progression, intolerable toxicity, or withdraws consent. Patients will receive ipatasertib/placebo prior to the IV infusions of paclitaxel and atezolizumab/placebo. If ipatasertib/placebo cannot be safely administered on Days 1–21 of any 28-day cycle, it is permitted to make up for the missed doses on any of the Days 22–28, if safe to do so (refer to management guidance in Appendix 14).

Each dose of ipatasertib/placebo should be taken in the morning with a minimum of 3 ounces (90 mL) of fluid. Ipatasertib/placebo may be taken with or without food. If a dose is missed (not taken within 8 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Skipped or vomited doses will not be made up later in the day, as this risks having the following day's dose scheduled too soon thereafter. The intent is to keep the dosing at approximately the same time each morning.

Following unblinding of treatment assignments, placebo for ipatasertib will no longer be administered to patients in Arm B of Cohort 2 and to patients in Arm C of Cohort 1 (see Section 3.1.1).

On study days requiring a predose blood draw for PK sampling, patients will be instructed to take their daily oral dose of ipatasertib/placebo in the clinic after completion of the pretreatment assessments (see Appendix 1). Ipatasertib/placebo should be taken at approximately the same time each day, and ideally, the time of dosing outside the clinic should be the same as the time of dosing at the clinic visit. Typically, the ideal dosing time will be in the morning. The time of dose administration will be collected on the PK sampling day and for prior doses administered, for up to 2 days before a PK sampling visit. Importantly, the dosing time should be the same, or similar, on the 3 days prior to and on the day of the PK visit. Any occurrences of vomiting within 3 hours after study drug administration should also be recorded on the day of PK sampling.

A sufficient amount of ipatasertib/placebo should be provided to the patient to last one treatment cycle. Notably, there is one extra dose of ipatasertib/placebo in each bottle. This should be explained to the patient to minimize the risk that the patient mistakenly takes the extra dose. Patients will be instructed to bring their bottles of ipatasertib/placebo and their medication diaries to each study visit.

Once a decision to reduce the dose of ipatasertib/placebo is implemented, no re-escalation is permitted.

#### 4.3.2.2 Atezolizumab and Placebo

Atezolizumab/placebo will be administered to patients by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle until the patient experiences disease progression, intolerable toxicity, or withdraws consent. Although a ± 1-day window is permitted for atezolizumab/placebo administration, it is discouraged to dose on days other than on Day 1 or 15 because of the risk that atezolizumab doses may fall too close together.

Administration of atezolizumab/placebo will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 7. Atezolizumab infusions will be administered per the instructions outlined in Table 1.

Following unblinding of treatment assignments, placebo for atezolizumab will no longer be administered to patients in Arm B and Arm C of Cohort 1.

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

| First Infusion | Subsequent Infusions |
|---|---|
| • Premedication should be limited to prophylaxis as outlined in Section 4.3.3 for the purpose of preventing rash.<br>• Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion.<br>• Atezolizumab/placebo should be infused over 60 (±15) minutes.<br>• If clinically indicated, vital signs should be measured every 15 (±5) minutes during the infusion and at 30 (±10) minutes after the infusion.<br>• Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms. | • On Day 15 of Cycle 1, premedication may be given as prophylaxis as outlined in Section 4.3.3 for the purpose of preventing rash.<br>• If the patient experienced an *IRR* with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator.<br>• Vital signs should be measured within 60 minutes prior to the infusion.<br>• Atezolizumab/placebo should be infused over 30 (±10) minutes if the previous infusion was tolerated without an *IRR*, or 60 (±15) minutes if the patient experienced an infu*IRR*with the previous infusion.<br>• If the patient experienced an *IRR* with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (±10) minutes after the infusion. |

*IRR = infusion-related reaction.*

Guidelines for medical management of infusion-related reactions (IRRs) are provided in the Appendix 13.

No dose modification for atezolizumab/placebo is allowed.

#### 4.3.2.3 Paclitaxel

The dose of paclitaxel in this study is 80 mg/m$^2$ administered to patients by IV infusion on Days 1, 8, and 15 of each 28-day cycle. If the dose on Day 1, 8, or 15 is missed, it can be given on Day 22. Although a ±1-day window is permitted for paclitaxel administration, it is discouraged to dose on days other than on Day 1, 8, 15, or 22 because of the risk that paclitaxel doses may fall too close together. Calculation of body surface area for the purposes of dosing of paclitaxel should be made according to the prescribing information. If a patient's weight changes by > 10% from baseline during the study, the body surface area and drug doses should be recalculated. Once recalculated, if the patient's weight changes by > 10% from the weight used to make the recalculation, the drug doses should again be recalculated. If the local standard is to calculate a paclitaxel dose more often, this is acceptable.

The paclitaxel infusion will be delivered over at least 60 minutes for each dose per institutional guidelines and administered after the oral dose of ipatasertib/placebo and after the IV dose of atezolizumab/placebo.

Patients should be monitored during paclitaxel administration per institutional policies. Patients may receive antiemetic and other prophylactic treatments, according to institutional practice.

If the dose of paclitaxel has been reduced, it may be re-escalated (when medically appropriate and following management guidance in Appendix 13) by a single dose level at a time. *The Medical Monitor is available to advise as needed.*

### 4.3.3 Other Treatments: Premedications and Prophylactic Treatment

Because of the known potential for allergic reactions to paclitaxel and/or the Cremophor® vehicle, precautions must be taken to decrease the risk of anaphylaxis. Patients must be premedicated prior to paclitaxel with dexamethasone, diphenhydramine, and an H2-receptor blocker (i.e., ranitidine or famotidine) or per institutional practice. Ranitidine and famotidine are recommended H2-receptor blockers for prophylactic treatment of paclitaxel infusion-related reactions. However, in cases when ranitidine and famotidine are not available, cimetidine may be used with caution. Cimetidine is a moderate CYP3A inhibitor, which can increase the exposure of ipatasertib up to approximately 2-fold. It can take up to 3 days for ipatasertib concentration to return to typical steady state levels.

Only applicable while the patient is receiving ipatasertib:

- For visits without PK sample collection, intravenous cimetidine can be administered irrespective of timing with the oral dose of ipatasertib. For visits that include PK sample collection, intravenous cimetidine can be administered after ipatasertib sampling is complete or 2 hours after ipatasertib dosing, whichever is later.
- For sites needing use of oral cimetidine, cimetidine should be administered at least 2 hours after ipatasertib or after completion of PK sampling, whichever is later.

Diarrhea is a common adverse event associated with ipatasertib and/or paclitaxel treatment. In this study, to improve diarrhea management and patient burden, loperamide (racecadotril as used in Europe) will be administered to patients daily as prophylaxis for diarrhea. Prophylactic use is mandated in the first cycle (if allowed by local guidance, per Section 1.3), and as clinically indicated in subsequent cycles to prevent diarrhea. Patients who experience diarrhea should be on treatment doses of loperamide per the management guidelines provided in Appendix 13; please refer to that section for additional details. *The Medical Monitor is available to advise as needed.*

Patients should be educated/reminded to be cognizant of the onset, duration, severity, and frequency of symptoms and the medications administered. If side effects of loperamide are not tolerated, doses may be reduced (or if necessary, discontinued) at

any time. Investigators are encouraged to continue prophylactic- and/or treatment-dose loperamide for the remainder of the study at their discretion based on clinical judgment.

Owing to the risk of rash in Cycle 1, patients should receive the following prophylaxis during the first cycle when all three study treatments will be given:

- Unless contraindicated, daily PO antihistamine prophylaxis should be used for at least the first cycle. It is suggested that a non-sedating longer-acting oral antihistamine be used (such as 10 mg of cetirizine PO QD or comparable dose of other antihistamines, e.g., loratadine, fexofenadine). The daily oral antihistamine used for rash prophylaxis may be held on the days of paclitaxel infusion if the paclitaxel premedication already includes an antihistamine.
- On days when patients will receive atezolizumab/placebo (typically, Days 1 and 15), patients should receive at least 10 mg/day of prednisone (or equivalent dosing of other steroids e.g., methylprednisolone, prednisolone) as premedication prior to atezolizumab, followed by a fixed dose of 10 mg/day prednisone (or equivalent) for 2–4 consecutive days thereafter, unless contraindicated. If institutional practice prior to paclitaxel is to give at least 10 mg of prednisone on the day of paclitaxel, then the additional 10 mg of prophylactic prednisone should not be given on that day to prevent rash. If the investigator determines that administration of the steroid immediately prior to paclitaxel, rather than prior to atezolizumab/placebo, is more appropriate, this is acceptable.

As of protocol Versions 4 and 5, rash and antidiarrheal prophylaxis is no longer applicable to patients in Arm C of Cohort 1 and Arm B of Cohort 2.

### 4.3.4 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

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

### 4.3.5 Continued Access to Ipatasertib and Atezolizumab

The Sponsor will offer continued access to Sponsor study drugs ipatasertib and/or 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 Sponsor study drug ipatasertib and/or 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 Sponsor study drug 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 Sponsor study drugs ipatasertib and/or atezolizumab after completing the study if any of the following conditions are met:

- The Sponsor study drug 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 study drug or data suggest that the study drug is not effective for breast cancer
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for breast cancer
- Provision of the study drug 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 website:

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

## 4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 14 days prior to initiation of study drug to the study drug discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

### 4.4.1 Permitted Therapy

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

- Oral contraceptives with a failure rate of $<1\%$ per year (see Section 4.1.1.1)
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted for a preexisting lesion, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be

irradiated must not be a site of measurable disease). Study treatment should be suspended during palliative radiotherapy (see Section 4.4.2.2).

Treatment with atezolizumab may be continued during palliative radiotherapy.

Treatment with ipatasertib should be temporarily held for at least 7 days before and after the procedure (at least 14 days after radiation is recommended). For single-day radiotherapy, this hold may be shorter, if discussed by the investigator. *The Medical Monitor is available to advise as needed.* The patient may continue ipatasertib treatment after the treatment hold has been completed and the patient has sufficiently recovered.

- Prophylactic use of loperamide (racecadotril as used in Europe) as outlined in Section 4.3.3
- Premedication with antihistamines, antipyretics, and/or analgesics for each paclitaxel administration
- Premedications prior to administration of atezolizumab

  Premedication with corticosteroids and antihistamines prior to administration of atezolizumab are allowed as outlined in Section 4.3.3.

  Premedication with antipyretics and/or analgesics may be administered for the second and subsequent atezolizumab infusions only, at the discretion of the investigator.
- Granulocyte colony-stimulating factor treatment for patients receiving paclitaxel

  The primary prophylaxis should be administered per the ASCO, EORTC, and European Society for Medical Oncology guidelines; namely, in patients who are≥60 years old and/or with comorbidities (Smith et al. 2006; Aapro et al. 2011).
- Bisphosphonate therapy or RANKL inhibitor therapy (e.g., zolendronic acid and denosumab) used specifically to prevent skeletal events (e.g., bone metastasis, osteoporosis)

  Both types of agents have potential immunomodulatory properties but may be used as clinically indicated.
- Luteinizing hormone-releasing hormone or gonadotropin-releasing hormone agonists for ovarian function preservation are allowed.
- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations *(such as influenza, COVID-19)*

  *Live, attenuated vaccines are not permitted (see Section 4.4.3)*
- Megestrol acetate administered as an appetite stimulant after initiation of study treatment
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled corticosteroids administered for chronic obstructive pulmonary disease or asthma

- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency

### 4.4.2 Cautionary Therapy

#### 4.4.2.1 Corticosteroidsand Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids are recommended, at the discretion of the investigator for the treatment of specific adverse events (refer to Section 4.3.3 for details). When used for adverse events attributed to atezolizumab, refer to Appendix 13 and Appendix 14 for guidance. Refer to Appendix 13 for instructions on holding ipatasertib/placebo and/or atezolizumab/placebo during systemic corticosteroid treatment (neither need to be held when corticosteroids are given as premedication prior to imaging studies, prior to paclitaxel, or as required in Cycle 1 prior to atezolizumab administration) (see Section 4.3.3).

TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, TNF-α inhibitors may be administered at the discretion of the investigator.

#### 4.4.2.2 Surgery and Palliative Radiotherapy

Patients who require radiotherapy or surgery as part of medical treatment in the absence of radiographic disease progression must exercise caution, and paclitaxel and ipatasertib/placebo should be temporarily withheld for at least 7 days before and after the procedure (at least 14 days after radiation is recommended). While withholding atezolizumab is not required, caution and clinical judgment should be exercised when administering atezolizumab concurrently with surgery or radiotherapy. For minor surgeries or single-day radiotherapy, this hold of paclitaxel and ipatasertib may be shorter, if discussed by the investigator. *The Medical Monitor is available to advise as needed*. After the temporary treatment hold is complete, study treatment may be re-initiated when the patient has sufficiently recovered.

#### 4.4.2.3 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

In vitro data suggest that ipatasertib is metabolized by CYP3A and may be a time-dependent inhibitor of CYP3A4. A clinical drug–drug interaction study with midazolam (a sensitive CYP3A substrate) showed a 2.2-fold increase in midazolam exposures in presence of steady-state ipatasertib at the 600-mg dose QD. Therefore, sensitive CYP3A substrates with narrow therapeutic window should be avoided. Given that ipatasertib is primarily metabolized by CYP3A, there is a high potential for drug–drug interactions of ipatasertib with any medication that strongly inhibits or induces CYP3A. Data from a clinical study showed that ipatasertib exposures were reduced by approximately 50% when co-administered with enzalutamide, a strong CYP3A inducer. Strong CYP3A inhibitors are expected to increase ipatasertib exposures significantly.

Therefore, the following drugs should be avoided or used with caution:

- Strong CYP3A4/5 inhibitors, such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and/or grapefruit juice
- Itraconazole, a strong CYP3A4 inhibitor, increased ipatasertib area under the concentration–time curve and maximum concentration by approximately 5-fold and 2-fold, respectively (drug–drug interaction study GP30057). Given that ipatasertib is a substrate of CYP3A4/5, other strong inhibitors of CYP3A4/5 may also result in an increase in ipatasertib exposure.
- Strong CYP3A4/5 inducers, such as, but not limited to, rifampin, carbamazepine, rifapentine, phenytoin, phenobarbital, and/or St. John's wort or hyperforin
- CYP3A4/5 substrates with a narrow therapeutic index, such as, but not limited to, alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, ergot alkaloids ergotamine, and/or dihydroergotamine
- Paclitaxel exposures may be increased due to CYP2C8 inhibition; therefore, strong and moderate CYP2C8 inhibitors, such as gemfibrozil, teriflunomide, clopidogrel, and deferasirox should be used with caution during treatment with paclitaxel. Similarly, CYP2C8 inducers should be avoided or used with caution.
- Patients who require short-term use of a strong CYP3A4/5 inhibitor or inducer or use of sensitive CYP3A substrates with a narrow therapeutic window for medical treatment (i.e., an alternative treatment cannot be used) must exercise caution and all study treatment should be temporarily held until at least 7 days after the final dose of strong CYP3A inhibitors and sensitive CYP3A substrates with narrow therapeutic window.
- Patients are permitted to take moderate inhibitors of CYP3A4 with caution.

Patients should be closely monitored. Refer to the following information for further guidance on CYP450–drug interactions and a list of common substrates, inhibitors, and inducers:

> Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (U.S. Food and Drug Administration [FDA]): https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

The above list of medications is not comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the Medical Monitor *is available to advise* if questions arise regarding medications not listed above.

#### 4.4.2.4 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally

unknown. However, herbal therapies not intended for the treatment of cancer (see Section 4.4.3) may be used during the study at the discretion of the investigator.

### 4.4.3 Prohibited Therapy

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

- Investigational therapy (other than protocol-mandated study treatment) within 14 days prior to initiation of study treatment and during study treatment.
- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy) for various time periods prior to starting study treatment, depending on the agent (see Section 4.1.2), and during study treatment, until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances (see Section 4.4.2.2 for details).
- Hormone-replacement therapy
- Chronic use of a strong CYP3A4/5 inhibitor or inducer or sensitive CYP3A substrates with a narrow therapeutic window. *The Medical Monitor is available to advise as needed .*
- Vaccination with a live vaccine should be avoided in patients receiving paclitaxel because of the potential for serious or fatal infections.
- Live, attenuated vaccines (e.g., FluMist®) within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the final dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, *IFNs* and interleukin-2) within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic immunosuppressive medications (including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab

### 4.4.4 Prohibited Food

Use of the following foods is prohibited as described below:

- Consumption of grapefruit juice, a potent CYP3A4 enzyme inhibitor, during the study treatment period and for 10 days after the final dose of study treatment.
- Consumption of St. John's wort, a potent CYP3A4 enzyme inducer, for up to 14 days prior to and during the study treatment period, and for 10 days after the final dose of study treatment.

Although there is no other prohibited food for this study, patients will be provided with general dietary guidance aimed at minimizing any risk of hyperglycemia and diarrhea.

### 4.4.5 Additional Restrictions

No food or fluids other than water will be allowed for 8 hours prior to each Day 1 study visit until after laboratory samples for fasting glucose and fasting lipid profile, as applicable, are obtained (see Appendix 1).

## 4.5 STUDY ASSESSMENTS

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

As of protocol Version 5, patients who choose to continue in the study will continue assessments as specified in the protocol (see Appendix 1).

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

Only essential data will be collected. Certain assessments that are required will not be recorded on the eCRF (except in the case of an adverse event). Required procedures should be reflected in the schedule of activities (see Appendix 1).

It should be assumed that, other than essential protocol-specific assessments, the current standard of care for the TNBC will be followed; thus, parameters such as temperature may be measured and recorded in the source documents but not entered on an eCRF (unless abnormal, in which case they may be reported as adverse events).

Study-related procedures, when required (see Appendix 1), should be performed in approximately the same order at each visit. For example, if PRO assessments are performed after the patient has had blood and/or urine sample collection, the appropriate clinical assessment, and initiation of the study drug administration, then this should generally be repeated at each visit to minimize bias.

### 4.5.1 Informed Consent Forms and Screening Log

Voluntary, written, dated, and signed informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Alternative methods for documenting consent may be locally recognized, and in such cases acceptability of these methods should not be assumed. In such cases, the operational lead for the study should be informed and approval must be obtained from the Sponsor before the patient is consented. 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 enrollment. The investigator will maintain a *detailed* record of

all patients screened, to *document* eligibility or record reasons for screening failure, as applicable.

Patients are permitted to re-screen once, if any delay to treatment is considered clinically reasonable, in the investigator's opinion. This includes, but is not limited to, the scenario in which a valid tumor PD-L1 status is not yet obtained or other screening procedures are not completed within the 28-day screening period.

### 4.5.2 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), and reproductive status, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 14 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

To further assess the actual intake of analgesic, antihistamine, and antidiarrheal medications taken outside of the clinic or hospital setting, patients will complete a medication diary each day. Patients will receive the diary on the first day of each cycle, with site staff completing information on any prescribed analgesic, antihistamine, or antidiarrheal medications, including the recommended dosage and route of administration. Patients should use the diary to record daily ipatasertib/placebo dosing and specifically any antidiarrheal, antihistamine, or analgesic medications used (prescribed or over the counter) taken during that cycle of treatment. The intake of analgesic, antihistamine, and loperamide medications will be reported on the Analgesics Medication, Antihistamine, and Targeted Loperamide Concomitant Medications eCRF, respectively.

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

### 4.5.3 Physical Examinations

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

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

### 4.5.4 Weight and Height

Weight should be recorded at each study visit, and height will be measured only at baseline and thereafter as clinically indicated.

### 4.5.5 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature while the patient is sitting or supine in a comfortable position. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Vital signs should be measured within 60 minutes prior to each in-clinic ipatasertib/placebo administration, atezolizumab/placebo infusion (one set may be performed to cover predose vital signs for both drug administrations), and between atezolizumab/placebo and paclitaxel infusions (on days when both drugs are administered). On days when no atezolizumab/placebo is given, one set may be performed as predose vital signs for both ipatasertib/placebo and paclitaxel. On paclitaxel dosing days, vital signs should be recorded prior to dosing and at the end of the infusion. Vital signs may be repeated if clinically indicated, during the infusion. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 1).

**Table 2 Timing for Vital Sign Measurements for First and Subsequent Infusions**

| Drug | Timing for Vital Sign Measurements | |
|---|---|---|
| | First Infusion | Subsequent Infusions |
| Ipatasertib | • Within 60 minutes prior to ipatasertib/placebo administration | • Within 60 minutes prior to ipatasertib/placebo administration |
| Atezolizumab | • Within 60 minutes prior to the atezolizumab/placebo infusion<br>• During or after the infusion if clinically indicated (refer to Table 1) | • Within 60 minutes prior to the atezolizumab/placebo infusion<br>• During or after the infusion if clinically indicated (refer to Table 1) |
| Paclitaxel | • On atezolizumab/placebo infusion days, after atezolizumab/placebo and before paclitaxel infusions<br>• On non-atezolizumab/placebo infusion days, within 60 minutes prior to the paclitaxel infusion<br>• After completion of paclitaxel | • On atezolizumab/placebo infusion days, after atezolizumab and before paclitaxel infusions<br>• On non-atezolizumab/placebo infusion days, within 60 minutes prior to the paclitaxel infusion<br>• After completion of paclitaxel |

### 4.5.6 ECOG Performance Status

Performance status will be measured using the ECOG Performance Status Scale and recorded on the eCRF (see Appendix 3).

### 4.5.7 Tumor and Response Evaluations

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator on the basis of physical examinations (with photography measurements) and imaging (CT, MRI, and bone scans) through use of RECIST v1.1 (see Appendix 5). Images for tumor assessments will be collected to enable retrospective blinded independent central review when needed. As of protocol Version 5, images for tumor assessments will no longer be collected for blinded independent central review.

All measurable and evaluable lesions identified at baseline should be re-assessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Assessments should be performed by the same evaluator to ensure internal consistency across visits. Confirmation of an objective response is only valid when the repeat assessments are performed $\geq$4 weeks after initial documentation. Per study requirements, tumor assessments are due every 8th week and do not need to be performed sooner for the purpose of confirming a response. At the investigator's discretion, and if clinically indicated, CT scans may be repeated at any time if progressive disease is suspected, and other methods of assessment of measurable disease may be used (e.g., brain scans using CT or MRI) in addition to those listed above. For symptomatic deterioration attributed to disease progression, every effort should be made to document progression through use of objective criteria per RECIST v1.1.

Baseline tumor assessments should be performed $\leq$28 days prior to Day 1, Cycle 1. CT scans should include chest, abdomen, and pelvic scans; CT scans of the neck should be included if clinically indicated. Screening (or documented standard of care) bone scans (technetium bone scan) and head scans (CT or MRI) should be performed within 6 weeks prior to Day 1 of Cycle 1.

Tumor assessments should be performed based on a schedule calculated from Cycle 1, Day 1 (study Day 1), with the first assessment performed at Week 8 and approximately every 8 weeks thereafter, regardless of treatment administration timing or prior early or late tumor assessments. A sample calendar is presented in Appendix 6 . Therefore, the window for each scan will be the 7 days of the given week. For patients with known or suspected bone metastasis, bone scans should be performed with every other tumor assessment starting at Week 16, adhering to the same 7-day window. Bone disease and any changes in bone imaging should be evaluated radiographically by CT scan, MRI, or X-ray to ascertain the presence of bone destruction versus a healing reaction.

An assessment must be done at the treatment completion visit, unless the most recent tumor assessment was completed ≤6 weeks before the treatment completion visit. Patients who discontinue study treatment for any reason other than disease progression will continue to undergo tumor response evaluations at disease follow-up visits (*as per statndard of care*) until documented progressive disease per RECIST v1.1.

A documented standard-of-care tumor assessment performed within 28 days prior to Day 1 of Cycle 1 (bone or head scans within 6 weeks prior to Day 1 of Cycle 1) may be used for the screening assessment, provided it meets the following requirements:

- CT scans are the preferred imaging modality for tumor assessments. Tumor assessments should include a diagnostic quality, contrast-enhanced CT scan of the chest, abdomen, and pelvis at baseline. CT scans of the neck should be included if clinically indicated. To be suitable for RECIST assessments, CT scans should have a maximum thickness of 5 mm and no gaps. Subsequent tumor assessments should include CT scans of the chest, abdomen, pelvis, and other known sites of disease.
- In patients for whom a CT scan is contraindicated because of an allergy to IV radiographic contrast, both a CT scan of the chest without contrast and a MRI scan of the abdomen and pelvis with contrast are recommended.
- MRI scans may be performed in lieu of CT scans. . At screening, tumor assessments should include a diagnostic quality, contrast-enhanced MRI scan of the chest (if approved), abdomen, and pelvis. MRI scans of the neck should be included if clinically indicated. To be suitable for RECIST assessments, MRI scans should ideally have a maximum thickness of 5 mm and minimal gaps. Subsequent tumor assessments should include MRI scans of the chest (if approved), abdomen, and pelvis, and other known sites of disease.
- If a CT scan for tumor assessment is performed in a positron emission tomography or CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan. *The Medical Monitor is available to advise as needed.*

Objective response at a single timepoint will be determined by the investigator according to RECIST v1.1 (see Appendix 5).

### 4.5.8 Electrocardiograms and Cardiac Function Assessment

A cardiac function assessment by echocardiogram or multiple-gated acquisition scan should be performed within 12 weeks of Day 1 of Cycle 1. Under exceptional circumstances cardiac function assessment by methods other than echocardiogram or multiple-gated acquisition scan may be acceptable (e.g., cardiac MRI), if consistent with local standard practice. *The Medical Monitor is available to advise as needed.*

Single 12-lead ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1) and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

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

If at a particular post-dose timepoint the mean QTcF is >500 ms and/or >60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. *The Medical Monitor is available to advise as needed.* Standard-of-care treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, concomitant medications known to prolong the QT interval, severe bradycardia).

### 4.5.9 Laboratory, Biomarker, and Other Biological Samples

Laboratory samples should be drawn according to the schedule of activities (see Appendix 1) and within 48 hours (see below for pregnancy test requirements) prior to study drug administration at the clinic; results of hematology, chemistry, and pregnancy tests should be available and reviewed prior to making the dosing decision. The following tests are essential assessments for Day 1 dosing of every cycle: hemoglobin, ANC, lymphocytes, and platelet count, $HbA_{1c}$, glucose, creatinine, potassium, calcium, total bilirubin, ALP (total ALP), AST, ALT, and a pregnancy test. Screening local laboratory assessments obtained within these windows prior to Day 1 of Cycle 1 do not have to be repeated on Day 1 of Cycle 1. For certain laboratory values, such as ANC, management tables provided in Appendix 13 should be reviewed before study treatment administration. Where specific guidance is not offered regarding holding study treatments based on a laboratory abnormality, clinical judgment should be used.

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

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells)
- Fasting serum chemistry panel (following ≥8-hour fast): glucose (plasma glucose is also acceptable per local practice), bicarbonate or total carbon dioxide (if considered

standard of care for the region), sodium, potassium, chloride, magnesium, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, and AST

- LDH
- Fasting lipid profile: total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides performed following a ≥8-hour fast
- $HbA_{1c}$
- Amylase and lipase
- Coagulation: INR and PTT (or aPTT)
- Thyroid-function testing: $TSH$, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- HIV serology: as per local standard, after any applicable local consenting requirements
- HBV serology: HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

  If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection, prior to randomization.
- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection, prior to randomization.
- Pregnancy test

  All women of childbearing potential will have a serum pregnancy test at screening. A negative serum pregnancy test must be confirmed either within 96 hours of Day 1, Cycle 1 study treatment administration, or within 7 days of Day 1 of Cycle 1 (in this case, confirmed by a negative urine pregnancy test on Day 1 of Cycle 1 prior to dosing).

  Urine pregnancy tests will be performed at specified subsequent visits.
  If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). *Per this definition, a woman with a tubal ligation is considered to be of childbearing potential.*
- Urinalysis: pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted

- Serum samples for C-reactive protein

The following samples may be performed outside of a health care facility:

- For any patients who initiate home glucose monitoring (see Appendix 13, Table 3, for management guidance of fasting hyperglycemia), a glucose log will be made available for capturing these results. The blood glucose log should be reviewed at each clinic visit (see Appendix 1).

The following samples will be sent to one or several central laboratories or to the Sponsor or a designee for analysis:

- Blood samples for exploratory research on biomarkers

  Blood will be collected for ctDNA analysis at Day 1 of Cycle 1, at the time of the first tumor assessment (±7 days), and at the study drug discontinuation visit. Blood should be drawn before the administration of any study drug, if applicable.

- Most recently collected tumor tissue for evaluation of PD-L1 expression, *PIK3CA/AKT1/PTEN*-altered positivity, tumor status, and for exploratory research on biomarkers

  A representative FFPE tumor specimen in a paraffin block (preferred) or *10–15 slides* at least *(15 preferred)* containing unstained, freshly cut, serial sections should be submitted.

  Tumor tissue should be of good quality based on total and viable tumor content. Samples collected via resection, core-needle biopsy (recommend at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. If less than 15 slides or only two cores are available, a patient may still be eligible for the study after Sponsor approval has been obtained and if sample contains a minimum of 50 viable tumor cells, regardless of needle gauge or retrieval method. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that are subject to decalcification is not acceptable.

  If the most recently collected tumor tissue is unsuitable for required testing (e.g., clearly insufficient in quantity or tumor cellularity), a pretreatment tumor biopsy (preferred, a minimum of three core biopsies is required for NGS evaluation), or older archival tissue may be submitted. If less than 15 slides or only two cores are available, a patient may still be eligible for the study, after Sponsor approval has been obtained and if sample contains a minimum of 50 viable tumor cells, regardless of needle gauge or retrieval method.

- Biomarker samples (blood, plasma, and tissue) for mandatory exploratory biomarker research include, but not limited to, the following assays and assay platforms:

  Single-nucleotide polymorphisms that may impact exposure or other responses, or NGS results interpretation

Somatic mutations and copy number variations by NGS or PCR-based methods in tumor tissue and ctDNA

Gene expression analysis (e.g., RNASeq) of genes related to PI3K/Akt pathway activity, immune infiltration/activation, apoptosis, and breast cancer biology (i.e., intrinsic subtypes)

IHC-based analysis or quantitative digital IHC of tumor suppressors, such as PTEN, and markers of immune infiltration and activation, such as CD8 and PD-L1

- Serum samples for atezolizumab PK analysis
- Plasma samples for ipatasertib and G-037720 PK analysis
- Serum samples for assessment of ADAs to atezolizumab

Note: As of protocol Version 5, blood samples for PK and ADA analyses will no longer be collected.

NGS may be performed by Foundation Medicine. For optional tumor biopsy tissues obtained at the time of progression, the investigator may request a NGS report if and when available. If *permitted* by local *law*, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. *The report may be included in the participant's medical record.* Results will not be available for samples that do not meet criteria for testing.

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

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

- Serum or plasma samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Tumor tissue and plasma samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed with the exception of tissue samples that undergo WGS or WES, which will be stored until they are no longer needed or until they are exhausted.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

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

### 4.5.10 Patient-Reported Outcome Assessments

As of protocol Version 5, PRO assessments will no longer be collected.

To more fully characterize ipatasertib plus atezolizumab and paclitaxel compared with control arm treatment as a first-line treatment in patients with metastatic breast cancer, PRO data will be obtained through the use of the following instruments: EORTC QLQ-C30, selected items from the PRO-CTCAE (when available in the local language), and the EQ-5D-5L.

Official versions of the PRO instruments in booklet format, translated as required in the local language, will be distributed by the investigator staff. PROs scheduled for administration during a clinic visit must be completed on paper by the patient in their entirety at the investigational site. To ensure instrument validity and that data standards meet health authority requirements, questionnaires must be completed by the patient at the start of the clinic visit before discussion of the patient's health state, laboratory results, or health record and prior to the administration of study treatment to avoid any bias to patient responses. It is common for patients to complete laboratory assessments before a scheduled clinic visit. Completion of PROs after laboratory tests is permitted so long as there is no prior discussion of the patients' laboratory results or health record with clinic staff and that the PROs are completed before drug infusion.

For patients who are unable to complete the measures on their own, interviewer assessment is allowed but can only be conducted by a member of the clinic staff who reads the questionnaire items to the patient verbatim; no interpretation, rephrasing, or rewording of the questions is allowed during interview-assisted completion.

Study personnel should review all questionnaires for completeness before the patient leaves the investigational site and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank. Hard copy originals of the questionnaires must be maintained as part of the patient's medical record at the site for source data verification. These originals should have the respondent's initials, study patient number, visit label, and date and time of completion recorded in compliance with good clinical practice. Sites will enter patient responses to the PRO questionnaires into the EDC system no later than 5 days after collection.

After treatment discontinuation to minimize burden on patients**,** only selected scales of the EORTC QLQ-C30 as well as the EQ-5D-5L measure will be administered over the telephone to patients or completed at the site during follow-up calls (or visits) (see Appendix 1). The following selected scales of the EORTC QLQ-C30 will be assessed: the GHS/QoL (which consists of Questions 29 and 30), Physical Function

(Questions 1–5), Role Function (Questions 6 and 7), Pain (Questions 9 and 19), Fatigue (Questions 10, 12, and 18), and Dyspnea (Question 8). Instructions and telephone scripts for administering the PRO assessments via telephone interviews (during the post-treatment follow-up period of the study) will be provided when available in the local language. Refer to Appendix 1 for the frequency and timing of PRO assessments.

#### 4.5.10.1 EORTC QLQ-C30

The EORTC QLQ-C30 (see Appendix 10) is a validated, reliable self-report measure (Aaronson et al. 1993; Sprangers 1996; Fitzsimmons et al. 1999) consisting of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), eight symptoms (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea), financial difficulties, and GHS/QoL with a recall period of the previous week. The functioning and symptoms items are scored on a 4-point scale that ranges from "not at all" to "very much," and the global health status/QoL items are scored on a 7-point scale that ranges from "very poor" to "excellent."

The EORTC QLQ-C30 data will be scored according to the EORTC scoring manual (Fayers et al. 2001). Scale scores will be obtained for each of the multi-item and single-item scales by using a linear transformation for standardization of the calculated raw score. The EORTC QLQ-C30 takes approximately 10 minutes to complete.

#### 4.5.10.2 PRO-CTCAE

The PRO-CTCAE is a validated item bank that is used to characterize the presence, frequency of occurrence, severity, and/or degree of interference with daily function of 78 patient-reportable symptomatic treatment toxicities (Basch et al. 2014; Dueck et al. 2015) (see Appendix 12). The item bank was designed and validated as a repository of standalone items (Basch et al. 2014).

To evaluate the patients' perspective of tolerability of ipatasertib in combination with atezolizumab and paclitaxel, patients will be asked to report on their experience of treatment-related symptoms selected from the validated PRO-CTCAE item bank (Basch et al. 2014). A subset of 8 symptoms deemed most applicable to the current treatments has been selected for this study (see Appendix 12). Symptoms selected for this study include those adverse events experienced at any grade that occurred in $\geq$20% of patients for any study drug (ipatasertib, atezolizumab, and/or paclitaxel) in previous studies. These symptoms were identified as being salient to patients' experience with ipatasertib in combination with atezolizumab and paclitaxel on the basis of preliminary safety data from the ongoing studies containing this triplet, as well as side effects pertinent to the individual drug classes.

Only adverse events that are patient self-reportable (Basch et al. 2014) were selected for PRO analysis in this study. Adverse events of which assessments rely on laboratory testing (e.g., neutropenia) that are presented as being primarily asymptomatic or with

nonspecific signs and symptoms were disregarded. Adverse events that do not have an identifiable symptom equivalent in the PRO-CTCAE were also excluded. Based on the above criteria, eight symptomatic adverse events were selected from the PRO-CTCAE item bank (i.e., diarrhea, nausea, vomiting, decreased appetite, fatigue, neuropathy, mouth sores, and rash symptoms), each with a varying number of corresponding attribute items, for a total of 14 items. An additional item providing an overall assessment of the burden of side effects will be collected in addition to the 14 selected items from the PRO-CTCAE. The selected PRO-CTCAE items will be completed per the schedule of activities, only when available in the local language of the investigational site. The PRO-CTCAE takes approximately 10 minutes to complete.

#### 4.5.10.3 EQ-5D-5L

The EQ-5D-5L is a validated self-reported health status questionnaire that is used to calculate health states for use in health economic analyses (EuroQoL Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013). There are two components of the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analog scale that measures health state (see Appendix 11). Utility scores will be used in this study to inform pharmacoeconomic evaluations and, as such, will not be included in the Clinical Study Report. The EQ-5D-5L takes approximately 3 minutes to complete.

### 4.5.11 Blood Samples for Whole Genome Sequencing (Patients at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety. The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 4.5.11) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

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

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

*Data generated from blood samples collected for WGS or WES will be analyzed in aggregate rather than on an individual patient basis. Thus, there will be no identification and reporting of incidental findings to investigators or patients.*

*If permitted by local law, a patient may request access to uninterpreted WGS or WES data derived from analysis of his or her blood sample. If a patient wishes to access these data, the investigator must inform the Sponsor, using the following email address: global.return-genomics-results@roche.com. The Sponsor will provide available data to the investigator in the form of a raw genomic sequencing data file, but will not provide any interpretation of the data. The investigator should not include the data file in the patient's medical record. Samples may be stored and analyzed in the future, and some samples may never be analyzed. Thus, data may not be available at the time of the request or may never be available.*

*The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.*

Refer to Section 4.5.12.6 for details on use of samples after patient withdrawal, confidentiality standards for data, and availability of data from biomarker analyses.

### 4.5.12 Optional Samples for Research Biosample Repository

#### 4.5.12.1 Overview of the Research Biosample Repository

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

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation

- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, 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

#### 4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.12) will not be applicable at that site.

#### 4.5.12.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to PI3K/Akt pathway activity, immune infiltration/activation, apoptosis, breast cancer biology, and drug safety:

- Leftover blood, serum, plasma, and tumor tissue samples (with the exception of remaining archival tissue blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)
- Optional tumor biopsy tissues obtained at the time of progression (e.g., at the study treatment discontinuation visit), if deemed clinically feasible

    If performed, these biopsies should be performed within 6 weeks after progression or prior to the next anti-cancer therapy, whichever is sooner. Samples collected via resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy of the growing lesion(s) are preferred.

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Exploratory research results will not be available to patients or investigators. However, patients who provided an optional biopsy at progression may request the FMI NGS report of the new biopsy; it will be provided when available through Foundation Medicine's web portal (results may not be available for samples that do not meet testing criteria).

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

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

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

#### 4.5.12.4 Confidentiality

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

Patient medical information associated with RBR samples 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.

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

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

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

#### 4.5.12.5 Consent to Participate in the Research Biosample Repository

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

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

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

#### 4.5.12.6 Withdrawal from the Research Biosample Repository

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

global_rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

#### 4.5.12.7 Monitoring and Oversight

RBR samples 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 samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. 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 RBR samples.

## 4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

### 4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment (ipatasertib/placebo, atezolizumab/placebo, and paclitaxel) if any of the following *criteria are met*:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that may jeopardize the patient's safety if he or she continues study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- All study drugs must be discontinued for use of another non–protocol-specified anti-cancer therapy
- All study drugs must be discontinued for pregnancy
- All study drugs must be discontinued for the following: Radiographic disease progression per RECIST v1.1 or symptomatic deterioration attributed to disease progression

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

Patients will return to the clinic for a treatment discontinuation visit ≤30 (close to but should not exceed 30) days after the final dose of study treatment (last dose of last study drug). The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. The treatment discontinuation visit must occur prior to initiation of new anti-cancer therapy. Patients who discontinue study treatment for any reason other than progressive disease will continue to undergo tumor response assessments, as outlined in the schedule of activities (see Appendix 1).

After treatment discontinuation, information on survival follow-up, new anti-cancer therapy and outcome will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). All patients will be followed for survival information unless the patient requests to be withdrawn from study; this request must be documented in the source file and signed by the investigator. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. *As of protocol Version 6, these long-term follow-up assessments are no longer required.*

### 4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. Patients should be asked to return to the clinic for a study treatment discontinuation visit (if applicable). The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

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

### 4.6.3 Study Discontinuation

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

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

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

### 4.6.4 Site Discontinuation

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice

- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

# 5. ASSESSMENT OF SAFETY

## 5.1 SAFETY PLAN

Ipatasertib is not currently approved for any indication, and clinical development is ongoing. Atezolizumab is approved for the treatment of urothelial carcinoma, non-small cell lung cancer, small-cell lung cancer, and TNBC. Atezolizumab has received accelerated approval in the United States for the treatment of patients with PD-L1–positive locally advanced or metastatic TNBC and is under evaluation by other health authorities for consideration for approval in metastatic TNBC. The safety plan for patients in this study is based on clinical experience with ipatasertib and atezolizumab (as monotherapy and in various combinations) in completed and ongoing studies. The anticipated important safety risks for ipatasertib, atezolizumab, and paclitaxel are outlined below (see Sections 5.1.1 and 5.1.3).

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including investigator's assessment of the nature, frequency, and severity of adverse events, as well as expedited reporting of protocol-defined adverse events of special interest regardless of seriousness. Administration of atezolizumab and paclitaxel will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

Guidelines for managing patients who experience anticipated adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided in Appendix 13 and Appendix 14.

The instructions provided are intended to serve as minimal safety guidance to improve safety and tolerability for patients to continue receiving ongoing treatment. Investigators may choose to implement dosage modification, treatment interruption, and/or discontinuation with a lesser degree of toxicity than instructed by the guidelines. Dose reductions for ipatasertib/placebo and paclitaxel are listed in Appendix 13. Dose reduction for atezolizumab/placebo is not allowed. General guidelines for dose modification are provided in Appendix 13.

The iDMC will be responsible for ongoing monitoring of patient safety. Following the unblinding of Cohort 1 and Cohort 2, the study team (see Safety Data Monitoring, Section 3.1.3) will be responsible for the ongoing monitoring of patient safety in the study.

Refer to Sections 5.4–5.6 for details on safety reporting (e.g., adverse events, pregnancies) for this study.

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

### 5.1.1 Risks Associated with Ipatasertib

Ipatasertib has been associated with identified risks including the following: nausea, vomiting, diarrhea, stomatitis/mucosal inflammation, asthenia/fatigue, hyperglycemia, erythema multiforme, and rash. Ipatasertib's potential risks include hematologic or immunosuppressant effects, hyperlipidemia, hepatotoxicity, pneumonitis, colitis, and developmental toxicity.

Refer to Section 6 of the Ipatasertib Investigator's Brochure for a detailed description of anticipated safety risks for ipatasertib. Refer to the Ipatasertib Investigator's Brochure for a complete summary of safety information of ipatasertib as a single-agent and in combination with chemotherapy and other anti-cancer therapies.

### 5.1.2 Risks Associated with Paclitaxel

In prior clinical trials of paclitaxel, the following safety signals associated with paclitaxel were identified: nausea, vomiting, diarrhea, stomatitis, peripheral neuropathy, hypersensitivity reactions, hematologic toxicity, pseudomembranous colitis, and cardiovascular effects such as hypotension, bradycardia, hypertension, arrhythmias, and other ECG abnormalities.

To be eligible for the current study, patients must have adequate hematologic function, as manifested by measurements of CBC counts. Furthermore, blood cells will be assessed prior to each treatment cycle.

Patients will be monitored for other paclitaxel-associated adverse events as outlined in this section. For more details regarding the safety profile of paclitaxel, see the Paclitaxel Prescribing Information or Summary of Product Characteristics.

### 5.1.3 Risks Associated with Ipatasertib in Combination with Paclitaxel

Ipatasertib in combination with paclitaxel has been administered to 61 breast cancer patients in Study GO29227 (LOTUS) and 76 patients in Study GO29505 (FAIRLANE).

In the LOTUS study, the incidence of the following adverse events related to ipatasertib/placebo was ≥10% higher in patients receiving ipatasertib plus paclitaxel versus placebo plus paclitaxel: diarrhea (88.5% vs. 16.1%) and nausea (41.0% vs. 19.4%). The most frequent Grade≥3 adverse events (reported in ≥5% of patients in either treatment arm) experienced by patients in the ipatasertib plus paclitaxel arm relative to the placebo plus paclitaxel arm were diarrhea (reported for 14 patients [23.0%] for all Grade 3 events vs. no patients), neutropenia (6 patients [9.8%] vs. 1 patient [1.6%]), decreased neutrophil count (5 patients [8.2%] vs. 4 patients [6.5%]), and fatigue (2 patients [3.3 %] vs. 4 patients [6.5%]), respectively.

In the FAIRLANE study, the incidence of the following adverse events related to ipatasertib/placebo was ≥10% higher in patients receiving ipatasertib plus paclitaxel versus placebo plus paclitaxel: diarrhea (ipatasertib plus paclitaxel: 75.0% vs. placebo plus paclitaxel: 26.7%), nausea (35.5% vs. 21.3%), vomiting (17.1% vs. 4.0%), and abdominal pain (14.5% vs. 2.7%). Diarrhea was the only Grade ≥3 adverse event reported in at least 5% of patients in either treatment arm (ipatasertib plus paclitaxel: 13 patients [17.1%] vs. placebo plus paclitaxel: 1 patient [1.3%]; all Grade 3 events).

The incidence of overall neutropenia in the LOTUS study was similar in both arms (34% in the ipatasertib plus paclitaxel arm vs. 39% in the placebo plus paclitaxel arm), but Grade ≥3 neutropenia, analyzed using grouped terms of similar medical concept, was higher in the ipatasertib plus paclitaxel arm (18% vs. 8%). The incidence of overall neutropenia in the FAIRLANE study (by group term) of any grade was similar in the ipatasertib plus paclitaxel arm (11 patients [14.5%]) and in the placebo plus paclitaxel arm (10 patients [13.3%]). The majority of the events were Grade 2 in severity (ipatasertib plus paclitaxel arm: 7 patients [9.2%]) (placebo plus paclitaxel arm 6 patients [8.0%]). Grade 3 neutropenia was reported in 2 patients (2.6%) in the ipatasertib plus paclitaxel arm and 3 patients (4.0%) in the placebo plus paclitaxel arm. One Grade 4 adverse event was reported in 1 patient (1.3%) in the placebo plus paclitaxel arm. For recurrent Grade ≥3 neutropenia, ipatasertib should be reduced by one dose level when treatment is restarted (refer to the management guidelines in Appendix 13).

*Refer to Section 6 of the ipatasertib Investigator's Brochure for a detailed description of anticipated safety risks for ipatasertib and* for further information regarding the nonclinical and clinical safety evaluation of ipatasertib given as a single agent and in combination with chemotherapy.

### 5.1.4 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis and severe cutaneous adverse reactions.

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab. Refer to Appendix 13 and Appendix 14 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

### 5.1.5 Risks Associated with Combination Use of Atezolizumab and Ipatasertib

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and ipatasertib: gastrointestinal, dermatologic, hepatic, pulmonary, and hyperglycemia events.

### 5.1.6 Risks Associated with Atezolizumab in Combination with Paclitaxel

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and paclitaxel: pulmonary, gastrointestinal, cardiac, dermatologic, hematologic, and neurologic events (refer to the Atezolizumab Investigator's Brochure for details).

### 5.1.7 Risks Associated with Ipatasertib in Combination with Atezolizumab and Paclitaxel

The following adverse events are potential overlapping toxicities associated with combination use of ipatasertib, atezolizumab, and paclitaxel: pulmonary, gastrointestinal, cardiac, hepatic, dermatologic, hematologic, and neurologic events (refer to the Atezolizumab Investigator's Brochure for details).

## 5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

### 5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered

a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)
- 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 treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

### 5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

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

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

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

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

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

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

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6)
- Suspected transmission of an infectious agent by the study treatment, 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 study treatment is suspected.
- Pneumonitis
- Grade ≥3 diarrhea
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Grade ≥3 hyperglycemia
- Hepatitis
- Grade ≥3 hepatotoxicity
- Grade ≥ 3 ALT/AST elevations
- Colitis
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis

- Grade ≥2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Grade ≥3 rash (e.g., maculopapular, erythema, urticarial, dermatitis, rash popular, skin exfoliation, toxic skin eruption)
- Severe cutaneous reactions (e.g., erythema multiforme, Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

### 5.2.4 Selected Adverse Events

Additional data may be analyzed for the following selected adverse events:

- Diarrhea
- Asthenia (fatigue)
- Nausea
- Neutropenia (neutrophil count decreased, febrile neutropenia)
- Rash (e.g., maculopapular, erythema, urticarial, dermatitis, rash popular, skin exfoliation, toxic skin eruption)
- Erythema multiforme
- Vomiting
- Oral mucositis (stomatitis, mucosal inflammation, mouth inflammation, mouth ulceration)
- Hyperlipidemia (hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, blood cholesterol increased, blood triglycerides increased)
- Hepatotoxicity (ALT, AST increased)
- Hyperglycemia (blood glucose increased)
- Pneumonitis (interstitial lung diseases)

## 5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

### 5.3.1 Adverse Event Reporting Period

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

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

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

After initiation of study treatment, all adverse events will be reported until 30 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.

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

### 5.3.2 Eliciting Adverse Event Information

A consistent methodology of 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?"

Note that PRO questionnaires should not be used as solicitation tools for adverse event data collection, nor should the PRO data be used as source documents for adverse event reporting (see Section 5.3.5.13, Patient-Reported Outcome Data), as these data will be collected on separate eCRFs and analyzed separately. To minimize interference between the investigator-assessed adverse event reporting (i.e., NCI CTCAE) and PRO adverse event data (i.e., PRO NCI CTCAE), the sites should not attempt to reconcile data nor elicit questions based upon the results of the PRO questionnaires. In the event that an investigator becomes aware of PRO data that may be indicative of a serious adverse event or an adverse event of special interest, the investigator will determine whether the criteria for a serious adverse event or adverse events of special interest have been met and, if so, will report the event on the Adverse Event eCRF.

### 5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 3 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

**Table 3 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE**

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

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

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htmNote: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

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

### 5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 4):

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

- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non–treatment-related factors that are known to be associated with the occurrence of the event

**Table 4 Causal Attribution Guidance**

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

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

### 5.3.5 Procedures for Recording Adverse Events

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

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

#### 5.3.5.1 Infusion-Related Reactions

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

#### 5.3.5.2 Diagnosis versus Signs and Symptoms

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

#### 5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

#### 5.3.5.4 Persistent or Recurrent Adverse Events

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

For selected adverse events, grade change will be captured in order to understand duration of each grade of the adverse event, as well as impact of any intervention on the adverse event. Details regarding any increases or decreases in severity of selected adverse events (e.g., diarrhea, rash, hyperglycemia; see Section 5.3.3 will be captured on the Adverse Event Intensity or Grade Changes eCRF.

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

#### 5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

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

#### 5.3.5.6 Abnormal Liver Function Tests

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

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

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

#### 5.3.5.7 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:

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

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

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

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

#### 5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protoco-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of TNBC should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse

event reporting period, regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An iDMC will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

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

#### 5.3.5.9 Preexisting Medical Conditions

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

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

#### 5.3.5.10 Lack of Efficacy or Worsening of Triple-Negative 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 v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

#### 5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration or performance of an efficacy measurement for the study or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

  The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

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

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

#### 5.3.5.12 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

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

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

*Note:* Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills

seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For ipatasertib/placebo, atezolizumab/placebo, and paclitaxel, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

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

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.

- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

#### 5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events. Because the processes of data collection and intent of interpretation of investigator-assessed adverse events (i.e., by NCI CTCAE) and patient-reported adverse events (e.g., NCI PRO-CTCAE) are inherently different, these data sets will not be reconciled by the Sponsor and should not be used as source documents for adverse event reporting by the site.

#### 5.3.5.14 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

### 5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

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

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

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

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

### 5.4.1 Emergency Medical Contacts

**Medical Monitor Contact Information for All Sites**

Medical Monitor/Roche Medical Responsible: [redacted], *M.D.*

Mobile Telephone No.: [redacted]

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

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

#### 5.4.2.1 Events That Occur prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper *Clinical Trial Adverse Event/Special Situations Form* provided to investigators should be completed and submitted to the Sponsor or its designee

immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

#### 5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 90 days after the final dose of study treatment or until initiation of new systemic 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 paper *Clinical Trial Adverse Event/Special Situations Form* provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

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

### 5.4.3 Reporting Requirements for Pregnancies

#### 5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 28 days after the final dose of ipatasertib/placebo, 5 months after the final dose of atezolizumab/placebo, or 6 months after the final dose of paclitaxel, whichever occurs later. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

#### 5.4.3.2 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 or within 28 days after the final dose of ipatasertib/placebo, or 6 months after the final dose of paclitaxel, whichever occurs later. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. 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 treatment. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. 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.

#### 5.4.3.3 Abortions

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

If a therapeutic or elective abortion was performed because of an underlying maternal or embryo–fetal 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 embryo–fetal 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 treatment or the female partner of a male patient exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

## 5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

### 5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, *or* the event is assessed as stable by the investigator, *or* 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 treatment or trial-related procedures until a final outcome can be reported.

During the adverse event reporting period (defined in Section 5.3.1 ), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

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

### 5.5.2 Sponsor Follow-Up

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

## 5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the reporting period for serious adverse events and adverse events of special interest (defined as 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

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

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

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

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through the use of the following reference safety information in the documents listed below:

| Drug | Document |
|---|---|
| Ipatasertib | Ipatasertib Investigator's Brochure |
| Atezolizumab | Atezolizumab Investigator's Brochure |
| Paclitaxel | Paclitaxel Summary of Product Characteristics |

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

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

# 6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a Phase III, two-cohort, randomized, placebo-controlled, double-blind study designed to evaluate the efficacy and safety of the combination of atezolizumab, ipatasertib, and paclitaxel in approximately 1155 patients with locally advanced unresectable or metastatic TNBC. This includes approximately 525 patients with PD-L1–non-positive tumors in Cohort 1 and 630 patients with PD-L1–positive tumors in Cohort 2.

Depending on the timing of the respective primary PFS analysis for these two cohorts, Cohort 1 and Cohort 2 may be unblinded separately. In such case, the treatment codes of patients in the cohort whose PFS data mature earlier will be sent to the Sponsor to unblind only that cohort to perform the primary analysis of PFS. The Sponsor will remain blinded to the treatment assignments of the other cohort.

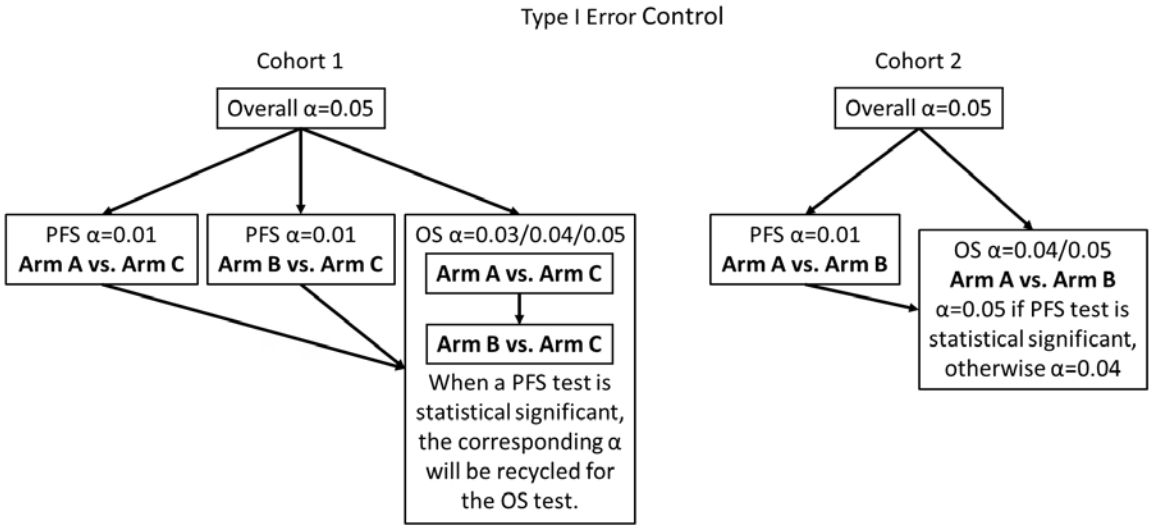
As of protocol Versions 4 and 5, statistical considerations and the analyses outlined in Section 6 are no longer applicable to the study as indicated in the respective sections. Due to the early termination of the enrollment, data from enrolled patients will only be summarized descriptively for endpoints that are deemed appropriate and necessary (e.g., demographics, disposition, and adverse events).

## 6.1 DETERMINATION OF SAMPLE SIZE

### 6.1.1 Type I Error Control

Cohort 1 (patients with PD-L1–non-positive tumors) and Cohort 2 (patients with PD-L1–positive tumors) are two independent cohorts and will be analyzed separately for all endpoints unless otherwise specified. Each cohort will be tested independently with an overall 5% type I error control as illustrated in Figure 2.

**Figure 2 Type I Error Control**




OS = overall survival; PFS = progression-free survival.

For Cohort 1, the overall type I error ($\alpha$) is 0.05 (two sided) and is split among the co-primary efficacy endpoints: 0.01 for PFS for Arm A versus Arm C, 0.01 for PFS for Arm B versus Arm C, and 0.03 for OS. PFS for Arm A versus Arm C and Arm B versus Arm C will be tested independently, whereas OS will be tested in a hierarchical sequence of Arm A versus Arm C followed by Arm B versus Arm C. The PFS data will mature earlier and PFS will be firstly tested with $\alpha$ of 0.01 for Arm A versus Arm C and 0.01 for Arm B versus Arm C. When a PFS test is passed at an $\alpha$ level of 0.01, that 0.01 $\alpha$ assigned will be recycled to OS (i.e., OS will be tested at the significance level of 0.05 [if both PFS tests are passed] or 0.04 [if only one PFS test is passed]; otherwise, OS will be tested at the significance level of 0.03 [when neither PFS tests is passed] to control the overall type I error at 0.05).

For Cohort 2, the overall type I error ($\alpha$) is 0.05 (two sided) and is split between the two co-primary efficacy endpoints PFS and OS. The PFS data will mature earlier and PFS will be firstly tested with $\alpha$ of 0.01. If the PFS test is passed at the significance level of 0.01, the 0.01 $\alpha$ assigned to PFS will be recycled to OS (i.e., OS will be tested at the significance level of 0.05; otherwise, OS will be tested at the significance level of 0.04 to control the overall type I error at 0.05).

### 6.1.2 Sample Size Consideration for Cohort 1

The following statistical considerations were applicable prior to the termination of enrollment on 18 September 2020 and subsequent unblinding of Cohort 1 on 21 September 2020. At that time, a total of 127 patients had been enrolled in Cohort 1.

Approximately 525 patients will be enrolled and randomized in a 1:1:1 ratio to Arm A (ipatasertib plus atezolizumab plus paclitaxel), Arm B (ipatasertib plus paclitaxel plus

placebo) and Arm C (paclitaxel plus placebo plus placebo). The sample size is determined by the co-primary endpoints: PFS comparing Arm A versus Arm C, PFS comparing Arm B versus Arm C, and OS comparing Arm A versus Arm C.

The primary analysis of PFS will be conducted when approximately 239 PFS events from all three arms (including approximately 171 PFS events for the comparison of Arm B vs. Arm C and approximately 166 PFS events for the comparison of Arm A vs. Arm C) are observed or when the last patient has been randomized, whichever occurs later.

With 172 PFS events for the comparison of Arm B versus Arm C, this allows for 80% power to detect an improvement in median PFS from 5.6 months to approximately 9.4 months (hazard ratio = 0.593) at the 1% level of significance (two sided). The largest hazard ratio deemed to be statistically significant at the 1% level will be approximately 0.675 (with median improvement in PFS from 5.6 to 8.3 months). With 166 PFS events for the comparison of Arm A vs. C, this allows for 94% power to detect an improvement in median PFS from 5.6 months to approximately 10.6 months (hazard ratio = 0.528) at the 1% level of significance (two sided). The largest hazard ratio deemed to be statistically significant at the 1% level will be approximately 0.670 (with median improvement in PFS from 5.6 to 8.4 months).

If the 0.02 $\alpha$ assigned to PFS is recycled, the co-primary endpoint, OS, will be tested at the 5% level of significance (two sided). The final OS analysis will be conducted when approximately 216 OS events for the comparison of Arm A vs. Arm C are observed. With $\alpha$ spending to the interim analyses of OS (see details in Section 6.9.2.1), at the OS final analysis, 216 OS events for the comparison of Arm A vs. C will allow for 80% power to detect an improvement in median OS from 18.4 to 27.1 months (hazard ratio = 0.680) at the 5% level of significance (two sided). The largest OS hazard ratio deemed to be statistically significant will be approximately 0.759 (with median OS improvement from 18.4 to 24.2 months).

If the 0.02 $\alpha$ assigned to PFS is not recycled or only 0.01 $\alpha$ is recycled, the co-primary endpoint, OS, will be tested at the 3% or 4% level of significance (two sided), respectively. The final OS analysis timing and the require number of OS events will be adjusted accordingly to allow 80% power to detect an improvement in median OS from 18.4 to 27.1 months (hazard ratio = 0.680) at the 3% or 4% level of significance (two sided). Further details will be provided in the Statistical Analysis Plan.

The enrollment duration is projected to be approximately 22 months (from the first patient randomized). For all three arms, an annual loss to follow-up rate of 5% and 2% are assumed for PFS and OS, respectively. Based on these, it is projected that the primary PFS analysis will occur when the last patient is randomized, and the final OS analysis is projected to occur approximately 49 months after the first patient is enrolled, if the 0.02 $\alpha$ assigned to PFS is recycled for OS.

### 6.1.3 Sample Size Consideration for Cohort 2

The following statistical considerations were applicable prior to the termination of enrollment on 6 August 2020 and subsequent unblinding of Cohort 2 on 7 August 2020. At that time, a total of 115 patients had been enrolled in Cohort 2.

Approximately 630 patients will be enrolled and randomized in a 1:1 ratio to Arm A (ipatasertib plus atezolizumab plus paclitaxel) and Arm B (atezolizumab plus paclitaxel plus placebo).

The primary analysis of PFS will be conducted when approximately 228 PFS events are observed or when the last patient has been randomized, whichever occurs later. Based on the enrollment assumption, it is most likely driven by the last patient's randomization as described at the end of this section.

With 228 PFS events, this allows for 80% power to detect an improvement in median PFS from 7.5 to approximately 11.8 months (hazard ratio=0.636) at the 1% level of significance (two sided). The largest hazard ratio deemed to be statistically significant at the 1% level will be approximately 0.711 (with median improvement in PFS from 7.5 to 10.5 months).

If the 0.01 $\alpha$ assigned to PFS is recycled, the co-primary endpoint, OS, will be tested at the 5% level of significance (two sided). The final OS analysis will be conducted when approximately 417 OS events are observed. With $\alpha$ spending to the interim analyses of OS (see details in Section 6.9.2.2), at the OS final analysis, it will allow for 80% power to detect a hazard ratio of 0.758 (median OS improvement from 25 to 33 months) at the 5% level of significance (two sided). The largest OS hazard ratio deemed to be statistically significant will be approximately 0.820 (with median OS improvement from 25 to 30.5 months).

If the 0.01 α assigned to PFS is not recycled, the co-primary endpoint, OS, will be tested at the 4% level of significance (two sided). The final OS analysis will be conducted when approximately 444 OS events are observed. With $\alpha$ spending to the interim analyses of OS (see details in Section 6.9.2.2), at the OS final analysis, it will allow for 80% power to detect a hazard ratio of 0.758 (median OS improvement from 25 to 33 months) at the 4% level of significance (two sided). The largest OS hazard ratio deemed to be statistically significant will be approximately 0.818 (with median OS improvement from 25 to 30.6 months).

The enrollment duration is projected to be approximately 36 months (from the first patient randomized). For both arms, an annual loss to follow-up rate of 5% and 2% are assumed for PFS and OS, respectively. Based on these, it is projected that the primary PFS analysis will occur when the last patient is randomized, and it is predicted that there will be approximately 372 PFS events. With 372 PFS events, the largest hazard ratio deemed to be statistically significant at the 1% level will be approximately 0.766 (with

median PFS improvement from 7.5 to 9.8 months). The final OS analysis is projected to occur approximately 70 months after the first patient is enrolled, if the 0.01 $\alpha$ assigned to PFS is recycled for OS.

## 6.2 SUMMARIES OF CONDUCT OF STUDY

Study enrollment and duration, study drug discontinuation, study discontinuation, reasons for study drug discontinuation and study discontinuation will be summarized by treatment arm independently for each cohort. Major protocol deviations, including major deviations of inclusion/exclusion criteria, will also be reported and summarized by treatment arms independently for each cohort.

## 6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

The independent evaluation of treatment group comparability between the treatment arms in each cohort will include demographics summaries, stratification factors, patient treatment history, and other baseline disease characteristics.

Continuous data will be summarized with means, standard deviations, and medians and ranges. Categorical data will be summarized by counts and proportions.

## 6.4 EFFICACY ANALYSES

Efficacy analyses will be performed independently for each cohort. All efficacy analyses will be based on the ITT population within each cohort according to the treatment arm to which patients are allocated. The analysis of DOR will include all patients with an objective response.

All primary and secondary endpoints based on tumor burden will be based on radiological (or photographic, if applicable) assessments by the local radiologist or investigator, unless otherwise specified.

### 6.4.1 Co-Primary Efficacy Endpoints

The co-primary efficacy endpoints are investigator-assessed PFS and OS.

Investigator-assessed PFS, defined as the time from randomization to the first occurrence of disease progression, as determined locally by the investigator using RECIST v1.1 (see Appendix 5) or death from any cause, whichever occurs first. Data for patients without the occurrence of disease progression or death as of the clinical data cutoff date will be censored at the time of the last tumor assessment (or at the time of randomization plus 1 day if no tumor assessment was performed after the baseline visit).

OS is defined as the time from randomization to death from any cause. Data for patients who have not died as of the clinical data cutoff date will be censored at the last date they are known to be alive. Data for patients who do not have postbaseline information will be censored at the randomization plus 1 day.

Both PFS and OS will be compared between treatment arms using the stratified log-rank test. The hazard ratio will be estimated using a stratified Cox proportional hazards model. The 95% CI for the hazard ratio will be provided. The stratification factors to be used will be the same as the randomization stratification factors. Results from an unstratified analysis will also be provided. For each treatment arm, Kaplan-Meier methodology will be used to estimate the median PFS and OS, and the Brookmeyer-Crowley method will be used to construct the 95% CI for the median PFS and OS (Brookmeyer and Crowley 1982). Kaplan-Meier curves will be produced as well.

### 6.4.2 Exploratory Efficacy Endpoints

#### 6.4.2.1 Objective Response Rate

An objective response is defined as response (CR or PR) on two consecutive occasions $\geq$4 weeks apart, as determined by the investigator using RECIST v1.1. Patients not meeting these criteria, including patients without any postbaseline tumor assessment, will be considered non-responders. ORR is defined as the proportion of patients who had an objective response. The analysis population for ORR will be all randomized patients with measurable disease at baseline.

An estimate of ORR and its 95% CI will be calculated using the Clopper-Pearson method for each treatment arm. ORR will be compared between treatment arms using the stratified Cochran-Mantel-Haenszel test. The stratification factors to be used will be the same as those used for the analysis of the primary endpoint. 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 Response

DOR will be assessed in patients who had an objective response as determined by the investigator using RECIST v1.1. DOR is defined as the time from the first occurrence of a documented objective response (CR or PR, whichever status is recorded first) to the first occurrence of progressive disease, as determined by the investigator according to RECIST v1.1, or death, whichever occurs first. Patients who have not progressed and who have not died at the time of analysis will be censored at the time of last tumor assessment date.

The Kaplan-Meier approach will be used to estimate the median DOR and the corresponding 95% CIs. Analysis of DOR will include only patients with objective responses. Because of the non-randomized nature of this analysis population, the analysis of DOR will be considered descriptive.

#### 6.4.2.3 Clinical Benefit Rate

CBR is defined as the proportion of patients who have a CR, PR, or stable disease for at least 24 weeks, as determined by the investigator using RECIST v1.1. The CBR will be analyzed using methods similar to those used for ORR.

#### 6.4.2.4 Patient Subgroup Analysis in Each Cohort

The co-primary endpoints, PFS and OS, and key secondary endpoints ORR, DOR, and CBR will also be explored in two subgroups: patients with *PIK3CA*/*AKT1*/*PTEN*-altered tumors and patients without *PIK3CA*/*AKT1*/*PTEN* -altered tumors.

#### 6.4.2.5 Patient-Reported Outcomes of Role and Physical Function and GHS/QoL and EORTC Data

The main PRO endpoints are the mean and the mean change from baseline scores in function (role, physical) and GHS/QoL. Summary statistics (mean, standard deviation, median, and range) of linearly transformed absolute scores and the mean change from baseline will be calculated for the Functional (role [Questions 6 and 7], physical [Questions 1–5]) and the GHS/QoL (Questions 29 and 30) scales of the EORTC QLQ-C30 at each assessment timepoint for each arm. The mean (and 95% CI) and median of the absolute scores and the change from baseline will be reported for interval and continuous variables. Previously published minimally important differences will be used to identify clinically meaningful change from baseline within each treatment group on the Functional and GHS/QoL scales (Osoba et al. 1998; Cocks et al. 2011).

The EORTC QLQ-C30 (Version 3) data will be scored according to the EORTC scoring manual (Fayers et al. 2001). PRO completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm.

Missing data will be assessed and reported by cycle. In the event of incomplete data, for all questionnaire subscales, if $>50\%$ of the constituent items are completed, a pro-rated score will be computed consistent with the scoring manuals and validation papers. For subscales with $<50\%$ of the items completed, the subscale will be considered as missing.

#### 6.4.2.6 Progression-Free Survival 2 (PFS2)

PFS2 is defined as the time from randomization to second occurrence of objective disease progression, as determined by the investigator using RECIST v1.1, or death from any cause (whichever occurs first). Data for patients alive and for whom a second objective disease progression has not been observed should be censored at the last time known to be alive and without second objective disease progression. This analysis will be performed as data allows.

#### 6.4.2.7 Patient-Reported Outcomes of Disease- and Treatment-Related Symptoms, and Cognitive, Emotional, and Social Function: EORTC Data

Summary statistics (mean, standard deviation, median, and range) of linearly transformed absolute scores and mean change from baseline scores will be calculated for all disease/treatment-related symptom items and scales, and the Cognitive, Emotional, and Social Function scales of the EORTC QLQ-C30 (see Appendix 10) at each assessment timepoint for each arm.

#### 6.4.2.8 Health Economic EQ-5D-5L Data

Health utility data from the EQ-5D-5L (see Appendix 11) will be evaluated in pharmacoeconomic models. The results from the health economic data analyses will be reported separately from the Clinical Study Report.

### 6.5 SAFETY ANALYSES

#### 6.5.1 Analyses of Exposure, Adverse Events, Laboratory Data, and Vital Signs

All safety analyses will be based on the safety-evaluable population (i.e., all patients who receive any study treatment) according to the treatment received.

The frequency, nature, and severity of treatment-emergent adverse events, adverse events leading to death, adverse events leading to study drug discontinuation and dose modification, serious adverse events, and adverse events of special interest will be summarized by treatment arm. All deaths will be summarized. Laboratory measurements outside of the normal range will be identified. Selected laboratory data will be summarized by treatment received and grade compared with baseline. Relevant vital signs will be presented using summary statistics by treatment received and visit. Drug exposure will be summarized as well, including duration of treatment, cumulative dose, and dose intensity.

Treatment-emergent adverse events are defined as adverse events that occur after the first dose of study treatment. Adverse events will be summarized by mapped MedDRA preferred terms and appropriate MedDRA hierarchy. Adverse event severity will be graded according to NCI CTCAE v5.0. Multiple occurrences of the same event will be counted once at the maximum severity.

#### 6.5.2 Exploratory Safety Analysis of Patient-Reported Symptomatic Adverse Events: PRO-CTCAE Data

PRO-CTCAE analyses will be primarily descriptive, with a focus on characterizing the pattern of symptomatic treatment toxicities during the study. Results from these exploratory analyses will be presented separately from the safety analyses for each cohort. PRO-CTCAE data will be analyzed at the item level consistent with current NCI recommendations for data handling (Basch et al. 2014).

PRO-CTCAE data will be summarized over time. The proportion of missing data at each assessment timepoint will also be summarized to facilitate interpretation of data.

The number and percentage of patients reporting each symptom, including overall side effect bother, and the change from baseline by category (frequency of occurrence, severity, interference) will be summarized at each assessment timepoint by treatment arm. For items that are rated on a 5-point Likert scale, the maximum postbaseline score and change from baseline will be summarized by treatment arm.

Graphical representation of PRO-CTCAE data over time will also be provided.

## 6.6 EXPLORATORY PHARMACOKINETIC ANALYSES

For each cohort, atezolizumab, ipatasertib, and G-037720, a metabolite of ipatasertib, serum or plasma concentration versus time data, together with information on dosing and patient characteristics, will be analyzed using a population-PK analysis approach. Concentration–time data will be compared with existing models to determine if exposures are consistent with previously characterized pharmacokinetic. Samples will also be used to characterize the immunogenicity of atezolizumab. Nonlinear mixed-effect modeling will be used for the estimation of population-PK parameters for the relevant analytes. Covariates, such as patient demographics (e.g., age, sex, body size), total protein, serum albumin, liver function tests (e.g., AST, ALT, and ALP), and serum creatinine will be tested for significance on PK parameters of interest, as needed.

For each cohort, the PK data will be combined with the safety and efficacy (e.g., PFS) data for exposure–response modeling as data permit for one or both study drugs, as appropriate. PK and PK/pharmacodynamic analyses may be reported in separate stand-alone reports. Additional analyses may be explored as warranted by the data. Population-PK results may be reported separately.

Additional analyses may be explored as warranted by the data.

## 6.7 EXPLORATORY IMMUNOGENICITY ANALYSES

Immunogenicity will be independently evaluated for each cohort. The immunogenicity analysis population will consist of all patients with at least one ADA assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after drug administration (postbaseline incidence) will be summarized by treatment group. When determining postbaseline incidence, patients are considered to be ADA-positive if they are ADA-negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA-positive at baseline and the titer of one or more postbaseline samples is at least 0.60-titer unit greater than the titer of the

baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA-negative if they are ADA-negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA-positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60-titer unit greater than the titer of the baseline sample (treatment unaffected).

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

## 6.8 EXPLORATORY BIOMARKER ANALYSES

Although no formal statistical analysis of exploratory biomarkers will be performed, data may be analyzed in the context of this study and may also be explored in aggregate with data from other studies. The exploratory biomarker endpoints, including the effects of breast intrinsic subtypes and expression of tumor suppressors, will be evaluated with appropriate methods in an effort to understand the association of these markers with study drug response. Biomarker analyses may be reported in a separate report.

## 6.9 INTERIM ANALYSES

### 6.9.1 Planned Interim Safety Analyses

An external iDMC will be formed to evaluate safety data in Cohorts 1 and 2 on a periodic basis, approximately every 6 months from the time of the first patient's enrollment until the time of the primary analysis of PFS for both cohorts are complete. All summaries/analyses by treatment arm for the iDMC's review will be prepared by an external iDCC for each cohort. Members of the iDMC will be external to the Sponsor and will follow a charter that outlines their roles and responsibilities. Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the IRB/EC. A detailed plan will be included in the iDMC Charter.

In the absence of extenuating circumstances, accrual will not be halted while the interim safety analysis is conducted. The iDMC will review the available data to make a recommendation as to the following: to continue without changes to the protocol, to modify the safety monitoring and/or eligibility criteria, to add additional safety reviews to address emerging safety issues, or to terminate the study. The final decision will rest with the Sponsor. In addition, the Sponsor may request ad-hoc meetings of the iDMC at any time during the study to review ongoing safety summary data.

Due to the early termination of enrollment and unblinding of patients, the iDMC's review of the ongoing safety summary data will be terminated after the unblinding. The study team (see Safety Data Monitoring, Section 3.1.3 ) will be responsible for the ongoing monitoring of patient safety in the study.

### 6.9.2 Planned Interim Analysis of OS at the Primary Analysis of PFS

#### 6.9.2.1 Planned Interim OS Analysis for Cohort 1

The following statistical considerations were applicable prior to the early termination of enrollment on 18 September 2020 and subsequent unblinding of Cohort 1 on 21 September 2020, and they are not appliacable as of protocol V5.

There are two planned OS interim analyses for the comparisons across the three treatment arms. The first OS interim analysis will be performed at the time of PFS analysis. The second OS interim analysis will be performed when around 80% of the OS events required for the final OS analysis for the comparison of Arm A versus Arm C is reached. As shown in Figure 2 in Section 6.1.1, OS will be tested in a hierarchical sequence of Arm A versus Arm C followed by Arm B versus Arm C, and the Lan-DeMets $\alpha$-spending function with an O'Brien-Fleming boundary will be used to control the type I error accounting for the interim and final analyses of OS. The comparison of Arm A versus Arm B will be conducted for descriptive purposes only with no type I error control.

If the 0.02 $\alpha$ assigned to PFS is recycled, the final OS will be analyzed when 216 OS events for the comparison of Arm A vs. Arm C occur at approximately 49 months after the first patient has been enrolled. It is estimated that there will be approximately (76, 176, 216) OS events at the first interim, the second interim, and the final OS analyses for the comparison of Arm A versus Arm C, with corresponding p-value boundaries of (0.0003, 0.0259, 0.0424) and hazard ratio boundaries of (0.438, 0.715, 0.759) at the first interim, the second interim, and the final OS analysis for the comparison of Arm A versus Arm C, respectively. The actual boundaries will be adjusted according to the actual information fractions at the interim analyses using the Lan-DeMets $\alpha$-spending function with an O'Brien-Fleming boundary.

If the 0.02 $\alpha$ assigned to PFS is not recycled or only 0.01 $\alpha$ is recycled, the final OS analysis timing, the required number of OS events, the p-value and hazard ratio boundaries for the interim and final analyses will be adjusted accordingly. The detailed analyses will be outlined in the Statistical Analysis Plan (SAP). The analyses specified in the SAP supersede those specified in the protocol for regulatory filing purposes.

At the time of each OS analysis, OS test comparing Arm B versus Arm C will be formally performed only if the OS test comparing Arm A versus Arm C is passed with statistical significance; otherwise, OS test for Arm B versus C will be descriptive only. When comparison of Arm B versus Arm C is formally tested, the same p-value and hazard ratio boundaries used by Arm A versus Arm C comparison will be used, so that the overall type I error of 5% is controlled. The OS test for Arm A versus Arm B will be performed descriptively only. Further details will be provided in the Statistical Analysis Plan.

#### 6.9.2.2 Planned Interim OS Analysis for Cohort 2

The following statistical considerations were applicable prior to the termination of enrollment on 6 August 2020 and subsequent unblinding of Cohort 2 on 7 August 2020, and they are not appliacable as of protocol V4.

There are two planned OS interim analyses for the comparisons between the two treatment arms. The first OS interim analysis will be performed at the time of PFS analysis. The second OS interim analysis will be performed when 80% of the OS events required for the final OS analysis is reached. The Lan-DeMets $\alpha$-spending function with an O'Brien-Fleming boundary will be used to control the type I error accounting for the interim and final analyses of OS.

If the 0.01 $\alpha$ assigned to PFS is recycled, the final OS will be analyzed when 417 OS events occur at approximately 70 months after the first patient has been enrolled. It is estimated that there will be approximately (184, 334, 417) OS events at the first interim, the second interim and the final OS analyses, with corresponding p-value boundaries of (0.0015, 0.0204, 0.0427) and corresponding hazard ratio boundaries of (0.626, 0.781, 0.820) at the first interim, the second interim, and the final OS analysis, respectively. The actual boundaries will be adjusted according to the actual information fractions at the interim analyses using the Lan-DeMets α-spending function with an O'Brien-Fleming boundary.

If the 0.01 $\alpha$ assigned to PFS is not recycled, the final OS will be analyzed when 444 OS events occur at approximately 76 months after the last patient has been enrolled. It is estimated that there will be approximately (184, 355, 444) OS events at the first interim, the second interim and the final OS analysis, with corresponding p-value boundaries of (0.0006, 0.0183, 0.0345) and corresponding hazard ratio boundaries of (0.603, 0.779, 0.818) at the first interim, the second interim, and the final OS analysis, respectively.

### 6.10 CHINA SUBPOPULATION ANALYSES

Due to the early termination of the enrollment, this section is no longer applicable.

After the enrollment of patients in the global phase of this study is complete, additional Chinese patients may be recruited into the China extension cohort. Data from the additional patients enrolled during the China extension phase will not be included in the analysis of the global study. The analysis population for China subpopulation analyses includes Chinese patients recruited in the global study population and China extension cohort combined. The total number of patients in China subpopulation is aimed to show treatment benefit consistency between global population and the China subpopulation. Similar to the global study, the enrollment of China extension in Cohort 1 and Cohort 2 may be closed separately depending on when the required number of patients in the China subpopulation in each cohort is reached. A prespecified clinical data cutoff for the China subgroup analysis will be planned before the PFS primary analysis.

China subpopulation analyses will be performed and summarized in a separate study report. Further details will be provided in the Statistical Analysis Plan.

# 7. DATA COLLECTION AND MANAGEMENT

## 7.1 DATA QUALITY ASSURANCE

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

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. 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.

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

Patient diaries to document specific home medication use, selected adverse events, and possibly home glucose values, will be collected in paper diaries. Selected data from these and diaries will be entered into the EDC system by site staff on the eCRFs.

## 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 that must be kept with the study records. Acknowledgement of receipt of the data is required.

## 7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered on 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 trial.

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

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

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

## 7.4 USE OF COMPUTERIZED SYSTEMS

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

## 7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, paper PRO data, Informed Consent Forms, laboratory test results, medication inventory records, and images 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.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

# 8. ETHICAL CONSIDERATIONS

## 8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

## 8.2 INFORMED CONSENT

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

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

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

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

If the Consent Forms are revised (through an amendment or an addendum) to communicate information that might affect a patient's willingness to continue in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. 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 (HIPAA) of 1996. 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 9.7).

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.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law (with the exception of the report from Foundation Medicine). The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

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

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

## 8.5 FINANCIAL DISCLOSURE

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

# 9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

## 9.1 STUDY DOCUMENTATION

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

## 9.2 PROTOCOL DEVIATIONS

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

## 9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor has implemented a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor identified potential risks associated with critical trial processes and data and implemented plans for evaluating and controlling these risks. Risk evaluation and control included the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits areprovided in a Quality Tolerance Limit Management Plan.

## 9.4 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.

## 9.5 ADMINISTRATIVE STRUCTURE

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

Up to 350 sites globally will participate to randomize approximately 1155 patients. Screening and enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker analyses, and PK analyses), as specified in Section 4.5.9. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will be employed to monitor and evaluate patient safety throughout the study. Tumor response and progression will be evaluated by an independent review committee.

As of protocol Version 5, images for tumor assessments will no longer be collected for blinded independent central review.

## 9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, 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 (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request, 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 Study Information at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any

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

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

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

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

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

## 9.7 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).

## 10. REFERENCES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# Appendix 1 Schedule of Activities

## Table 1 Schedule of Activities: Applicable before unblinding

| Assessment/Procedure | Screening (Days –28 to –1) | Treatment Cycle (28-Day Cycles) [a] | | | | | | | | | | | | SDDV [b] | Post-Treat. Follow-Up [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycles 1 and 2 | | | Cycle 3 | | | Cycle 4 | | | Cycles 5 and Beyond | | | | |
| | | D1 | D8 | D15 | D1 | D8 | D15 | D1 | D8 | D15 | D1 | D8 | D15 | | |
| Signed informed consent(s) | x | | | | | | | | | | | | | | |
| Viral serology [d] | x [d] | | | | | | | | | | | | | | |
| Demographics, medical history, and prior cancer treatment | x | | | | | | | | | | | | | | |
| Tumor tissue sample submitted at screening [e] | x | | | | | | | | | | | | | | |
| Blood sample for WGS [f] | | x [f] | | | | | | | | | | | | | |
| Blood sample for biomarkers [g] | | x [g] | | | x | | | | | | | | | x | |
| Complete physical examination [h] | x | | | | | | | | | | | | | | |
| Limited physical examination [i] | | x | x | x | x | | x | x | | x | x | | | x | |
| Weight | x | x | | | x | | | x | | | x | | | x | |
| Height | x | | | | | | | | | | | | | | |
| Vital signs [j] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| ECOG Performance Status | x | x | | | x | | | x | | | x | | | x | |
| Cardiac function (ECHO or MUGA scan) | x [k] | | | | | | | | | | | | | | |
| 12-Lead ECG [l] | x | | | | | | | | | | | | | x | |

**Appendix 1: Schedule of Activities**

| Assessment/Procedure | Screening (Days –28 to –1) | Treatment Cycle (28-Day Cycles) [a] | | | | | | | | | | | | SDDV [b] | Post-Treat. Follow-Up [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycles 1 and 2 | | | Cycle 3 | | | Cycle 4 | | | Cycles 5 and Beyond | | | | |
| | | D1 | D8 | D15 | D1 | D8 | D15 | D1 | D8 | D15 | D1 | D8 | D15 | | |
| Hematology [m] | x | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x | |
| INR and PTT (or aPTT) | x | | | | | | | | | | | | | x | |
| Fasting serum chemistry [o] | x | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x | |
| TSH, free T3 (or total T3), free T4 [p] | x | x | | | | | | x | | | x [p] | | | x | |
| Fasting lipid profile, and amylase and lipase [q] | x | | | | x [q] | | | | | | x [q] | | | x | |
| $HbA_{1C}$ | x | x | | | x | | | x | | | x | | | x | |
| C-reactive protein [r] | | x [r] | | | | | | | | | | | | | |
| Urinalysis [s] | x | As clinically indicated | | | | | | | | | | | | x | |
| Pregnancy test [t] | x | x [t] | | | x | | | x | | | x | | | x | |
| Tumor assessments [u] | x | | | | x [v] | | | | | | x [v] | | | x [w] | x [w] |
| Bone scan | x [x,y] | See Footnotes "x" and "y." | | | | | | | | | | | | x [x,y] | x [x,y] |
| Head scan (CT or MRI scan) | x [x,z] | | | | | | | | | | | | | | |
| Prophylaxis with 10 mg of prednisone (or equivalent) for 3–5 consecutive days [aa, bb] | | x | | x | | | | | | | | | | | |
| Daily antihistamine prophylaxis [bb] | | x | x | x | | | | | | | | | | | |
| Prophylaxis antidiarrheal (2 mg of loperamide BID or equivalent, as allowed per local guidelines, 2 mg after each loose watery stool, and up to 16 mg per day or per local guidelines) [bb] | | If side effects are not tolerated, doses may be reduced. After one cycle without any diarrhea, continuation is at physician's discretion. If diarrhea occurs, it should be managed per the guidelines in Appendix 13, Table 2; antidiarrheal treatment should also be resumed with loperamide prophylaxis as needed. | | | | | | | | | | | | | |

**Appendix 1: Schedule of Activities**

| Assessment/Procedure | Screening (Days –28 to –1) | Treatment Cycle (28-Day Cycles) [a] | | | | | | | | | | | | SDDV [b] | Post-Treat. Follow-Up [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycles 1 and 2 | | | Cycle 3 | | | Cycle 4 | | | Cycles 5 and Beyond | | | | |
| | | D1 | D8 | D15 | D1 | D8 | D15 | D1 | D8 | D15 | D1 | D8 | D15 | | |
| Ipatasertib/placebo dispensing and accountability | | x [cc] | | | x | | | x | | | x | | | | |
| Atezolizumab/placebo administration | | x [cc] | | x | x | | x | x | | x | x | | x | | |
| Paclitaxel administration [dd] | | x [cc] | x | x | x | x | x | x | x | x | x | x | x | | |
| Record all historical cancer-related medications, radiotherapy, and surgical procedures | x | | | | | | | | | | | | | x | x |
| Concomitant medications [ee] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| Adverse events [ff] | x | x | x | x | x | x | x | x | x | x | x | x | x | x [ff] | x [gg] |
| EORTC QLQ-C30 [hh, ii] | | x | | x | x | | | x | | | x | | | x | x [ii] |
| PRO-CTCAE [hh] | | x | | x | x | | | x | | | x | | | x | |
| EQ-5D-5L [hh,ii] | | x | | x | x | | | x | | | x | | | x | x [ii] |
| PK and ADA samples | | Refer to Appendix 2 for the PK and ADA sample collection. | | | | | | | | | | | | | |
| Tumor tissue sample obtained at time of progression (optional) [jj] | | | | | | | | | | | | | | x [jj] | |
| Site personnel review of patient diary (medication, dosing log, and kit ID) | | x | x | x | x | x | x | x | x | x | x | x | x | x | |

## Appendix 1: Schedule of Activities

ADA = anti-drug antibody; BID = twice a day; CT = computed tomography; D = day; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; EQ-5D-5L = EuroQol 5-Dimension Questionnaire, 5-Level Version; FNA = fine-needle aspiration; $HbA_{1C}$ = glycosylated hemoglobin; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV–hepatitis B virus; HCV = hepatitis C virus; QoL = quality of life; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; NGS = next-generation sequencing; PK = pharmacokinetic; PRO = patient-reported outcome; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; RBR = Roche Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SDDV = study drug discontinuation visit; T3 = triiodothyronine; T4 = thyroxine; WGS = whole genome sequencing.

Notes: Results of standard-of-care tests or examinations performed prior to obtaining informed consent but within the screening window (Days −28 to −1) may be used for the study. Screening assessments are to be performed within 28 days preceding Day 1 of Cycle 1 unless otherwise noted, and patients must have adequate hematologic and organ function within 14 days before the first study treatment on Day 1 of Cycle 1, as defined in Section 4.1.1.1. All assessments or procedures are to be performed predose unless otherwise specified.

[a] Except for Day 1 of Cycle 1, all other study visits and assessments during the treatment period should be performed within ±3 days of the scheduled date. Please note that with rare exception, the actual study visit and IV study treatment administration should only occur on Days 1, 8, 15, or on Day 22 if any of the prior days must be skipped. Visit windows may be utilized to accommodate holidays, vacations, and unforeseen delays; however, study cycle day count continues without breaks (a sample calendar is presented in Appendix 6.

[b] The SDDV should occur approximately ≤ 28 days after the last administration of ipatasertib/placebo, atezolizumab/placebo, or paclitaxel, whichever is discontinued last, or prior to initiation of another anti-cancer treatment. If it is anticipated that the patient will be unable to return for a visit, then it is acceptable to perform this visit on the date of last study drug discontinuation.

[c] After treatment discontinuation, PROs and information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a 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 the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. *As of protocol Version 6, these long-term follow-up assessments are no longer required.*

[d] Viral serology includes HIV, HBsAg, total HBcAb, and HCV antibody. HIV serology will be performed as per local standard after any applicable local consenting requirement is met. HBV serology includes HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection, prior to randomization. HCV serology includes HCV antibody and (if HCV antibody test is positive) HCV RNA. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection, prior to randomization. If HCV antibody is positive, then need to test HCV RNA to confirm that HCV RNA is undetectable.

[e] Archival tissue (either formalin-fixed, paraffin-embedded tumor specimens or a minimum of 15 unstained serial paraffin slides) and an associated pathology report must be confirmed to be available prior to entry into the study. In the absence of archival tissue, newly obtained tissue biopsy samples of non-target lesions (excluding cytology, FNA specimens, and bone metastasis requiring decalcification) are acceptable (if it is assessable and the biopsy can be safely obtained). In general, a minimum of three core biopsies is preferred. If less than 15 slides or only two cores are available, a patient may still be eligible for the study, after Sponsor approval has been obtained and if sample contains a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method.

[f] Not applicable for a site that has not been granted approval for WGS. Samples will be collected on Day 1 of Cycle 1 only.

[g] To be performed on Day 1 of Cycle 1, the first tumor assessment ±7 days, and at the study drug discontinuation visit. Blood should be drawn before the administration of any study drug, if applicable.

[h] A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

[i] Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated.

[j] Vital signs include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature while the patient is sitting or supine in a comfortable position. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. Vital signs should be measured within 60 minutes prior to each in-clinic ipatasertib/placebo administration, atezolizumab/placebo infusion (one set may be performed to cover predose vital signs for both drug administrations), and between atezolizumab/placebo and paclitaxel infusions (on days when both drugs are administered). Refer to Section 4.5.5, Table 2, for the timing of vital sign measurements for the first and subsequent infusions. On days when no atezolizumab/placebo is given, one set may be performed as predose vital signs for both ipatasertib/placebo and paclitaxel. On paclitaxel dosing days, vital signs should be recorded prior to dosing and at the end of the infusion. Vital signs may be repeated if clinically indicated, during the infusion.

[k] Perform within 12 weeks prior to Day 1 of Cycle 1. If the left ventricular ejection fraction result as assessed by either of these imaging modalities is felt to be inconsistent with the clinical picture, then the investigator may choose an alternative modality (i.e., cardiac MRI scan), if this is consistent with local standard practice.

[l] A single 12-lead ECG measurement at screening and at the treatment discontinuation visit and may be obtained at unscheduled timepoints as clinically indicated (refer to Section 4.5.8). All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during the ECG recording.

[m] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[n] Laboratory samples should be drawn within 48 hours prior to study drug administration at the clinic with at least 8-hour fasting for glucose measurement as indicated. The chemistry and hematology results should be available to assess prior to dosing.

[o] Fasting serum chemistry panel (following ≥8-hour fast) includes glucose (plasma glucose is also acceptable per local practice), bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, magnesium, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH. At investigational sites in countries where bicarbonate may not be collected as part of the standard chemistry panel, bicarbonate will not be measured. Chemistry evaluation to be conducted per local guidelines.

[p] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).

[q] Fasting lipid profile, which includes total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides performed following a ≥8-hour fast, as well as (fasting or non-fasting) amylase, and lipase will be assessed at screening, every 3 cycles starting on Day 1 of Cycle 3 and at treatment discontinuation visit.

[r] C-reactive protein in serum collections will be assessed only on Day 1 of Cycle 1 prior to dosing.

[s] Urinalysis consists of pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[t] For women of childbearing potential, a negative serum pregnancy test must be confirmed either within 96 hours of Day 1, Cycle 1 study treatment administration, or within 7 days of Day 1 of Cycle 1 (in this case, confirmed by a negative urine pregnancy test on Day 1 of Cycle 1 prior to dosing). In addition, pregnancy tests (serum or urine) are to be performed within 96 hours of Day 1 of each treatment cycle, and a pregnancy test should be performed when clinically indicated. If urine pregnancy test is positive, it must be confirmed by a serum pregnancy test before any further study treatment may be administered. For all other women, documentation must be present in medical history confirming that patient is not of childbearing potential.

[u] Tumor assessments performed according to RECIST v1.1. The method used for a patient (CT or MRI scan or photographic measurements) must be the same throughout the study. An objective response should be confirmed by repeat assessments ≥ 4 weeks after initial documentation. A missed tumor assessment should be rescheduled as soon as possible. Images for tumor assessments will be prospectively collected to enable retrospective blinded independent central review when needed. Please note that PET/CT imaging is not an acceptable alternative to CT or MRI, unless the CT portion of the PET/CT scan is of diagnostic quality; in such cases where the CT portion is of diagnostic quality, *consult with* the Medical Monitor prior to using PET/CT for study-related tumor assessments.

[v] Tumor assessments should be calculated from Day 1 of Cycle 1 and completed during Week 8 and every 8 weeks thereafter. Therefore, the window for each scan will be the 7 days of the given week. Images for tumor assessments will be prospectively collected to enable retrospective blinded independent central review when needed (refer to the sample calendar in Appendix 6.

[w] At treatment discontinuation visit, tumor assessments should be performed only if not performed within the previous 6 weeks. If a patient discontinues from study treatment for any reason other than disease progression per RECIST v1.1, every effort should be made to obtain follow-up CT scans to assess disease response approximately every 8 weeks until documented progressive disease per RECIST v1.1, elective withdrawal from the study, or study completion or termination.

[x] Images for tumor assessments will be prospectively collected to enable retrospective blinded independent central review.

[y] An initial technetium bone scan should be performed within 6 weeks prior to Day 1 of Cycle 1. In addition, bone disease identified on bone imaging should be evaluated radiographically on contrast-enhanced CT or MRI scan or X-ray to ascertain the presence of bone destruction versus a healing reaction. For patients with known or suspected bone metastasis, follow-up bone scans should be performed during Days 16–28 of every fourth cycle (every 16 weeks) and at the study termination visit. If a patient discontinues from the study for any reason other than disease progression per RECIST v1.1, every effort should be made to obtain follow-up CT scans to assess disease response approximately every 8 weeks until documented progressive disease per RECIST v1.1. Please note that positron emission tomography imaging is not an acceptable alternative to the bone scan.

[z] Perform contrast-enhanced CT or MRI scan of head within 6 weeks prior to Day 1 of Cycle 1.

[aa] For the first cycle (or the first 28 days of triplet combination dosing) only: On days when patients will receive atezolizumab (typically, on Days 1 and 15), patients should receive at least 10 mg/day prednisone (or equivalent) as premedication prior to atezolizumab, followed by 10 mg/day prednisone (or equivalent) for 2–4 consecutive days thereafter, unless contraindicated. If institutional practice prior to paclitaxel administration is to give at least 10 mg/day prednisone on the day of paclitaxel, then the additional 10 mg of prophylactic prednisone should not be given on that day to prevent rash. Unless contraindicated, daily oral antihistamine prophylaxis should be used for at least the first cycle. It is suggested that a non-sedating oral antihistamine (such as loratadine, cetirizine, fexofenadine) and a longer-acting formulation be used. The daily oral antihistamine used for rash prophylaxis may be held on the days of paclitaxel infusion if the paclitaxel premedication already includes an antihistamine.

[bb] Following the unblinding of treatment assignments in Cohort 2, rash, and antidiarrheal prophylaxis is no longer applicable to patients in Arm B of Cohort 2.

[cc] Patients should receive their first dose of study drug on the day of enrollment, if possible. If this is not possible, the first dose should occur no later than 3 days after enrollment. Please note the specific instructions for corticosteroid prophylaxis in Section 4.3.3, applicable on days when the patient will receive both atezolizumab and paclitaxel. Please note that non-dosing of initial study drug on the day of enrollment may impact accurate data entry on the eCRFs, which are located in folders specifically labeled with the number of cycles and days. Following the unblinding of treatment assignments in Cohort 2, placebo for ipatasertib will no longer be administered to patients in Arm B of Cohort 2.

[dd] If the patient's weight changes by $>10\%$ from baseline during the study, the body surface area and dose of paclitaxel should be recalculated. Recalculation based on a lesser change from baseline weight is left to the investigator's discretion.

[ee] At screening and on Day 1 of Cycle 1, record all concomitant medications taken between 14 days prior to screening and Day 1 of Cycle 1; at subsequent timepoints, record new concomitant medications and any changes to the daily dosing. Actual intake of antidiarrheal and pain medications, antihistamines, steroids, and other premedications at each dosage change should be recorded by patients using the diary to record daily ipatasertib/placebo dosing and specifically any antidiarrheal, antihistamine, or analgesic medications used (prescribed or over the counter) taken during that cycle of treatment. The intake of analgesic, antihistamine, and loperamide medications will be reported on the Analgesics Medication, Antihistamine, and Targeted Loperamide Concomitant Medications eCRF, respectively (see Section 4.5.2).

[ff] 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 final 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 trial-related procedures until a final outcome can be reported.

[gg] Patients with an unresolved adverse event or serious adverse event will be followed until the event is resolved or stabilized, the patient is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the event. Refer to Section 5.6 for adverse events that occur after the adverse event reporting period (defined as 30 days after the final dose of study drug). An additional adverse event follow-up visit may be scheduled (even after the treatment discontinuation visit); follow-up by telephone for adverse event resolution date as applicable.

[hh] All PRO questionnaires are required to be completed prior to the administration of study treatment and/or prior to any other study assessment(s) that could bias patients' responses. The EORTC QLQ-C30, PRO-CTCAE, and EQ-5D-5L should be completed in this order (EORTC QLQ-C30 first, then PRO-CTCAE second, followed by the EQ-5D-5L last) on Day 1 of each cycle, on Day 15 of Cycles 1 and 2, and at the SDDV visit. The PRO-CTCAE questionnaire will be completed when available in the local language of the investigational site.

[ii] Selected scales of the EORTC QLQ-C30: the GHS/QoL (Questions 29 and 30), Physical Function (Questions 1–5), Role Function (Questions 6 and 7), Pain (Questions 9 and 19), Fatigue (Questions 10, 12, and 18) and Dyspnea (Question 8), as well as the EQ-5D-5L will be administered during post-treatment follow-up calls (or visits) approximately every 3 (±1) months until death. Questionnaires during the follow-up period do not need to be conducted in person (i.e., do not require an office visit); however, when administered by telephone, they must be conducted by interview assessment (using instructions and telephone scripts for administering the PRO assessments when available in the local language). These should be conducted prior to the disease follow-up tumor assessment, if applicable.

[jj] Tumor biopsy collection is optional for study participation. For patients who sign an Informed Consent Form for Optional Tumor Tissue Biopsy and if tumor biopsies can be obtained with minimal risk and discomfort to the patient, a tumor biopsy would be collected at the time of progression within 6 weeks of the progression assessment and prior to initiation of a new anti-cancer therapy; tumor biopsy of the growing lesion is preferred.

## Table 2 Schedule of Activities: Applicable after unblinding and thereafter

| Assessment/Procedure | Screening (Days –28 to –1) | Treatment Cycle (28-Day Cycles) [a] | | | | | | | | | | | | SDDV [b] | Post-Treat. Follow-Up [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycles 1 and 2 | | | Cycle 3 | | | Cycle 4 | | | Cycles 5 and Beyond | | | | |
| | | D1 | D8 | D15 | D1 | D8 | D15 | D1 | D8 | D15 | D1 | D8 | D15 | | |
| Signed informed consent(s) | x | | | | | | | | | | | | | | |
| Viral serology [d] | x [d] | | | | | | | | | | | | | | |
| Demographics, medical history, and prior cancer treatment | x | | | | | | | | | | | | | | |
| Tumor tissue sample submitted at screening [e] | x | | | | | | | | | | | | | | |
| Blood sample for WGS [f] | | x [f] | | | | | | | | | | | | | |
| Blood sample for biomarkers [g] | | x [g] | | | x | | | | | | | | | x | |
| Complete physical examination [h] | x | | | | | | | | | | | | | | |
| Limited physical examination [i] | | x | x | x | x | | x | x | | x | x | | | x | |
| Weight | x | x | | | x | | | x | | | x | | | x | |
| Height | x | | | | | | | | | | | | | | |
| Vital signs [j] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| ECOG Performance Status | x | x | | | x | | | x | | | x | | | x | |
| Cardiac function (ECHO or MUGA scan) | x [k] | | | | | | | | | | | | | | |
| 12-Lead ECG [l] | x | | | | | | | | | | | | | x | |

**Appendix 1: Schedule of Activities**

| Assessment/Procedure | Screening (Days –28 to –1) | Treatment Cycle (28-Day Cycles) [a] | | | | | | | | | | | | SDDV [b] | Post-Treat. Follow-Up [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycles 1 and 2 | | | Cycle 3 | | | Cycle 4 | | | Cycles 5 and Beyond | | | | |
| | | D1 | D8 | D15 | D1 | D8 | D15 | D1 | D8 | D15 | D1 | D8 | D15 | | |
| Hematology [m] | x | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x | |
| INR and PTT (or aPTT) | x | | | | | | | | | | | | | x | |
| Fasting serum chemistry [o] | x | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x [n] | x | |
| TSH, free T3 (or total T3), free T4 [p] | x | x | | | | | | x | | | x [p] | | | x | |
| Fasting lipid profile, and amylase and lipase [q] | x | | | | x [q] | | | | | | x [q] | | | x | |
| HbA1C | x | x | | | x | | | x | | | x | | | x | |
| C-reactive protein [r] | | x [r] | | | | | | | | | | | | | |
| Urinalysis [s] | x | As clinically indicated | | | | | | | | | | | | x | |
| Pregnancy test [t] | x | x [t] | | | x | | | x | | | x | | | x | |
| Tumor assessments [u] | x | | | | x [v] | | | | | | x [v] | | | x [w] | x [w] |
| Bone scan | x [x,y] | See Footnotes "x" and "y." | | | | | | | | | | | | x [x,y] | x [x,y] |
| Head scan (CT or MRI scan) | x [x,z] | | | | | | | | | | | | | | |
| Prophylaxis with 10 mg of prednisone (or equivalent) for 3–5 consecutive days [aa, bb] | | x | | x | | | | | | | | | | | |
| Daily antihistamine prophylaxis bb | | x | x | x | | | | | | | | | | | |
| Prophylaxis antidiarrheal (2 mg of loperamide BID or equivalent, as allowed per local guidelines, 2 mg after each loose watery stool, and up to 16 mg per day or per local guidelines) [bb] | | If side effects are not tolerated, doses may be reduced. After one cycle without any diarrhea, continuation is at physician's discretion. If diarrhea occurs, it should be managed per the guidelines in Appendix 13, Table 2; antidiarrheal treatment should also be resumed with loperamide prophylaxis as needed. | | | | | | | | | | | | | |

**Appendix 1: Schedule of Activities**

| Assessment/Procedure | Screening (Days −28 to −1) | Treatment Cycle (28-Day Cycles) a | | | | | | | | | | | | SDDV [b] | Post-Treat. Follow-Up [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Cycles 1 and 2 | | | Cycle 3 | | | Cycle 4 | | | Cycles 5 and Beyond | | | | |
| | | D1 | D8 | D15 | D1 | D8 | D15 | D1 | D8 | D15 | D1 | D8 | D15 | | |
| Ipatasertib dispensing and accountability | | x [cc] | | | x | | | x | | | x | | | | |
| Atezolizumab administration | | x [cc] | | x | x | | x | x | | x | x | | x | | |
| Paclitaxel administration [dd] | | x [cc] | x | x | x | x | x | x | x | x | x | x | x | | |
| Record all historical cancer-related medications, radiotherapy, and surgical procedures | x | | | | | | | | | | | | | x | x |
| Concomitant medications [ee] | x | x | x | x | x | x | x | x | x | x | x | x | x | x | |
| Adverse events [ff] | x | x | x | x | x | x | x | x | x | x | x | x | x | x [ff] | x [gg] |
| Tumor tissue sample obtained at time of progression (optional) [hh] | | | | | | | | | | | | | | x [hh] | |
| Site personnel review of patient diary (medication, dosing log, and kit ID) | | x | x | x | x | x | x | x | x | x | x | x | x | x | |

**Appendix 1: Schedule of Activities**

ADA = anti-drug antibody; BID = twice a day; CT = computed tomography; D = day; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; EQ-5D-5L = EuroQol 5-Dimension Questionnaire, 5-Level Version; FNA = fine-needle aspiration; HbA1C = glycosylated hemoglobin; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV–hepatitis B virus; HCV = hepatitis C virus; QoL = quality of life; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; NGS = next-generation sequencing; PK = pharmacokinetic; PRO = patient-reported outcome; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; RBR = Roche Biosample Repository; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; SDDV = study drug discontinuation visit; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; WGS = whole genome sequencing.

Notes: Results of standard-of-care tests or examinations performed prior to obtaining informed consent but within the screening window (Days –28 to –1) may be used for the study. Screening assessments are to be performed within 28 days preceding Day 1 of Cycle 1 unless otherwise noted, and patients must have adequate hematologic and organ function within 14 days before the first study treatment on Day 1 of Cycle 1, as defined in Section 4.1.1.1. All assessments or procedures are to be performed predose unless otherwise specified.

[a] Except for Day 1 of Cycle 1, all other study visits and assessments should be performed within ±3 days of the scheduled date. Please note that with rare exception, the actual study visit and IV study treatment administration should only occur on Days 1, 8, 15, or on Day 22 if any of the prior days must be skipped. Visit windows may be utilized to accommodate holidays, vacations, and unforeseen delays; however, study cycle day count continues without breaks (a sample calendar is presented in Appendix 6.

[b] The SDDV should occur approximately 28 (±3) days after the last administration of ipatasertib/placebo, atezolizumab/placebo, or paclitaxel, whichever is discontinued last, or prior to initiation of another anti-cancer treatment. If it is anticipated that the patient will be unable to return for a visit, then it is acceptable to perform this visit on the date of last study drug discontinuation.

[c] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 ( ± 1) months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a 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 the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. *As of protocol Version 6, these long-term follow-up assessments are no longer required.*

[d] Viral serology includes HIV, HBsAg, total HBcAb, and HCV antibody. HIV serology will be performed as per local standard after any applicable local consenting requirement is met. HBV serology includes HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection, prior to randomization. HCV serology includes HCV antibody and (if HCV antibody test is positive) HCV RNA. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an HCV infection, prior to randomization. If HCV antibody is positive, then need to test HCV RNA to confirm that HCV RNA is undetectable.

[e] Archival tissue (either formalin-fixed, paraffin-embedded tumor specimens or a minimum of 15 unstained serial paraffin slides) and an associated pathology report must be confirmed to be available prior to entry into the study. In the absence of archival tissue, newly obtained tissue biopsy samples of non-target lesions (excluding cytology, FNA specimens, and bone metastasis requiring decalcification) are acceptable (if it is assessable and the biopsy can be safely obtained). In general, a minimum of three core biopsies is preferred. If less than 15 slides or only two cores are available, a patient may still be eligible for the study, after Sponsor approval has been obtained and if sample contains a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method.

[f] Not applicable for a site that has not been granted approval for WGS. Samples will be collected on Day 1 of Cycle 1 only.

[g] To be performed on Day 1 of Cycle 1, the first tumor assessment ± 7 days, and at the study drug discontinuation visit. Blood should be drawn before the administration of any study drug, if applicable.

[h] A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

[i] Limited, symptom-directed physical examinations should be performed at specified postbaseline visits and as clinically indicated.

[j] Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature while the patient is sitting or supine in a comfortable position. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. Vital signs should be measured within 60 minutes prior to each in-clinic ipatasertib/placebo administration, atezolizumab/placebo infusion (one set may be performed to cover predose vital signs for both drug administrations), and between atezolizumab/placebo and paclitaxel infusions (on days when both drugs are administered). Refer to Section 4.5.5, Table 2, for the timing of vital sign measurements for the first and subsequent infusions. On days when no atezolizumab/placebo is given, one set may be performed as predose vital signs for both ipatasertib/placebo and paclitaxel. On paclitaxel dosing days, vital signs should be recorded prior to dosing and at the end of the infusion. Vital signs may be repeated if clinically indicated, during the infusion.

[k] Perform within 12 weeks prior to Day 1 of Cycle 1. If the left ventricular ejection fraction result as assessed by either of these imaging modalities is felt to be inconsistent with the clinical picture, then the investigator may choose an alternative modality (i.e., cardiac MRI scan), if this is consistent with local standard practice.

[l] A single 12-lead ECG measurement at screening and at the treatment discontinuation visit and may be obtained at unscheduled timepoints as clinically indicated (refer to Section 4.5.8). All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during the ECG recording.

[m] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and other cells).

[n] Laboratory samples should be drawn within 48 hours prior to study drug administration at the clinic with at least 8-hour fasting for glucose measurement as indicated. The chemistry and hematology results should be available to assess prior to dosing.

[o] Fasting serum chemistry panel (following ≥8-hour fast) includes glucose (plasma glucose is also acceptable per local practice), bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, magnesium, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total bilirubin, ALP, ALT, AST, and LDH. At investigational sites in countries where bicarbonate may not be collected as part of the standard chemistry panel, bicarbonate will not be measured. Chemistry evaluation to be conducted per local guidelines.

[p] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).

[q] Fasting lipid profile, which includes total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides performed following a ≥ 8-hour fast, as well as (fasting or non-fasting) amylase, and lipase will be assessed at screening, every 3 cycles starting on Day 1 of Cycle 3 and at treatment discontinuation visit.

[r] C-reactive protein in serum collections will be assessed only on Day 1 of Cycle 1 prior to dosing.

[s] Urinalysis consists of pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[t] For women of childbearing potential, a negative serum pregnancy test must be confirmed either within 96 hours of Day 1, Cycle 1 study treatment administration, or within 7 days of Day 1 of Cycle 1 (in this case, confirmed by a negative urine pregnancy test on Day 1 of Cycle 1 prior to dosing). In addition, pregnancy tests (serum or urine) are to be performed within 96 hours of Day 1 of each treatment cycle, and a pregnancy test should be performed when clinically indicated. If urine pregnancy test is positive, it must be confirmed by a serum pregnancy test before any further study treatment may be administered. For all other women, documentation must be present in medical history confirming that patient is not of childbearing potential.

[u] Tumor assessments performed according to RECIST v1.1. The method used for a patient (CT or MRI scan or photographic measurements) must be the same throughout the study. An objective response should be confirmed by repeat assessments ≥ 4 weeks after initial documentation. A missed tumor assessment should be rescheduled as soon as possible. Images for tumor assessments will be prospectively collected to enable retrospective blinded independent central review when needed. Please note that PET/CT imaging is not an acceptable alternative to CT or MRI, unless the CT portion of the PET/CT scan is of diagnostic quality; in such cases where the CT portion is of diagnostic quality, *consult with* the Medical Monitor prior to using PET/CT for study-related tumor assessments. As of protocol Version 5, images for tumor assessments will no longer be collected for blinded independent central review.

[v] Tumor assessments should be calculated from Day 1 of Cycle 1 and completed during Week 8 and every 8 weeks thereafter. Therefore, the window for each scan will be the 7 days of the given week. Images for tumor assessments will be prospectively collected to enable retrospective blinded independent central review when needed (refer to the sample calendar in Appendix 6).

[w] At treatment discontinuation visit, tumor assessments should be performed only if not performed within the previous 6 weeks. If a patient discontinues from study treatment for any reason other than disease progression per RECIST v1.1, every effort should be made to obtain follow-up CT scans as per standard of care to assess disease response until documented progressive disease per RECIST v1.1, elective withdrawal from the study, or study completion or termination.

[x] Images for tumor assessments will be prospectively collected to enable retrospective blinded independent central review. As of protocol Version 5, images for tumor assessments will no longer be collected for blinded independent central review.

[y] An initial technetium bone scan should be performed within 6 weeks prior to Day 1 of Cycle 1. In addition, bone disease identified on bone imaging should be evaluated radiographically on contrast-enhanced CT or MRI scan or X-ray to ascertain the presence of bone destruction versus a healing reaction. For patients with known or suspected bone metastasis, follow-up bone scans should be performed every 16 weeks (window is 7 days of the given week) and at the study termination visit only if not performed within the previous 12 weeks. If a patient discontinues from the study for any reason other than disease progression per RECIST v1.1, every effort should be made to obtain follow-up CT scans and bone scans as per standard of care to assess disease until documented progressive disease per RECIST v1.1. Please note that positron emission tomography imaging is not an acceptable alternative to the bone scan.

[z] Perform contrast-enhanced CT or MRI scan of head within 6 weeks prior to Day 1 of Cycle 1.

[aa] For the first cycle (or the first 28 days of triplet combination dosing) only: On days when patients will receive atezolizumab (typically, on Days 1 and 15), patients should receive at least 10 mg/day prednisone (or equivalent) as premedication prior to atezolizumab, followed by 10 mg/day prednisone (or equivalent) for 2–4 consecutive days thereafter, unless contraindicated. If institutional practice prior to paclitaxel administration is to give at least 10 mg/day prednisone on the day of paclitaxel, then the additional 10 mg of prophylactic prednisone should not be given on that day to prevent rash. Unless contraindicated, daily oral antihistamine prophylaxis should be used for at least the first cycle. It is suggested that a non-sedating oral antihistamine (such as loratadine, cetirizine, fexofenadine) and a longer-acting formulation be used. The daily oral antihistamine used for rash prophylaxis may be held on the days of paclitaxel infusion if the paclitaxel premedication already includes an antihistamine.

[bb] As of protocol Version 5, rash and antidiarrheal prophylaxis is no longer applicable to patients in Arm C of Cohort 1 and Arm B of Cohort 2.

[cc] Patients should receive their first dose of study drug on the day of enrollment, if possible. If this is not possible, the first dose should occur no later than 3 days after enrollment. Please note the specific instructions for corticosteroid prophylaxis in Section 4.3.3, applicable on days when the patient will receive both atezolizumab and paclitaxel. Please note that non-dosing of initial study drug on the day of enrollment may impact accurate data entry on the eCRFs, which are located in folders specifically labeled with the number of cycles and days. As of protocol Version 5, placebo for ipatasertib and placebo for atezolizumab will no longer be administered.

[dd] If the patient's weight changes by > 10% from baseline during the study, the body surface area and dose of paclitaxel should be recalculated. Recalculation based on a lesser change from baseline weight is left to the investigator's discretion.

[ee] At screening and on Day 1 of Cycle 1, record all concomitant medications taken between 14 days prior to screening and Day 1 of Cycle 1; at subsequent timepoints, record new concomitant medications and any changes to the daily dosing. The intake of analgesic, antihistamine, and loperamide medications will be reported on the Concomitant Medications eCRF(see Section 4.5.2).

[ff] 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 final 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 trial-related procedures until a final outcome can be reported.

[gg] Patients with an unresolved adverse event or serious adverse event will be followed until the event is resolved or stabilized, the patient is lost to follow-up, or it has been determined that the study treatment or participation is not the cause of the event. Refer to Section 5.6 for adverse events that occur after the adverse event reporting period (defined as 30 days after the final dose of study drug). An additional adverse event follow-up visit may be scheduled (even after the treatment discontinuation visit); follow-up by telephone for adverse event resolution date as applicable.

[hh] Tumor biopsy collection is optional for study participation. For patients who sign an Informed Consent Form for Optional Tumor Tissue Biopsy and if tumor biopsies can be obtained with minimal risk and discomfort to the patient, a tumor biopsy would be collected at the time of progression within 6 weeks of the progression assessment and prior to initiation of a new anti-cancer therapy; tumor biopsy of the growing lesion is preferred.

# Appendix 2
# Schedule of Pharmacokinetic and Immunogenicity Samples

As of protocol Version 5, blood samples for PK and ADA analyses will no longer be collected.

| Visit | Timepoint(s) | Sample Type(s) |
|---|---|---|
| Day 1 of Cycle 1 | Prior to start of first atezolizumab/placebo infusion | • Atezolizumab PK (serum)<br>• Atezolizumab ADA (serum) |
| | 30 (± 10) minutes after end of atezolizumab/placebo infusion | • Atezolizumab PK (serum) |
| | 1–3 hours after ipatasertib/placebo dose | • Ipatasertib and G-037720 (plasma) |
| Day 15 of Cycle 1 | Prior to start of atezolizumab/placebo infusion | • Atezolizumab PK (serum)<br>• Atezolizumab ADA (serum) |
| | Prior to ipatasertib/placebo dose [a] | • Ipatasertib and G-037720 (plasma) |
| | 1–3 hours after ipatasertib/placebo dose | • Ipatasertib and G-037720 (plasma) |
| Day 1 of Cycle 2 | Prior to start of atezolizumab/placebo infusion | • Atezolizumab PK (serum)<br>• Atezolizumab ADA (serum) |
| Day 1 of Cycle 3 | Prior to start of atezolizumab/placebo infusion | • Atezolizumab PK (serum)<br>• Atezolizumab ADA (serum) |
| Day 15 of Cycle 3 | Prior to ipatasertib/placebo dose [a] | • Ipatasertib and G-037720 (plasma) |
| | 2–4 hours after ipatasertib/placebo dose | • Ipatasertib and G-037720 (plasma) |
| Day 1 of Cycle 4 | Prior to start of atezolizumab/placebo infusion | • Atezolizumab PK (serum)<br>• Atezolizumab ADA (serum) |
| Day 1 of Cycle 8 | Prior to start of atezolizumab/placebo infusion | • Atezolizumab PK (serum)<br>• Atezolizumab ADA (serum) |
| Day 1 of Cycles 12 and 16 | Prior to start of atezolizumab/placebo infusion | • Atezolizumab PK (serum)<br>• Atezolizumab ADA (serum) |
| SDDV (≤ 28 days after final dose) | At visit | • Atezolizumab PK (serum)<br>• Atezolizumab ADA (serum) |

ADA = anti-drug antibody; PK = pharmacokinetic; SDDV = study drug discontinuation visit.

Notes: Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays. Dose time on the day before and day of PK sampling should be accurately reported. Any incidence of vomiting within 3 hours after ipatasertib administration should also be recorded for the day of PK sampling. PK sampling timepoint should be accurately reported. With the exception of the Cycle 1, Day 1 visit, if 3 or more consecutive doses of ipatasertib/placebo are withheld immediately prior to the PK sample collection, the sample collection may be delayed to another day when at least 3 consecutive days of ipatasertib/placebo dosing have been administered. The sampling can be performed any day after Day 12 of the relevant cycle corresponding with a planned ipatasertib/placebo dosing day. Prior to start of atezolizumab/placebo and ipatasertib/placebo dose = 0 to 3 hours prior to dosing of the drug(s) on the day of the visit.

# Appendix 3
# Eastern Cooperative Oncology Group Performance Status Scale

| Grade | Description |
|---|---|
| 0 | Fully active; able to carry on all pre-disease 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 4
# Preexisting Autoimmune Diseases and Immune Deficiencies

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 listed in the table below 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-related 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). Caution should be used when considering atezolizumab for patients who have previously experienced a severe or life-threatening skin adverse reaction while receiving another immunostimulatory anti-cancer agent. The Medical Monitor *is available to advise on* any uncertainty over autoimmune exclusions.

## Autoimmune Diseases and Immune Deficiencies

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

# Appendix 5
# Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) (Eisenhauer et al. 2009), are presented below, with the addition of explanatory text as needed for clarity.[1]

## TUMOR MEASURABILITY

At baseline, tumor lesions *and* lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

## DEFINITION OF MEASURABLE LESIONS

### Tumor Lesions

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

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$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 $\geq$15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

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

## DEFINITION OF NON-MEASURABLE LESIONS

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

## SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

- Technetium-99m bone scans, positron emission tomography $(PET)$ scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

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

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

## METHODS FOR ASSESSING 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 *not usually* more than 4 weeks *prior to* the beginning of the treatment.

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

### CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and $\geq$10 mm in diameter 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 *because* 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 AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is $\leq$5 mm. When CT scans have slice thickness of $>$5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (*with or* without *MRI* IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (*with* or *without MRI IV contrast*) 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 and interpretation of non-target disease

or new lesions on a different modality *because*, the same lesion may appear to have a different size using a new modality.

## ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, *AND* HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be used for objective tumor evaluation.

## ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

## IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

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

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

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geq 15$ mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being $20 \times 30$ mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis $\geq 10$ mm

but $<$15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

## CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

### Measuring 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 node regresses to $<$10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, $given\ that$ a normal lymph node is defined as having a short axis of $<$10 mm.

### Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement 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 $is$ too small to measure, a default value of 5 mm should be assigned and "too small to measure" 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 $is$ too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is $<5$ mm, and in that case "too small to measure" should not be ticked.

### Measuring Lesions That Split or Coalesce *During* Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining *the* maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

## EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to $<10$ mm in *the* short axis. Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "*unequivocal* progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis $<10$ mm), this should be captured on the CRF as part of the assessment of non-target lesions.

## RESPONSE CRITERIA

## CRITERIA FOR TARGET LESIONS

Definitions of the *following* criteria used to determine objective tumor response for target lesions are provided:

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

  Any pathological lymph nodes must have reduction in short axis to $<10$ mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of $\geq 5$ mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for *a* CR or *a* PR nor sufficient increase to qualify for PD

## CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions

  All lymph nodes must be non-pathological in size ($<$10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions
- PD: Unequivocal progression of existing non-target lesions

## SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

### Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

## NEW LESIONS

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

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

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

## CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients.

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

### Table 1 Criteria for Overall Response at a Single Timepoint

| Target Lesions | Non-Target Lesions | New Lesions | *Timepoint* Response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | Non-CR/non-PD *or* *NE* | No | PR |
| PR | *CR, non-CR*/Non-PD, or *NE* | No | PR |
| SD | *CR, non-CR*/Non-PD, or *NE* | No | SD |
| *NE* | Non-PD | No | NE |
| PD | Any | Yes or no | PD |
| Any | PD | Yes or no | PD |
| Any | Any | Yes | PD |
| *CR* | *NED* [b] | *No* | *CR* |
| *PR* | *NED* [b] | *No* | *PR* |
| *SD* | *NED* [b] | *No* | *SD* |
| *NED* [a] | *Non-CR/non-PD* | *No* | *Non-CR/non-PD* |
| *NED* [a] | *CR* | *No* | *CR* |
| *NED* [a] | *NE* | *No* | *NE* |
| *NED* [a] | *NED* [b] | *No* | *NED* |

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

[a] *No target lesions identified at baseline*

[b] *No non-target lesions identified at baseline.*

## MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging *or* measurement is *performed* at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, 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 lesions 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.

## SPECIAL NOTES ON RESPONSE ASSESSMENT

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

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

*Fluorodeoxyglucose (FDG)-PET is **not yet validated** for use in clinical trials to determine response but may complement CT/MRI in the assessment of progression.*

*FDG-PET imaging to identify new lesions is described in the following table.*

| *Baseline FDG-PET* | *Post-Baseline FDG-PET* | *Determination* |
|---|---|---|
| *Negative FDG-PET* | *Positive FDG-PET* | *New lesion (PD)* |
| *None* | *Positive FDG-PET corresponds to a new site of disease confirmed by CT/MRI* | *New lesion (PD)* |
| *None* | *Positive FDG-PET not confirmed as a new site of disease on CT/MRI* | *Additional follow-up CT/MRI scans are needed to determine if there is truly progression occurring at that site.*<br>*If so, new lesion (PD) with the date of PD being the date of the initial abnormal FDG-PET scan date*<br>*If not, it is not a new lesion.* |
| *None* | *Positive FDG-PET that corresponds to a preexisting site of disease on CT/MRI that is not progressing on the basis of the anatomic images* | *Not a new lesion* |

*CT =computed tomography; FDG =fluorodeoxyglucose; MRI =magnetic resonance imaging; PD =progressive disease; PET =positron emission tomography.*

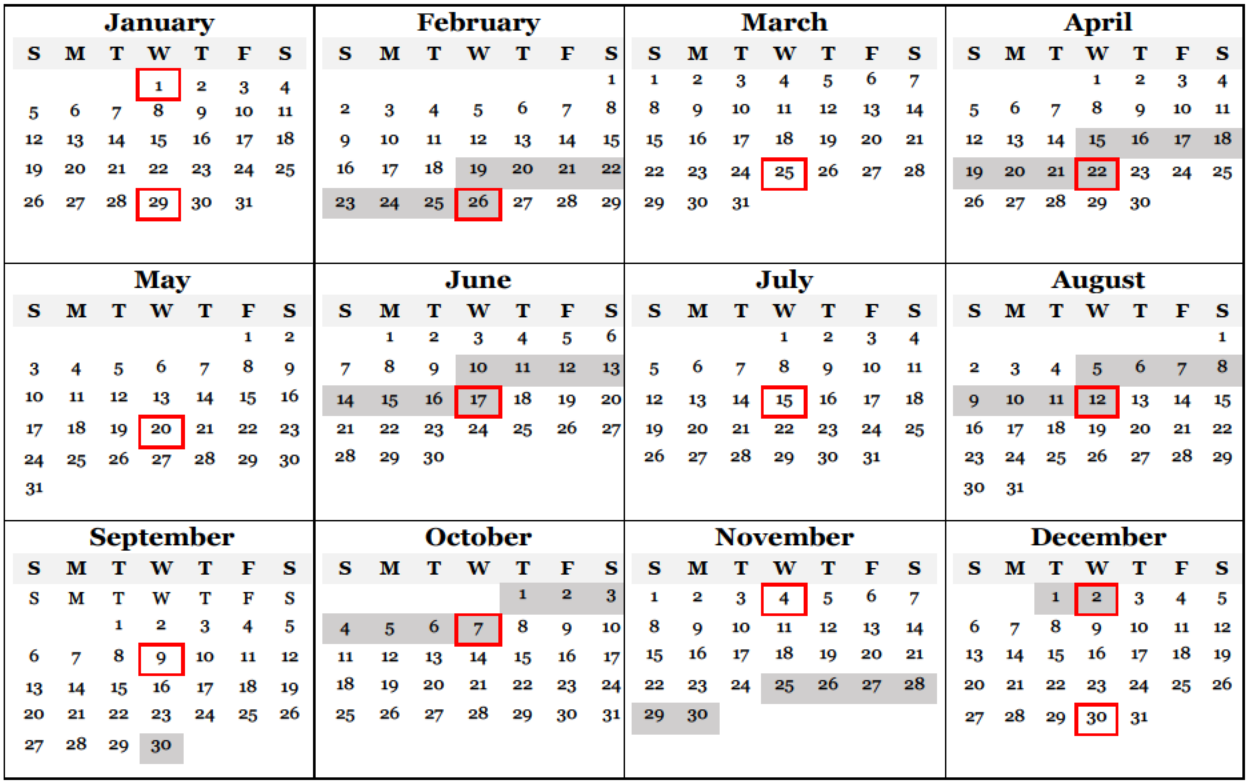
*Note: A positive FDG-PET scan lesion indicates one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.*

## REFERENCES

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.

*Schwartz LH., Litiére S, de Vries SE, et al. RECIST 1.1–update and clarification: from RECIST Committee. Eur J Cancer 2016; 62:132–7.*

# Appendix 6
# Example of Treatment Cycle and Tumor Assessment Calendar



# Appendix 7
# 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 treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Maintain an adequate airway.
3. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
4. Continue to observe the patient and document observations.

# Appendix 8
# ASCO/CAP Estrogen Receptor and Progesterone Receptor Guideline Recommendations

## Summary of ASCO/CAP ER and PgR Guideline Recommendations

**Optimal tissue handling requirements***
***Revised per the 2011 ASCO/CAP Clinical Notice on HER2 and ER/PgR**

**Recommendation:**

Time from tissue acquisition to fixation should be ≤ one hour. Samples for ER and PgR testing are fixed in 10% NBF for 6–72 hours. Samples should be sliced at 5-mm intervals after appropriate gross inspection and margins designation and placed in sufficient volume of NBF to allow adequate tissue penetration. If tumor comes from remote location, it should be bisected through the tumor on removal and sent to the laboratory immersed in a sufficient volume of NBF. Cold ischemia time, fixative type, and time the sample was placed in NBF must be recorded.

As in the ASCO/CAP HER2 guideline, storage of slides for more than 6 weeks before analysis is not recommended.

Time tissue is removed from patient, time tissue is placed in fixative, duration of fixation, and fixative type must be recorded and noted on accession slip or in report.

**Optimal internal validation procedure**

**Recommendation:**

Validation of any test must be done before test is offered. See separate article on testing validation (Fitzgibbons et al[1]).

Validation must be done using a clinically validated ER or PgR test method.

Revalidation should be done whenever there is a significant change to the test system, such as a change in the primary antibody clone or introduction of new antigen retrieval or detection systems.

**Optimal internal QA procedures**

**Recommendation:**

Initial test validation. See separate article on testing validation (Fitzgibbons et al[1]).

Ongoing quality control and equipment maintenance.

Initial and ongoing laboratory personnel training and competency assessment.

Use of standardized operating procedures including routine use of external control materials with each batch of testing and routine evaluation of internal normal epithelial elements or the inclusion of normal breast sections on each tested slide, wherever possible.

Regular, ongoing assay reassessment should be done at least semiannually (as described in Fitzgibbons et al[1]). Revalidation is needed whenever there is a significant change to the test system.

Ongoing competency assessment and education of pathologists.

**Optimal external proficiency assessment**

**Recommendation:**

Mandatory participation in external proficiency testing program with at least two testing events (mailings) per year.

Satisfactory performance requires at least 90% correct responses on graded challenges for either test.

**Comments:**

Unsatisfactory performance will require laboratory to respond according to accreditation agency program requirements.

**Optimal laboratory accreditation**

**Recommendation:**

On-site inspection every other year with annual requirement for self-inspection.

**Comments:**

Reviews laboratory validation, procedures, QA results and processes, and reports.

Unsuccessful performance results in suspension of laboratory testing for ER or PgR.

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor; IHC, immunohistochemistry; QA, quality assurance; NBF, neutral buffered formalin; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; HER2, human epidermal growth factor receptor 2.

1. Fitzgibbons PL, Murphy DA, Hammond ME, et al. Recommendations for validating estrogen and progesterone receptor immunohistochemistry assays. *Arch Pathol Lab Med.* 2010;134:930–935.

## REFERENCE

Fitzgibbons PL, Murphy DA, Hammond ME, et al. Recommendations for validating estrogen and progesterone receptor immunohistochemistry assays. Arch Path Lab Med 20101;134;930–5.

# Appendix 9
# ASCO/CAP HER2 Test Guideline Recommendations

**Table 1.** Summary of All Recommendations (original recommendations and focused update recommendations)

| Topic | 2013 Recommendations | 2018 Focused Update Recommendations |
|---|---|---|
| Specimens to be tested | All newly diagnosed patients with breast cancer must have a HER2 test performed. Patients who then develop metastatic disease must have a HER2 test performed in a metastatic site, if tissue sample is available. | No change. |
| Optimal algorithm for HER2 testing | Must report HER2 test result as positive for HER2 if:<br>IHC 3+ based on circumferential membrane staining that is complete, intense<br>ISH positive based on:<br>Single-probe average *HER2* copy number ≥ 6.0 signals/cell<br>Dual-probe *HER2*/CEP17 ratio of ≥ 2.0; with an average *HER2* copy number ≥ 4.0 signals/cell<br>Dual-probe *HER2*/CEP17 ratio of ≥ 2.0; with an average *HER2* copy number < 4.0;<br>Dual-probe *HER2*/CEP17 ratio of < 2.0 with an average *HER2* copy number ≥ 6.0 signals/cell<br>Must report HER2 test result as equivocal and order reflex test (same specimen using the alternative test) or new test (new specimen, if available, using same or alternative test) if:<br>IHC 2+ based on circumferential membrane staining that is incomplete and/or weak to moderate and within > 10% of the invasive tumor cells or complete and circumferential membrane staining that is intense and within ≤ 10% of the invasive tumor cells<br>ISH equivocal based on:<br>Single-probe ISH average *HER2* copy number ≥ 4.0 and ≤ 6.0 signals/cell<br>Dual-probe *HER2*/CEP17 ratio of < 2.0 with an average *HER2* copy number ≥ 4.0 and ≤ 6.0 signals/cell<br>Must report HER2 test result as negative if a single test (or both tests) performed show:<br>IHC 1+ as defined by incomplete membrane staining that is faint or barely perceptible and within > 10% of the invasive tumor cells<br>IHC 0 as defined by no staining observed or membrane staining that is incomplete and is faint or barely perceptible and within ≤ 10% of the invasive tumor cells<br>ISH negative based on:<br>Single-probe average *HER2* copy number < 4.0 signals/cell<br>Dual-probe *HER2*/CEP17 ratio of < 2.0 with an average *HER2* copy number of 4.0 signals/cell<br>Must report HER2 test result as indeterminate if technical issues prevent one or both tests (IHC and ISH) from being reported as positive, negative, or equivocal. Conditions may include:<br>Inadequate specimen handling<br>Artifacts (crush or edge artifacts) that make interpretation difficult<br>Analytic testing failure<br>Another specimen should be requested for testing to determine HER2 status.<br>Reason for indeterminate testing should be noted in a comment in the report. | 1. In the revised Figure 1, the revised definition of IHC 2+ (equivocal) is invasive breast cancer with "weak to moderate complete membrane staining observed in > 10% of tumor cells."<br>2. In the revised Table 2, it is now stated that, on the basis of some criteria (including a tumor grade 3), "If the initial HER2 test result in a core needle biopsy specimen of a primary breast cancer is negative, a new HER2 test may be ordered on the excision specimen . . ."<br>3. If a case has a *HER2*/CEP17 ratio of ≥ 2.0 but the average *HER2* signals/cell is < 4.0, a definitive diagnosis will be rendered based on additional work-up. If not already assessed by the institution or laboratory performing the ISH test, IHC testing for HER2 should be performed using sections from the same tissue sample used for ISH, and the slides from both ISH and IHC should be reviewed together to guide the selection of areas to score by ISH (local practice considerations will dictate the best procedure to accomplish this concomitant assessment):<br>a. If the IHC result is 3+, diagnosis is HER2 positive<br>b. If the IHC result is 2+, recount ISH by having an additional observer, blinded to previous ISH results, count at least 20 cells that include the area of invasive cancer with IHC 2+ staining:<br>If reviewing the count by the additional observer changes the result into another ISH category, the result should be adjudicated per internal procedures to define the final category.<br>If the count remains an average of < 4.0 *HER2* signals/cell and the *HER2*/CEP17 ratio is ≥ 2.0, diagnosis is HER2 negative with a comment*<br>c. If the IHC result is 0 or 1+, diagnosis is HER2 negative with a comment.*<br>4. If a case has an average of ≥ 6.0 *HER2* signals/cell with a *HER2*/CEP17 ratio of < 2.0, formerly diagnosed as ISH positive for HER2, a definitive diagnosis will be rendered based on additional work-up. If not already assessed by the institution or laboratory performing the ISH test, IHC testing for HER2 should be performed using sections from the same tissue sample used for ISH, and the slides from both ISH and IHC should be reviewed together to guide the selection of areas to score by ISH (local practice considerations will dictate the best procedure to accomplish this concomitant review):<br>a. If the IHC result is 3+, diagnosis is HER2 positive<br>b. If the IHC result is 2+, recount ISH by having an additional observer, blinded to previous ISH results, count at least 20 cells that include the area of invasion with IHC 2+ staining:<br>If reviewing the count by the additional observer changes the result into another ISH category, the result should be adjudicated per internal procedures to define the final category<br>If the *HER2*/CEP17 ratio remains < 2.0 with ≥ 6.0 *HER2* signals/cell, diagnosis is HER2 positive<br>c. If the IHC result is 0 or 1+, diagnosis is HER2 negative with a comment*<br>5. If the case has an average *HER2* signals/tumor cell of ≥ 4.0 and < 6.0 and the *HER2*/CEP17 ratio is < 2.0, formerly diagnosed as ISH equivocal for HER2, a definitive diagnosis will be rendered based on additional work-up. If not already assessed by the institution or laboratory performing the ISH test, IHC testing for HER2 should be performed using sections from the same tissue sample used for ISH, and the slides from both ISH and IHC should be reviewed together to guide the selection of areas to score by ISH (local practice considerations will dictate the best procedure to accomplish this concomitant review):<br>a. If the IHC result is 3+, diagnosis is HER2 positive<br>b. If the IHC result is 2+, recount ISH by having an additional observer, blinded to previous ISH results, count at least 20 cells that include the area of invasion with IHC 2+ staining: |

(continued on following page)

## Appendix 9: ASCO/CAP HER2 Test Guideline Recommendations

**Table 1.** Summary of All Recommendations (original recommendations and focused update recommendations) (continued)

| Topic | 2013 Recommendations | 2018 Focused Update Recommendations |
|---|---|---|
| | | If reviewing the count by the additional observer changes the result into another ISH category, the result should be adjudicated per internal procedures to define the final category<br>If the count remains an average of ≥ 4.0 and < 6.0 *HER2* signals/cell with a *HER2*/CEP17 ratio of < 2.0, diagnosis is HER2 negative with a comment*<br>c. If the IHC result is 0 or 1+, diagnosis is HER2 negative with a comment* |
| ISH rejection criteria | Test is rejected and repeated if:<br>Controls are not as expected<br>Observer cannot find and count at least two areas of invasive tumor<br>> 25% of signals are unscorable due to weak signals<br>> 10% of signals occur over cytoplasm<br>Nuclear resolution is poor<br>Autofluorescence is strong<br>Report **HER2 test result as Indeterminate** as per parameters described. | No change |
| ISH interpretation | The pathologist should scan the entire ISH slide before counting at least 20 cells or use IHC to define the areas of potential *HER2* amplification.<br>If there is a second population of cells with increased *HER2* signals/cell and this cell population consists of > 10% of tumor cells on the slide (defined by image analysis or visual estimation of the ISH or IHC slide), a separate counting of at least 20 nonoverlapping cells must also be performed within this cell population and reported.<br>For brightfield ISH, counting requires comparison between patterns in normal breast and tumor cells because artifactual patterns may be seen that are difficult to interpret. If tumor cell pattern is neither normal nor clearly amplified, test should be submitted for expert opinion. | The pathologist should scan the entire ISH slide before counting at least 20 cells or use IHC to define the areas of potential *HER2* amplification.<br>If there is a second population of contiguous cells with increased *HER2* signals/cell and this cell population consists of > 10% of tumor cells on the slide (defined by image analysis or visual estimation of the ISH or IHC slide), a separate counting of at least 20 nonoverlapping cells must also be performed within this cell population and reported. |
| Acceptable (IHC and ISH) tests | Should preferentially use an FDA-approved IHC, brightfield ISH, or FISH assay. | No change |
| IHC rejection criteria | Test is rejected and repeated or tested by FISH if:<br>Controls are not as expected<br>Artifacts involve most of sample<br>Sample has strong membrane staining of normal breast ducts (internal controls) | No change |
| IHC interpretation criteria | Should interpret IHC test using a threshold of > 10% of tumor cells that must show homogeneous, dark circumferential (chicken wire) pattern to call result 3+, HER2 positive. | No change |
| Reporting requirements for all assay types | Report must include guideline-detailed elements except for changes to reporting requirement and algorithms defined in this table. | No change |
| Optimal tissue handling requirements | Time from tissue acquisition to fixation should be as short as possible; samples for HER2 testing are fixed in 10% neutral buffered formalin for 6-72 hours; cytology specimens must be fixed in formalin.<br>Samples should be sliced at 5- to 10-mm intervals after appropriate gross inspection and margin designation and placed in a sufficient volume of neutral buffered formalin.<br>Any exceptions to this process must be included in the report. | No change |
| Optimal tissue sectioning requirements | Sections should ideally not be used for HER2 testing if cut > 6 weeks earlier; this may vary with primary fixation or storage conditions | No change |
| Optimal internal validation procedure | Validation of test must be performed before test is offered | No change |
| Optimal initial test validation | Laboratories performing these tests should be following all accreditation requirements, one of which is initial testing validation. The laboratory should ensure that initial validation conforms to the published 2010 ASCO/CAP recommendations for IHC testing of ER and PgR guideline validation requirements with 20 negative and 20 positive for FDA-approved assays and 40 negative and 40 positive for LDTs. This requirement does not apply to assays that were previously validated in conformance with the 2007 ASCO/CAP HER2 testing guideline, and those who routinely participate in external proficiency testing for HER2 tests, such as the program offered by CAP. | No change |

(continued on following page)

**Table 1.** Summary of All Recommendations (original recommendations and focused update recommendations) (continued)

| Topic | 2013 Recommendations | 2018 Focused Update Recommendations |
|---|---|---|
| Optimal initial test validation | Laboratories are responsible for ensuring the reliability and accuracy of their testing results, by compliance with accreditation and proficiency testing requirements for HER2 testing assays. Specific concordance requirements are not required. | No change |
| Optimal monitoring of test concordance between methods | See text following under Optimal Laboratory Accreditation | No change |
| Optimal internal QA procedures | Should review and document external and internal controls with each test and each batch of tests.<br>Ongoing quality control and equipment maintenance<br>Initial and ongoing laboratory personnel training and competency assessment<br>Use of standardized operating procedures including routine use of control materials<br>Revalidation of procedure if changed<br>Ongoing competency assessment and documentation of the actions taken as a part of the laboratory record. | No change |
| Optimal external proficiency assessment | Participation in and successful completion of external proficiency testing program with at least two testing events (mailings) a year<br>Satisfactory performance requires at least 90% correct responses on graded challenges for either test<br>Unsatisfactory performance will require laboratory to respond according to accreditation agency program requirements | No change |
| Optimal laboratory accreditation | Onsite inspection every other year with annual requirement for self-inspection<br>Reviews laboratory validation, procedures, QA results and processes, results, and reports<br>Unsatisfactory performance results in suspension of laboratory testing for HER2 for that method | No change |

Abbreviations: CAP, College of American Pathologists; CEP17, chromosome enumeration probe 17; ER, estrogen receptor; FDA, US Food and Drug Administration; FISH, fluorescent in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; LDT, laboratory-developed test; PgR, progesterone receptor; QA, quality assurance.
*Refer to text for the specific comments associated with each recommendation.

## REFERENCES

Wolff AC, Hale Hammond ME, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice guideline focused update. J Clin Oncol 2018;36:2105–22.

# Appendix 10
# European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire (EORTC QLQ-C30)

Note: Copies of the official version of the selected scales of the EORTC QLQ-C30 along with instructions for administration of the questionnaire during the follow-up period will be provided to sites.

**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.

| | 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 10: European Organisation for Research and Treatment of Cancer Quality of Life–Core 30 Questionnaire (EORTC QLQ-C30)

ENGLISH

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

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

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

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

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

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

# Appendix 11
# EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L)

Note: Copies of the official version of the ED-5D-5L along with instructions for administration of the questionnaire during the follow-up period will be provided to sites.


**Health Questionnaire**

**English version for the UK**

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

**MOBILITY**

I have no problems in walking about ☐
I have slight problems in walking about ☐
I have moderate problems in walking about ☐
I have severe problems in walking about ☐
I am unable to walk about ☐

**SELF-CARE**

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

**USUAL ACTIVITIES** *(e.g. work, study, housework, family or leisure activities)*

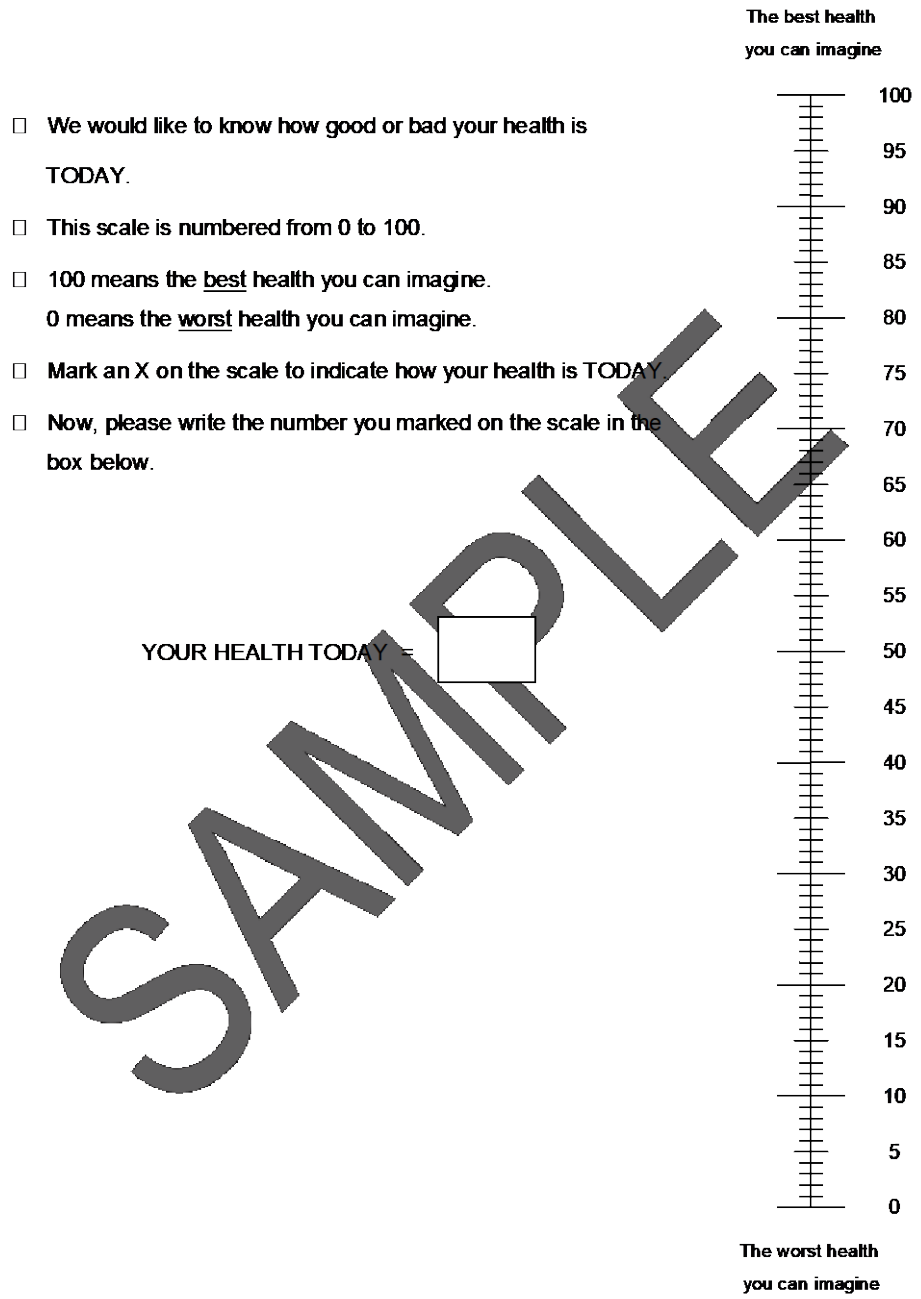
I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

**PAIN / DISCOMFORT**

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

**ANXIETY / DEPRESSION**

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐




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

YOUR HEALTH TODAY =

# Appendix 12
# Selected Items from the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

## NCI PRO-CTCAE™ ITEMS

**Item Library Version 1.0**

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ⊠ in the one box that best describes your experiences over the past 7 days...

| | | | | | |
|---|---|---|---|---|---|
| 1. | In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 2. | In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 3. | In the last 7 days, how OFTEN did you have NAUSEA? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | | | | |
|---|---|---|---|---|---|
| 4. | In the last 7 days, how OFTEN did you have VOMITING? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |
| | In the last 7 days, what was the SEVERITY of your VOMITING at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |

| | | | | | |
|---|---|---|---|---|---|
| 5. | In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)? | | | | |
| | ○ Never | ○ Rarely | ○ Occasionally | ○ Frequently | ○ Almost constantly |

| | | |
|---|---|---|
| 6. | In the last 7 days, did you have any RASH? | |
| | ○ Yes | ○ No |

## NCI PRO-CTCAE™ ITEMS

**Item Library Version 1.0**

| | | | | | |
|---|---|---|---|---|---|
| 7. | In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 8. | In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST? | | | | |
| | ○ None | ○ Mild | ○ Moderate | ○ Severe | ○ Very severe |
| | In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

| | | | | | |
|---|---|---|---|---|---|
| 9. | In the last 7 days, how BOTHERED were you by the side effect(s) of your treatment? | | | | |
| | ○ Not at all | ○ A little bit | ○ Somewhat | ○ Quite a bit | ○ Very much |

# Appendix 13
# Overall Guidelines for Management of Patients Who Experience Adverse Events

## DOSE MODIFICATIONS

Guidelines for dosage modification and treatment interruption or discontinuation are provided below. There will be no dose modifications for atezolizumab/placebo in this study.

Note: Reference to ipatasertib/placebo refers to the placebo for ipatasertib and atezolizumab/placebo refers to the placebo for atezolizumab in this appendix.

Any dose interruption, dose modification, overdose or incorrect administration of ipatasertib/placebo (for ipatasertib), atezolizumab/placebo (for atezolizumab), or paclitaxel should be noted on the corresponding Study Drug Administration and Adverse Event (Special Situations) electronic Case Report Form (eCRF).

## GENERAL GUIDELINES

Dose modifications for paclitaxel chemotherapy will be performed as clinically appropriate, based on the investigator's medical judgment. Details in this section can be used as guidance; however, only the specific dose levels shown should be used (see Table 1 and Table 2). Reasons for dose modifications (interruption or reduction) and discontinuation, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded on the eCRF. Reasons for not adhering to the following guidance should also be documented in the patient's chart.

On the planned day of treatment, the general parameters for chemotherapy administration include the following:

- ANC $\geq$ 1500/$\mu$L
- Platelet count $\geq$ 100,000/$\mu$L
- (Maximum) Grade $\leq$ 2 clinically significant chemotherapy-related gastrointestinal toxicity

General guidelines for dosage/schedule modification are summarized as follows:

- If any treatment component is interrupted (dose hold), the study cycle day count continues and does not shift, i.e., every cycle is exactly 28 days in length. It is recommended that once the first date of study treatment administration is confirmed, that a calendar be laid out for the remainder of the study. The first day of study treatment administration should be considered Day 1 of Cycle 1 (i.e., the first day of the first 28-day cycle) and should be considered Day 1 of Cycle 1 and used for the purposes of utilizing the appropriate eCRF folder and page. (Note: Each folder encompasses one 28-day cycle and is to be used to record anticipated study treatments and procedures falling within the 28-day calendar period. The recording of actual treatment and procedure dates within each folder will account for

treatments and procedures that occur on study days other than those that were expected.)

- Interruption or discontinuation of individual study drugs:
  - If ipatasertib/placebo treatment is interrupted, atezolizumab/placebo and/or paclitaxel treatment may continue if medically appropriate (per investigator discretion).
  - If atezolizumab/placebo treatment is interrupted, ipatasertib and/or paclitaxel treatment may continue if medically appropriate (per the investigator's discretion).
  - If paclitaxel treatment is interrupted, ipatasertib/placebo and/or atezolizumab/placebo treatment may continue if medically appropriate (per investigator discretion). If paclitaxel treatment is interrupted, consider delaying the ipatasertib/placebo treatment concurrently for up to 7 days (i.e., shifting the 7 days off week for ipatasertib/placebo in order that 21 daily doses every 28 days is maintained), at the discretion of the investigator. The interrupted dose of paclitaxel may be administered later in the same cycle, ideally on Day 22, taking into consideration the paclitaxel dosing starting on Day 1 of the next cycle.
  - If both atezolizumab/placebo and paclitaxel have been permanently discontinued, a documented discussion should take place between the investigator and the patient regarding the possibility of receiving ipatasertib/placebo alone, and if medically appropriate the patient may continue ipatasertib/placebo alone. The upcoming tumor assessment should be performed as scheduled.
  - If both ipatasertib/placebo and paclitaxel have been permanently discontinued, a documented discussion should take place between the investigator and the patient regarding the possibility of receiving atezolizumab/placebo alone, and if medically appropriate the patient may continue atezolizumab/placebo alone. The upcoming tumor assessment should be performed as scheduled.
  - Although there are prespecified windows allowed around dosing days, it is strongly suggested that paclitaxel administration occur only on Days 1, 8, and 15 (or Day 22 as a day to compensate for missed paclitaxel on any of the 3 previous days), and that atezolizumab/placebo be given only on Days 1 and 15. *The Medical Monitor is available to advise as needed.*

- If toxicity causes paclitaxel treatment to be omitted, clinic visits (and study procedures) associated with the administration of paclitaxel chemotherapy in that cycle may also be omitted (e.g., Day 8, 15, or 22). However, laboratory assessments and clinical visits should be scheduled as needed for follow-up of adverse events. In addition, the tumor assessment during every 8$^{th}$ week should not be delayed. Once the toxicity has resolved to the required level, study treatment and study procedures will be resumed, according to the original study cycle day count, i.e., every cycle contains exactly 28 days.
- For toxicities assessed by the investigator to be unrelated to study treatment and unlikely to develop into serious or life-threatening events, treatment may be continued at the same dose without reduction or interruption. Because this is broad guidance, please refer to specific adverse event management guidelines, as certain minimal safety guidance is to be followed regardless of attribution to study drugs.
- Dose reductions or interruptions may not be required for anemia (non-hemolytic) if satisfactorily managed by transfusions.
- Dose modifications for isolated abnormal hematologic laboratory values will be based on hematologic parameters on days when scheduled labs are due or on days when infusions are scheduled (i.e., normal hematologic values on Day 1 should not prevent dose modification, if indicated, based on a Day 8, 15, or 22 laboratory value).
- Study treatment may be interrupted to manage toxicity.
  - Paclitaxel or ipatasertib/placebo: A dosing gap of up to 4 consecutive weeks (approximately 28 days) is permitted. A dose hold for longer than 4 weeks for a study treatment–related adverse event requires permanent discontinuation of the attributable treatment component and per specific adverse event management guidelines below.

    Atezolizumab/placebo may be held for up to 12 weeks. For additional details, see below and Appendix 14.

## DOSAGE MODIFICATION

If the patient does not tolerate the once a day (QD) dosing of ipatasertib/placebo, dosing with food may be used to alleviate gastrointestinal symptoms, including nausea, vomiting, and/or diarrhea. No more than two dose reductions of ipatasertib/placebo per patient (i.e., doses $<$200 mg/day of ipatasertib/placebo) will be allowed (see Table 1). Dose re-escalation is not permitted for ipatasertib/placebo.

### Table 1 Dose Reductions for Ipatasertib/Placebo

| Dose | Dose of Ipatasertib/Placebo |
|---|---|
| Starting dose | 400 mg |
| First dose reduction | 300 mg |
| Second dose reduction [a] | 200 mg |
| Third dose reduction | Not permitted |

[a] If the patient continues to experience specified study drug–related adverse events after the second reduction, treatment should be discontinued.

To manage paclitaxel-related toxicity, no more than one dose reduction for paclitaxel will be allowed (see Table 2). Paclitaxel doses other than specified in Table 2 will not be allowed.

### Table 2 Dose Reductions for Paclitaxel

| Dose [a] | Dose of Paclitaxel |
|---|---|
| Starting dose | 80 mg/m$^2$ |
| First dose reduction | 65 mg/m$^2$ |
| Second dose reduction | Not permitted |
| Third dose reduction | Not applicable |

[a] If the patient continues to experience specified study drug–related adverse events after dose reduction, treatment should be discontinued.

## TREATMENT INTERRUPTION

Ipatasertib/placebo, atezolizumab/placebo, and/or paclitaxel treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed*. Particular care should be taken to maintain the schedule of tumor assessments even when treatment is interrupted. For both surgery and palliative radiotherapy, all study treatment should be suspended temporarily. The length of paclitaxel suspension must be considered sufficient in the investigator's judgment and be explained in the source documents. No study treatment should be resumed before sufficient recovery from the procedure (i.e., no Grade $>1$ procedure-related adverse events).

## Interruption of Ipatasertib/Placebo

Ipatasertib/placebo treatment may be temporarily interrupted in patients who experience toxicity considered to be related to study drug. If ipatasertib/placebo has been withheld for >28 consecutive days (as measured from the first day of interruption of scheduled ipatasertib dosing) because of treatment-related toxicity, the patient should be discontinued from ipatasertib/placebo. If ipatasertib/placebo is held for >28 consecutive days for reasons other than toxicity, and in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming study treatment after a hold of >28 consecutive days and there is no evidence of progression, study drug may be restarted.

If daily systemic corticosteroids are initiated for treatment of any toxicity or other condition, they must be tapered to ≤10 mg/day of oral prednisone or equivalent before ipatasertib or ipatasertib/placebo can be resumed. Steroids used as prophylaxis (i.e., as premedication prior to scans, as protocol-directed rash prophylaxis, or as standard premedication prior to paclitaxel or atezolizumab) do not require holding of ipatasertib/placebo. Steroids used on a single day to manage infusion-related reactions (IRRs) or allergic reactions similarly do not require holding of ipatasertib/placebo.

## Interruption of Atezolizumab/Placebo

Atezolizumab/placebo treatment may be temporarily suspended in patients experiencing toxicity considered to be related to atezolizumab/placebo. If atezolizumab/placebo (is withheld for >12 weeks owing to atezolizumab/placebo-related toxicity (as measured from the first day of interruption of scheduled atezolizumab/placebo dosing), the patient will be discontinued from atezolizumab/placebo.

If daily corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥1 month to ≤10 mg/day of oral prednisone or equivalent before atezolizumab/placebo (for atezolizumab) can be resumed. If atezolizumab/placebo (for atezolizumab) is withheld for >12 weeks after event onset, the patient will be discontinued from atezolizumab/placebo. Given that a slow taper of steroids, as directed above, is required by protocol, atezolizumab/placebo may be withheld for >12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab/placebo can then be resumed after being withheld for >12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

The acceptable length of treatment interruption *must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the*

*duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

## MANAGEMENT GUIDELINES

### Adverse Event Management Guidelines for Ipatasertib/Placebo Plus Atezolizumab/Placebo Plus Paclitaxel

Guidelines for the management of patients who experience specific adverse events are provided in Appendix 14 and Table 3, as outlined below:

- Table provides guidelines for the management of patients who experience the following potential overlapping toxicities: gastrointestinal, dermatologic, hepatic, pulmonary, and hyperglycemia events. It is recommended that study treatments be withheld or discontinued per the guidelines in Table 3. For these potential overlapping toxicities, guidelines in Table 3 override any other instruction in this document.
- Table 3 provides guidelines for the management of patients who experience adverse events associated with ipatasertib/placebo. It is recommended that atezolizumab/placebo and/or ipatasertib/placebo be withheld or discontinued per the guidelines in Table 3.
- Appendix 14 provides guidelines for the management of patients who experience atezolizumab/placebo-associated IRRs and immune-mediated adverse events. It is recommended that atezolizumab/placebo be withheld or discontinued per the guidelines in Appendix 14 and that ipatasertib/placebo be withheld or discontinued per the guidelines in Table 3.

For cases in which management guidelines are not covered in Table 3 elsewhere in this appendix or in Appendix 14, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment. See Appendix 14 for further management guidelines for events not described herein that are related to atezolizumab/placebo alone.

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel

| Event | Action to Be Taken |
|---|---|
| **Infusion-related reactions and anaphylaxis** | • Follow guidelines for atezolizumab/placebo in Appendix 14.<br>• Withhold ipatasertib/placebo.<br>• For anaphylaxis precautions, see Appendix 14.<br>• For severe hypersensitivity reactions, permanently discontinue atezolizumab/placebo and ipatasertib/placebo. |
| **Gastrointestinal toxicity** | |
| General guidance | • For all patients, dispense loperamide 4 mg once per day as prophylaxis for diarrhea in the first cycle.<br>• After the first cycle, continue this dosing for the remainder of the study as clinically indicated.<br>• Thoroughly evaluate all events of diarrhea or colitis for more common etiologies other than drug-induced effects.<br>• For diarrhea that persists for more than 5 days, despite treatment with antidiarrheal agent(s) and/or with dose hold of ipatasertib/placebo, consult with gastroenterologists to rule out the risk of colitis and infection. Educate patients on the symptoms and importance of early reporting of diarrhea and provide instructions for treatment and prevention of dehydration so that patients can be promptly and appropriately managed. (Educational materials will be provided to investigators and patients outlining these guidelines.)<br>• 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.<br>Administer antidiarrheal agents and other supportive care per institutional guidelines or per suggested supportive care outlined below:<br><u>Medication</u><br>As early as possible, institute treatment modifications for diarrhea (any grade) when it occurs. Guidelines for treatment of diarrhea, following the prophylactic dose of loperamide 4 mg initial daily dose, include use of loperamide 2 mg after each loose watery stool, up to the maximum total dose of 16 mg/day or per institutional guidelines and standard of care, including, but not limited to, additional therapy with diphenoxylate and atropine, |

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| **Gastrointestinal toxicity (cont.)** | |
| General guidance (cont.) | codeine, or octreotide. Please note that loperamide prophylaxis alone is not sufficient if diarrhea occurs despite prophylaxis; if diarrhea occurs while on loperamide prophylaxis, loperamide use should be increased as noted above, or additional medications added. Medication (cont.)<br>– To minimize duration of diarrhea, encourage taking ipatasertib/placebo with food, avoiding lactose-containing foods, and hydrating with 8–10 glasses per day (approximately 12 oz/glass) of electrolyte-containing clear liquid, such as broth and Gatorade® drinks.<br>– Reduce dose of ipatasertib/placebo by one level at a time (i.e., from 400 to 300 mg; from 300 to 200 mg) as outlined in Table 1. If Grade ≥2 diarrhea persists following dose reductions of ipatasertib/placebo to 200 mg daily and with maximum treatment for diarrhea, discontinue ipatasertib/placebo.<br>Oral Supplementation<br>– Initiate potassium and/or magnesium if serum levels are less than the lower limit of normal.<br>– Consider rehydration therapy with oral electrolyte solution for Grade ≥1 diarrhea or vomiting.<br>Dietary Modifications<br>– Instruct patient to eat small meals and eliminate lactose-containing products from diet.<br>– Suggest diet of bananas, rice, apples, and toast, while avoiding fiber from vegetables and other fruits.<br>– Encourage adequate hydration with salt-containing liquids (e.g., broth, sports drinks such as Gatorade®). |
| Diarrhea, Grade 1 | • Continue atezolizumab/placebo and ipatasertib/placebo.<br>• Initiate supportive care and monitor patient closely.<br>• Investigate etiology, referring patient to gastrointestinal specialist for evaluation of possible colitis if appropriate.<br>• Upon resolution, loperamide prophylaxis can be considered and continued as clinically indicated, if allowed by local guidance. Loperamide prophylaxis is to be taken throughout at least the first cycle. |

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| **Gastrointestinal toxicity (cont.)** | |
| Diarrhea, Grade 2 | • Withhold atezolizumab/placebo and ipatasertib/placebo.<br>• Initiate supportive care and monitor patient closely.<br>• Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology.<br>• Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate.<br>• If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab/placebo at a fixed dose. If not, permanently discontinue atezolizumab/placebo. [a, b, c]<br>• Interrupt ipatasertib/placebo until diarrhea improves to Grade 1 or better. Ipatasertib/placebo can be resumed at the same dose or one dose lower per investigator's evaluation upon improvement to Grade 1 or better.<br>• Reduce ipatasertib/placebo by one (or one additional) dose level (see Table 1) for recurrent Grade 2 diarrhea.<br>• When study treatment is resumed, loperamide prophylaxis should also be resumed and continued as clinically indicated, if allowed by local guidance. Please note, loperamide prophylaxis is to be taken throughout at least the first cycle. |

GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug.

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

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

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

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| Diarrhea, Grade 3 | • Withhold ipatasertib/placebo, atezolizumab/placebo, and paclitaxel.<br>• Initiate supportive care and monitor patient closely.<br>• Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology.<br>• Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate.<br>• If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab/placebo (for atezolizumab) at a fixed dose. If not, permanently discontinue atezolizumab/placebo and contact Medical Monitor. [a, b, c]<br>• Interrupt ipatasertib/placebo and paclitaxel until diarrhea improves to Grade 1 or better. Ipatasertib/placebo should be reduced by one dose level (see Table 1) when treatment is restarted. Consider resuming paclitaxel at the same dose.<br>• For recurrent Grade 3 diarrhea, reduce ipatasertib/placebo dose by one additional dose level (see Table 1). Consider reducing paclitaxel by one dose level when treatment is restarted (see Table 2).<br>• When study treatment is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated, if allowed by local guidance. Please note, loperamide prophylaxis is to be taken throughout at least the first cycle. |

GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug.

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

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

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

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (Placebo for Ipatasertib) Plus Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| Diarrhea, Grade 4 | • Permanently discontinue atezolizumab/placebo and ipatasertib/placebo and contact Medical Monitor. [c]<br>• Initiate supportive care and monitor patient closely.<br>• Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology.<br>• Rule out bowel perforation.<br>• Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate.<br>• Interrupt paclitaxel until diarrhea improves to Grade 1 or better. Consider resuming paclitaxel by one dose level lower or discontinuing paclitaxel per investigator's discretion (see Table 2). |

GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug.

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

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

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

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (Placebo for Ipatasertib) Plus Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| **Gastrointestinal toxicity (cont.)** | |
| Colitis, Grade 1 | • Continue atezolizumab/placebo and ipatasertib/placebo.<br>• Initiate supportive care and monitor patient closely.<br>• Discontinue medications that may exacerbate colitis (e.g., NSAIDs).<br>• Refer patient to GI specialist for evaluation and confirmatory biopsy if symptoms persist for >5 days. |
| Colitis, Grade 2 | • Withhold atezolizumab/placebo and ipatasertib/placebo.<br>• Initiate supportive care and monitor patient closely.<br>• Discontinue medications that may exacerbate colitis (e.g., NSAIDs).<br>• Refer patient to GI specialist for evaluation and confirmatory biopsy.<br>• For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab/placebo at a fixed dose. If not, permanently discontinue atezolizumab/placebo and ipatasertib/placebo and contact Medical Monitor. [a, b, c]<br>• If event resolves to Grade 1 or better within 28 days, resume ipatasertib/placebo with the dose reduced by one level. If not, permanently discontinue ipatasertib/placebo. |

GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug.

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

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

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

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (Placebo for Ipatasertib) Plus Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| **Gastrointestinal toxicity (cont.)** | |
| Colitis, Grade 3 | • Withhold atezolizumab/placebo and ipatasertib/placebo.<br>• Initiate supportive care and monitor patient closely.<br>• Discontinue medications that may exacerbate colitis (e.g., NSAIDs).<br>• Refer patient to GI specialist for evaluation and confirmatory biopsy.<br>• 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.<br>• If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab/placebo at a fixed dose. If not, permanently discontinue atezolizumab/placebo and ipatasertib/placebo and contact Medical Monitor. [a, b, c]<br>• If event resolves to Grade 1 or better within 28 days, resume ipatasertib/placebo with dose reduced by one level. If not, permanently discontinue ipatasertib. |
| Colitis, Grade 4 | • Permanently discontinue atezolizumab/placebo and ipatasertib/placebo and contact Medical Monitor. [c]<br>• Initiate supportive care and monitor patient closely.<br>• Discontinue medications that may exacerbate colitis (e.g., NSAIDs).<br>• Refer patient to GI specialist for evaluation and confirmatory biopsy.<br>• 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.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month. |

**Appendix 13: Overall Guidelines for Management of Patients Who Experience Adverse Events**

GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug.

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

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

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

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (Placebo for Ipatasertib) Plus Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| **Endocrine disorders** | |
| Asymptomatic hypothyroidism | • Follow guidelines for atezolizumab/placebo in Appendix 14.<br>• Continue ipatasertib/placebo. |
| Symptomatic hypothyroidism | • Follow guidelines for atezolizumab/placebo in Appendix 14.<br>• Continue ipatasertib/placebo. |
| Asymptomatic hyperthyroidism | **Thyroid-stimulating hormone ≥0.1 mU/L and <0.5 mU/L:**<br>• Follow guidelines for atezolizumab/placebo in Appendix 14.<br>• Continue ipatasertib/placebo.<br>**Thyroid-stimulating hormone <0.1 mU/L:**<br>• Follow guidelines for symptomatic hyperthyroidism. |
| Symptomatic hyperthyroidism | • Follow guidelines for atezolizumab/placebo in Appendix 14.<br>• Continue ipatasertib/placebo.<br>• For life-threatening immune-mediated hyperthyroidism, withhold ipatasertib/placebo. If event becomes clinically manageable within 28 days, resume ipatasertib/placebo with the dose reduced by one level (see Table 1). If not, permanently discontinue ipatasertib/placebo. |

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (Placebo for Ipatasertib) Plus Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| **Endocrine disorders (cont.)** | |
| Symptomatic adrenal insufficiency, Grade 2, 3, or 4 | • Follow guidelines for atezolizumab/placebo in Appendix 14.<br>• Continue ipatasertib/placebo. |
| Hyperglycemia, general guidance | • Thoroughly evaluate all events of hyperglycemia for more common etiologies other than drug-induced effects.<br>• Investigate for diabetes. If patient has Type 1 diabetes, treat as an event of fasting glucose value 250–500 mg/dL.<br>• In workup, include confirmation of fasting blood glucose, urinary glucose and ketones, arterial blood gas, serum bicarbonate, hemoglobin $A_{1C}$, C-peptide levels, anti-islet antibodies, and anti-GAD45 antibody.<br>• Treat hyperglycemia per institutional guidelines with fluid replacement, insulin, and correction of electrolyte abnormalities. |
| Hyperglycemia, fasting glucose value > ULN to 160 mg/dL (8.9 mmol/L) | • Continue atezolizumab/placebo and ipatasertib/placebo.<br>• Provide patient with education on a diabetic diet and consider home glucose monitoring.<br>• Consider oral anti-diabetic medications (e.g., metformin) or insulin replacement, guided by etiology of hyperglycemia. |
| Hyperglycemia, fasting glucose value >160–250 mg/dL (> 8.9–13.9 mmol/L) | • Withhold atezolizumab/placebo and ipatasertib/placebo dosing until fasting glucose value resolves to ≤160 mg/dL. (Investigate for diabetes. If patient has Type 1 diabetes, treat as a fasting glucose value 250–500 mg/dL event. If patient does not have Type 1 diabetes, treat as per institutional guidelines.)<br>• Encourage a diabetic diet and initiate home glucose monitoring.<br>• Start oral anti-diabetic medications (e.g., metformin) or insulin replacement, guided by etiology of hyperglycemia.<br>• If patient is already on an oral anti-diabetic medication, the dose of ipatasertib/placebo should be reduced by one dose level (refer to Table 1).<br>• If the patient previously has not been receiving any oral anti-diabetic medication, ipatasertib/placebo may be resumed at the previous dose level with initiation of oral anti-diabetic medication. |

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (Placebo for Ipatasertib) Plus Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| **Endocrine disorders (cont.)** | |
| Hyperglycemia, glucose value >250–500 mg/dL (>13.9–27.8 mmol/L) | • Withhold atezolizumab/placebo and ipatasertib/placebo dosing until fasting glucose value resolves to ≤160 mg/dL and contact Medical Monitor.<br>• Treat hyperglycemia as per standard of care, noting risk of hypoglycemia if insulin is used. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin).<br>• Encourage a diabetic diet and initiate home glucose mo nitoring.<br>• If the patient is already on an oral anti-diabetic medication, ipatasertib/placebo should be reduced by one dose level when treatment is restarted.<br>• If previously, the patient has not been receiving any oral anti-diabetic medication, ipatasertib/placebo may be resumed at the previous dose level with initiation of oral anti-diabetic medication.<br>• If hyperglycemia 250–500 mg/dL recurs, the dose of ipatasertib/placebo should be reduced by one dose level (see Table 1) when treatment is restarted.<br>• Resume atezolizumab/placebo when symptoms resolve and glucose levels are stable. |
| Hyperglycemia, glucose value >500 mg/dL (>27.8 mmol/L); life-threatening consequences | • Withhold atezolizumab/placebo and ipatasertib/placebo dosing until fasting glucose value resolves to ≤160 mg/dL.<br>• Treat hyperglycemia as per standard of care, noting risk of hypoglycemia if insulin is used. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin).<br>• Assess for volume depletion and appropriate intravenous or oral hydration.<br>• Encourage a diabetic diet and initiate home glucose monitoring.<br>• Upon recovery of fasting glucose to ≤160 mg/dL, reduce ipatasertib/placebo by one dose level (see Table 1) when treatment is restarted.<br>• Resume atezolizumab/placebo when symptoms resolve and glucose levels are stable.<br>• If glucose value >500 mg/dL recurs, permanently discontinue ipatasertib/placebo and atezolizumab/placebo and contact Medical Monitor. |

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (Placebo for Ipatasertib) Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| **Pulmonary events** | |
| General guidance | • Thoroughly evaluate all pulmonary events for other commonly reported etiologies, such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension.<br>• Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. |
| Pulmonary event, Grade 1 | • Continue atezolizumab/placebo and ipatasertib/placebo.<br>• Re-evaluate on serial imaging.<br>• Consider patient referral to pulmonary specialist.<br>• *For Grade 1 pneumonitis, consider withholding atezolizumab.* |
| Pulmonary event, Grade 2 | • Withhold atezolizumab/placebo and ipatasertib/placebo.<br>• Refer patient to pulmonary specialist and consider bronchoscopy or BAL.<br>• If bronchoscopy is consistent with immune-mediated etiology, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab/placebo at a fixed dose. If not, permanently discontinue atezolizumab/placebo and ipatasertib/placebo and contact Medical Monitor. [a, b, c]<br>• If event resolves to Grade 1 or better within 28 days, resume ipatasertib/placebo at current dose.<br>• For recurrent events, treat as a Grade 3 or 4 event. |

BAL = bronchoscopic alveolar lavage.

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

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

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

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (Placebo for Ipatasertib) Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| **Pulmonary events (cont.)** | |
| Pulmonary event, Grade 3 or 4 | • Permanently discontinue atezolizumab/placebo and ipatasertib/placebo and contact Medical Monitor. [c]<br>• Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL.<br>• If bronchoscopy is consistent with immune-mediated etiology, initiate treatment with *corticosteroids* 1−2 mg/kg/day oral prednisone or equivalent.<br>• If pulmonary event does not improve within 48 hours or worsens, consider adding an immunosuppressive agent.<br>• When event resolves to Grade 1 or better, taper corticosteroids over ≥1 month. |
| **Hepatic events** | |
| AST/ALT > ULN to ≤3 × ULN with total bilirubin ≤2 × ULN | • Continue atezolizumab/placebo and ipatasertib/placebo.<br>• Monitor LFTs [d] until values resolve to within normal limits or to baseline values. |

BAL = bronchoscopic alveolar lavage; LFT = liver function test; ULN = upper limit of normal.

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

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

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

[d] The LFT panel should include AST, ALT, alkaline phosphatase, and total bilirubin.

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (Placebo for Ipatasertib) Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| **Hepatic events (cont.)** | |
| AST/ALT > 3 × ULN to 5 × ULN with total bilirubin ≤ 2 × ULN | • Continue atezolizumab/placebo and ipatasertib/placebo.<br>• Monitor LFTs [d, f] every 48–72 hours until decreasing and then weekly until return to baseline.<br>• Consider patient referral to a hepatologist [e] and liver biopsy.<br>**Suspected immune-mediated events of > 5 days' duration:**<br>• *Withhold* atezolizumab *for up to 12 weeks after event onset.*<br>• *Initiate* treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If atezolizumab/placebo is withheld and event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks, resume atezolizumab/placebo at a fixed dose. If not, permanently discontinue atezolizumab/placebo and ipatasertib/placebo and contact Medical Monitor. [a, b, c] |

LFT = liver function test; ULN = upper limit of normal.

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

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

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

[d] The LFT panel should include AST, ALT, alkaline phosphatase, and total bilirubin.

[e] When the cause of the hepatic event is unclear, suggested workup may include a review of symptoms, concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets; ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease; reviewing exposure to environmental chemical agents and additional tests to evaluate liver function (e.g., INR, direct bilirubin).

[f] In instances when patients have baseline elevation of LFTs clinical judgment should be used when determining appropriate frequency for monitoring LFTs (e.g., patients with documented liver or bone metastases may have baseline AST/ALT < 5x ULN); monitoring of LFTs for such patients may be as per clinical judgment until a threshold of ALT/AST 5x ULN.

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (Placebo for Ipatasertib) Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| **Hepatic events (cont.)** | |
| AST/ALT > 5 × ULN to < 10 × ULN with total bilirubin > ULN to ≤ 2 × ULN | • Continue atezolizumab/placebo and ipatasertib/placebo.<br>• Monitor LFTs [d, f] every 48–72 hours until decreasing and then weekly until return to baseline.<br>• Consider patient referral to hepatologist [e] and liver biopsy.<br>**Suspected immune-mediated events:**<br>• Withhold atezolizumab/placebo.<br>• Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent.<br>• If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks, resume atezolizumab/placebo at a fixed dose. If not, permanently discontinue atezolizumab/placebo and ipatasertib/placebo and contact Medical Monitor. [a, b, c] |

LFT = liver function test; ULN = upper limit of normal.

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

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

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

[d] The LFT panel should include AST, ALT, alkaline phosphatase, and total bilirubin.

[e] When the cause of the hepatic event is unclear, suggested workup may include a review of symptoms, concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets; ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease; reviewing exposure to environmental chemical agents and additional tests to evaluate liver function (e.g., INR, direct bilirubin).

[f] In instances when patients have baseline elevation of LFTs clinical judgment should be used when determining appropriate frequency for monitoring LFTs (e.g., patients with documented liver or bone metastases may have baseline AST/ALT < 5 × ULN); monitoring of LFTs for such patients may be as per clinical judgment until a threshold of ALT/AST 5 × ULN.

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (Placebo for Ipatasertib) Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| **Hepatic events (cont.)** | |
| AST/ALT > ULN to ≤ 3 × ULN with total bilirubin > 2 × ULN | • Investigate causes for elevated bilirubin and initiate treatment as indicated per institutional guidelines.<br>• Use best medical judgment when determining whether to continue study treatment. |
| AST/ALT > 3 × to < 10 × ULN with total bilirubin > 2× ULN | • Withhold atezolizumab/placebo and ipatasertib/placebo.<br>• Monitor LFTs [d, f] every 48–72 hours until decreasing and then monitor weekly.<br>• Refer patient to hepatologist [e] and consider liver biopsy.<br>• Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent.<br>• If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent.<br>• If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks, resume atezolizumab/placebo at a fixed dose. If not, permanently discontinue atezolizumab/placebo and contact Medical Monitor. [a, b, c]<br>• If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 28 days, resume ipatasertib/placebo with dose reduced by one level (see Table 1). If not, permanently discontinue ipatasertib/placebo.<br>• Permanently discontinue atezolizumab/placebo and ipatasertib/placebo for life-threatening hepatic events and contact the Medical Monitor. |

LFT = liver function test; ULN = upper limit of normal.

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

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

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

[d] The LFT panel should include AST, ALT, alkaline phosphatase, and total bilirubin.

[e] When the cause of the hepatic event is unclear, suggested workup may include a review of symptoms, concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets; ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease; reviewing exposure to environmental chemical agents and additional tests to evaluate liver function (e.g., INR, direct bilirubin).

[f] In instances when patients have baseline elevation of LFTs clinical judgment should be used when determining appropriate frequency for monitoring LFTs (e.g., patients with documented liver or bone metastases may have baseline AST/ALT < 5 × ULN); monitoring of LFTs for such patients may be as per clinical judgment until a threshold of ALT/AST 5 × ULN.

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (Placebo for Ipatasertib) Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| **Hepatic events (cont.)** | |
| AST/ALT ≥ 10 × ULN | • Permanently discontinue atezolizumab/placebo and ipatasertib/placebo and contact Medical Monitor. [c]<br>• Monitor LFTs [d, f] every 48–72 hours until decreasing and then monitor weekly.<br>• Refer patient to hepatologist [e] and consider liver biopsy.<br>• Consider administering 1–2 mg/kg/day oral prednisone or equivalent.<br>• If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent or escalating the corticosteroid dose.<br>• When event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN, taper corticosteroids over ≥ 1 month. |

LFT = liver function test; ULN = upper limit of normal.

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

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

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

[d] The LFT panel should include AST, ALT, alkaline phosphatase, and total bilirubin.

[e] When the cause of the hepatic event is unclear, suggested workup may include a review of symptoms, concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets; ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease; reviewing exposure to environmental chemical agents and additional tests to evaluate liver function (e.g., INR, direct bilirubin).

[f] In instances when patients have baseline elevation of LFTs clinical judgment should be used when determining appropriate frequency for monitoring LFTs (e.g., patients with documented liver or bone metastases may have baseline AST/ALT < 5 × ULN); monitoring of LFTs for such patients may be as per clinical judgment until a threshold of ALT/AST 5 × ULN.

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (Placebo for Ipatasertib) Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| **Dermatologic toxicity** | |
| General guidance | • Consider having a dermatologist evaluate persistent and/or severe rash or pruritus.<br>• Unless contraindicated, daily oral antihistamine prophylaxis should be used for at least the first cycle. It is suggested that a non-sedating oral antihistamine (such as loratadine, cetirizine, fexofenadine) and longer-acting formulation be used. The daily oral antihistamine used for rash prophylaxis may be held on the days of paclitaxel infusion if the paclitaxel premedication already includes an antihistamine.<br>• For the first 28-day cycle of triplet study drug combination: On days when patients will receive atezolizumab/placebo (typically, Days 1 and 15), patients should receive at least 10 mg prednisone (or equivalent) as premedication prior to atezolizumab/placebo, followed by 10 mg/day prednisone (or equivalent) for 2–4 consecutive days thereafter, unless contraindicated. If institutional practice prior to paclitaxel is to give at least 10 mg/day prednisone on the day of paclitaxel, then the additional 10 mg prophylactic prednisone should not be given on that day to prevent rash.<br>• Ipatasertib/placebo should be permanently discontinued for rash- associated with Stevens-Johnson syndrome, toxic epidermal necrolysis, or other suspected severe hypersensitivity or allergic reaction. Dosage modification and symptom management guidelines for skin toxicity, including erythema multiforme, attributable to ipatasertib/placebo are shown below.<br>• Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab and atezolizumab should be permanently discontinued for confirmed cases. |
| Dermatologic event, Grade 1 | • Consider referring patient to a dermatologist.<br>• Continue atezolizumab/placebo and ipatasertib/placebo.<br>• Initiate supportive care (e.g., topical corticosteroids and continue antihistamine administration).<br>• Consider treatment with 10 mg/day oral prednisone or equivalent. |

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (Placebo for Ipatasertib) Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| **Dermatologic toxicity (cont.)** | |
| • Dermatologic event, Grade 2 | • Consider referring patient to dermatologist for evaluation and perform a biopsy, if appropriate.<br>• Continue topical corticosteroids and antihistamine administration.<br>• Consider treatment with 10 mg/day oral prednisone or equivalent; treatment with a higher steroid dose may be necessary as clinically indicated.<br>• *If unresponsive to topical corticosteroids, consider oral prednisone*<br>• Ipatasertib/placebo: Interrupt ipatasertib/placebo treatment until resolution to Grade 1 or better or the toxicity is no longer clinically significant. If steroid dose is ≤ 10 mg/day, ipatasertib/placebo may be resumed if clinically appropriate.<br>• Atezolizumab/placebo: If steroid dose is ≤ 10 mg/day, atezolizumab/placebo should be continued. |
| Dermatologic event, Grade 3 | • Withhold atezolizumab/placebo and ipatasertib/placebo.<br>• Refer patient to dermatologist. Perform a biopsy if appropriate.<br>• If no prior steroid treatment has been initiated, consider treatment with 10 mg/day oral prednisone or equivalent.<br>• If prior oral steroid treatment or no improvement within 48 hours, consider increasing prednisone or equivalent dose to 1–2 mg/kg/day.<br>• Atezolizumab/placebo: if event resolves to Grade 1 or better within 12 weeks, resume atezolizumab/placebo at a fixed dose. If not, permanently discontinue atezolizumab/placebo and contact Medical Monitor. Only restart atezolizumab/placebo (if steroid dose is ≤10 mg/day) [a, b, c].<br>• Ipatasertib/placebo: If event resolves to Grade 1 or better or the toxicity is no longer clinically significant, resume ipatasertib/placebo at the same dose or dose reduced by one level if considered medically appropriate. Only restart ipatasertib/placebo if steroid dose is ≤10 mg/day oral prednisone. If not, permanently discontinue ipatasertib/placebo. |
| Dermatologic event, Grade 4 | • Permanently discontinue atezolizumab/placebo and ipatasertib/placebo and contact Medical Monitor. |

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

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

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

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (Placebo for Ipatasertib) Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| **Neutropenia** | |
| Grade 2 | • Ipatasertib/placebo may be continued at the original dose.<br>• Withhold the taxane until ANC has recovered to ≥1500/mL.<br>– If clinically appropriate based on the investigator's medical judgment, the taxane may be administered up to 14 days (2 doses), even with Grade 2 neutropenia, without a dose reduction, as long as G-CSF is used to manage the neutropenia.<br>• If neutropenia does not recover to Grade 1 or better within the 14-day window of treating for ongoing Grade 2 neutropenia, the subsequent taxane dose(s) must be held until recovery to Grade 1 or better.<br>• If event resolves, administer the taxane at the previous dose. |
| Grade 3 | • Withhold ipatasertib/placebo and taxane until recovery to Grade 1 and, if clinically appropriate based on the investigator's medical judgment, to Grade 2 as long as G-CSF is used to manage the neutropenia. Please see guidelines in this table regarding treatment for ongoing Grade 2 neutropenia.<br>– First episode: If recovery is to Grade 1, resume the original dose. If recovery to Grade 1 is achieved with the use of G-CSF, then continued use of G-CSF is recommended once dosing of the study drug is resumed. If recovery is to Grade 2, follow the guidance above.<br>– Recurrent episode: Ipatasertib/placebo and taxane should be reduced by one dose level when treatment is restarted. If patient has had more than three Grade 3 neutropenia episodes during the study, despite the maximum dose reduction to 65 mg/m$^2$ for paclitaxel, the taxane should be permanently discontinued, but the patient may continue to receive ipatasertib/placebo following discussion with the Medical Monitor.<br>• Following a treatment hold of 4 weeks, if recovery of neutropenia to Grade 2 or better has not occurred, the patient will permanently discontinue taxane but may continue ipatasertib/placebo following discussion with the Medical Monitor. |

G-CSF = granulocyte colony-stimulating factor.

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (Placebo for Ipatasertib) Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| **Neutropenia (cont.)** | |
| Febrile neutropenia and Grade 4 neutropenia | • All study treatment should be withheld until recovery to Grade 1, and if clinically appropriate based on the investigator's medical judgment to Grade 2, as long as G-CSF is used to manage the neutropenia. Please see guidelines in this table regarding treatment for ongoing Grade 2 neutropenia.<br>– First episode: Ipatasertib/placebo and taxane should be reduced by one dose level when treatment is restarted.<br>– Recurrent episode: Ipatasertib/placebo and taxane should be discontinued. Atezolizumab/placebo (for atezolizumab) maybe continued after discussion with the Medical Monitor<br>• Following a treatment hold of up to 4 weeks, if recovery to Grade 2 or better neutropenia does not occur, the patient will permanently discontinue all treatment. |
| **Ipatasertib/placebo-related toxicities not described above** | |
| Grade ≥3 | • Withhold ipatasertib/placebo. Continue atezolizumab/placebo.<br>• If the toxicity resolves to Grade 1 or better within 2 weeks, treatment may resume with ipatasertib/placebo at the prior dose level.<br>• If the toxicity resolves to Grade 1 or better within 2–4 weeks, the dose of the ipatasertib/placebo should be reduced by one level per the suggested guidelines in Table 1 and Table 2.<br>• Depending on the nature and the severity of the adverse event, if recovery to Grade 1 or better takes >4 weeks, treatment may resume with the ipatasertib/placebo with dose reduction, or the ipatasertib/placebo may be permanently discontinued, at the discretion of the investigator. |

G-CSF = granulocyte colony-stimulating factor.

## Table 3 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (Placebo for Ipatasertib) Atezolizumab/Placebo (for Atezolizumab) Plus Paclitaxel (cont.)

| Event | Action to Be Taken |
|---|---|
| **Atezolizumab/placebo-related toxicities not described in Appendix 13** | |
| Grade ≥3 | • Follow guidelines for atezolizumab/placebo in Appendix 14.<br>• Withhold ipatasertib/placebo until resolution to Grade 1.<br>• If the toxicity resolves to Grade 1 or better within 2 weeks, treatment with ipatasertib/placebo may resume at the prior dose level.<br>• If the toxicity resolves to Grade 1 or better within 2–4 weeks, the dose of ipatasertib/placebo should be reduced by one level per the suggested guidelines in Table 1.<br>• Depending on the nature and the severity of the adverse event, if recovery to Grade 1 or better takes >4 weeks, treatment may resume with ipatasertib/placebo with dose reduction, or ipatasertib/placebo may be permanently discontinued, at the discretion of the investigator. |

# Appendix 14
# 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/placebo 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/placebo. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab/placebo may be considered if the patient is deriving benefit and has fully recovered from the immune-mediated event. *The decision to* re-*challenge patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator. The Medical Monitor *is available to advise as needed.*

## PULMONARY EVENTS

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Even in the absence of pulmonary events, patients will be assessed for pulmonary signs and symptoms throughout the study and will have imaging 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 Appendix 13, Table 3.

## 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 Appendix 13, Table 3.

## GASTROINTESTINAL EVENTS

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Appendix 13, Table 3.

## 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 1. For events of hyperglycemia see Appendix 13, Table 3.

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. 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.

## Table 1 Management Guidelines for Endocrine Events

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

MRI = magnetic resonance imaging

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

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

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

## Table 1 Management Guidelines for Endocrine Events (cont.)

| Event | Management |
|---|---|
| Symptomatic adrenal insufficiency, Grades 2–4 | • Withhold atezolizumab/placebo for up to 12 weeks after event onset. [a]<br>• Refer patient to endocrinologist.<br>• Perform appropriate imaging.<br>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab/placebo. [b]<br>• If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab/placebo, permanently discontinue atezolizumab/placebo and contact Medical Monitor. [c] |

MRI = magnetic resonance imaging.

onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator.* The Medical Monitor *is available to advise as needed.*

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

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

## Table 1 Management Guidelines for Endocrine Events (cont.)

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

MRI = magnetic resonance imaging

onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator.* The Medical Monitor *is available to advise as needed.*

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

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

## OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 2.

### Table 2 Management Guidelines for Ocular Events

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

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

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

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

## IMMUNE-MEDIATED MYOCARDITIS

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. *Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly.* Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of 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 3.

## Table 3 Management Guidelines for Immune-Mediated Myocarditis

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

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

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

## INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

Although no premedication is normally indicated for the administration of Cycle 1 of atezolizumab, in this study premedication is given to prevent rash (see Section 4.3.3). Patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretics, and/or analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

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

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

therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs are provided in Table 4.

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

## Table 4 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

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

## Table 4 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

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

**Table 4 Management Guidelines for Infusion-Related Reactions** and Cytokine-Release Syndrome (cont.)

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell–related toxicities (Version 2.2019).

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, antipyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.

[e] There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.

[f] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the *immune-mediated* event. *The decision to* re-*challenge patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate*)*. The Medical Monitor *is available to advise as needed*. For subsequent infusions, administer oral premedication with antihistamines, antipyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after *assessing* the benefit–risk ratio.

[g] Refer to Riegler et al. (2019) for information on experimental treatments for CRS.

## 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 workup 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 5.

## Table 5 Management Guidelines for Pancreatic Events, Including Pancreatitis

| Event | Management |
|---|---|
| Amylase and/or lipase elevation, Grade 2 | **Amylase and/or lipase > 1.5–2.0 × ULN:**<br>• Continue atezolizumab/placebo.<br>• Monitor amylase and lipase weekly.<br>• For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone.<br>**Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN:**<br>• Treat as a Grade 3 event. |
| Amylase and/or lipase elevation, Grade 3 or 4 | • Withhold atezolizumab/placebo for up to 12 weeks after event onset. [a]<br>• Refer patient to GI specialist.<br>• Monitor amylase and lipase every other day.<br>• If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.<br>• If event resolves to Grade 1 or better, resume atezolizumab/placebo. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab/placebo, permanently discontinue atezolizumab/placebo and contact Medical Monitor. [c]<br>• For recurrent events, permanently discontinue atezolizumab/placebo and contact Medical Monitor. [c] |

GI = gastrointestinal; ULN = upper limit of normal.

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

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

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

## Table 5 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

| Event | Management |
|---|---|
| Immune-mediated pancreatitis, Grade 2 or 3 | • Withhold atezolizumab/placebo for up to 12 weeks after event onset. [a]<br>• Refer patient to GI specialist.<br>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event resolves to Grade 1 or better, resume atezolizumab/placebo. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab/placebo, permanently discontinue atezolizumab/placebo and contact Medical Monitor. [c]<br>• For recurrent events, permanently discontinue atezolizumab/placebo and contact Medical Monitor. [c] |
| Immune-mediated pancreatitis, Grade 4 | • Permanently discontinue atezolizumab/placebo and contact Medical Monitor. [c]<br>• Refer patient to GI specialist.<br>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month. |

GI=gastrointestinal; ULN=upper limit of normal.

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

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

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

## 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. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab.
A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events deemed solely related to atezolizumab/placebo are provided in Table 6. For management of events that are related to ipatasertib, paclitaxel, or combination therapy, refer to guidelines in Appendix 13, Table 3.

## Table 6 Management Guidelines for Dermatologic Events

| Event | Management |
|---|---|
| Dermatologic event, Grade 1 | • Continue atezolizumab/placebo.<br>• Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines). |
| Dermatologic event, Grade 2 | • Continue atezolizumab/placebo.<br>• Consider patient referral to dermatologist for evaluation and, if indicated, biopsy.<br>• Initiate treatment with topical corticosteroids.<br>• Consider treatment with higher-potency topical corticosteroids if event does not improve<br>• *If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day..* |
| Dermatologic event, Grade 3 | • Withhold atezolizumab/placebo for up to 12 weeks after event onset. [a]<br>• Refer patient to dermatologist for evaluation and, if indicated, biopsy.<br>• Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours.<br>• If event resolves to Grade 1 or better, resume atezolizumab/placebo. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab/placebo, permanently discontinue atezolizumab/placebo and contact Medical Monitor. [c] |

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

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

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

## Table 6 Management Guidelines for Dermatologic Events (cont.)

| | |
|---|---|
| Dermatologic event, Grade 4 | • Permanently discontinue atezolizumab/placebo and contact Medical Monitor. [c] |
| Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade) | Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:<br>• Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis.<br>• Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy.<br>• Follow the applicable treatment and management guidelines above.<br>If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab. |

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

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

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

## NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 7.

## Table 7 Management Guidelines for Neurologic Disorders

| Event | Management |
|---|---|
| Immune-mediated neuropathy, Grade 1 | • Continue atezolizumab/placebo.<br>• Investigate etiology. |
| Immune-mediated neuropathy, Grade 2 | • Withhold atezolizumab/placebo for up to 12 weeks after event onset. [a]<br>• Investigate etiology *and refer patient to neurologist.*<br>• Initiate treatment as per institutional guidelines.<br>• If event resolves to Grade 1 or better, resume atezolizumab/placebo. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab/placebo and contact Medical Monitor. [c] |
| Immune-mediated neuropathy, Grade 3 or 4 | • Permanently discontinue atezolizumab/placebo and contact Medical Monitor. [c]<br>• *Refer patient to neurologist.*<br>• Initiate treatment as per institutional guidelines. |
| Myasthenia gravis and Guillain-Barré syndrome (any grade) | • Permanently discontinue atezolizumab/placebo and contact Medical Monitor. [c]<br>• Refer patient to neurologist.<br>• Initiate treatment as per institutional guidelines.<br>• Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone. |

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

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

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

## IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated meningoencephalitis should be

suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 8.

### Table 8 Management Guidelines for Immune-Mediated Meningoencephalitis

| Event | Management |
|---|---|
| Immune-mediated meningoencephalitis, all grades | • Permanently discontinue atezolizumab/placebo and contact Medical Monitor. [a]<br>• Refer patient to neurologist.<br>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month. |

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

## RENAL EVENTS

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if

clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 9.

## Table 9 Management Guidelines for Renal Events

| Event | Management |
|---|---|
| Renal event, Grade 1 | • Continue atezolizumab/placebo.<br>• Monitor kidney function, including creatinine *and urine protein*, closely until values resolve to within normal limits or to baseline values. |
| Renal event, Grade 2 | • Withhold atezolizumab/placebo for up to 12 weeks after event onset. [a]<br>• Refer patient to renal specialist.<br>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.<br>• If event resolves to Grade 1 or better, resume atezolizumab/placebo. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab/placebo, permanently discontinue atezolizumab/placebo and contact Medical Monitor. [c] |
| Renal event, Grade 3 or 4 | • Permanently discontinue atezolizumab/placebo and contact Medical Monitor.<br>• Refer patient to renal specialist and consider renal biopsy.<br>• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month. |

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

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

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

## IMMUNE-MEDIATED MYOSITIS

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (increased serum creatine kinase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. *Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.*

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 10.

## Table 10 Management Guidelines for Immune-Mediated Myositis

| Event | Management |
|---|---|
| Immune-mediated myositis, Grade 1 | • Continue atezolizumab/placebo.<br>• Refer patient to rheumatologist or neurologist.<br>• Initiate treatment as per institutional guidelines. |
| Immune-mediated myositis, Grade 2 | • Withhold atezolizumab/placebo for up to 12 weeks after event onset [a] and contact Medical Monitor.<br>• Refer patient to rheumatologist or neurologist.<br>• Initiate treatment as per institutional guidelines.<br>• 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.<br>• If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, resume atezolizumab/placebo. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab, /placebo permanently discontinue atezolizumab/placebo and contact Medical Monitor. [c] |

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

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

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

## Table 10 Management Guidelines for Immune-Mediated Myositis (cont.)

| Event | Management |
|---|---|
| Immune-mediated myositis, Grade 3 | • Withhold atezolizumab/placebo for up to 12 weeks after event onset [a] and contact Medical Monitor.<br>• Refer patient to rheumatologist or neurologist.<br>• Initiate treatment as per institutional guidelines.<br>• Respiratory support may be required in more severe cases.<br>• 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.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, resume atezolizumab/placebo. [b]<br>• If event does not resolve to Grade 1 or better while withholding atezolizumab/placebo, permanently discontinue atezolizumab/placebo and contact Medical Monitor. [c]<br>• For recurrent events, treat as a Grade 4 event. |
| Immune-mediated myositis, Grade 4 | • Permanently discontinue atezolizumab/placebo and contact Medical Monitor. [c]<br>• Refer patient to rheumatologist or neurologist.<br>• Initiate treatment as per institutional guidelines.<br>• Respiratory support may be required in more severe cases.<br>• 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.<br>• If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month. |

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

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

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

## HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), *which are considered to be potential risks for atezolizumab*.

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever $\geq$ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin $<$ 90 g/L (9 g/dL) ($<$ 100 g/L [10 g/dL] for infants $<$ 4 weeks old)
  - Platelet count $<$ 100 $\times$ 109/L (100,000/$\mu$L)
  - ANC $<$ 1.0 $\times$ 109/L (1000/$\mu$L)
- Fasting triglycerides $>$ 2.992 mmol/L (265 mg/dL) and/or fibrinogen $<$ 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin $>$ 500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated $\geq$ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin $>$ 684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count $\leq$ 181 $\times$ 109/L (181,000/$\mu$L)
  - AST $\geq$ 48 U/L
  - Triglycerides $>$ 1.761 mmol/L (156 mg/dL)
  - Fibrinogen $\leq$ 3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 11.

### Table 11 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

| Event | Management |
|---|---|
| Suspected HLH or MAS | • Permanently discontinue atezolizumab and contact Medical Monitor.<br>• Consider patient referral to hematologist.<br>• Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines.<br>• Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy.<br>• If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019).<br>• If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month. |

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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# Appendix 15
# Drugs with Known Risk of TdP; https://www.crediblemeds.org



The last revision date: June 25, 2019

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**See Note below for safe use of this Table**

**Filters:**
TdP Risk Category: **Drugs with known TdP risk**
Keyword:

| Generic Name | Brand Names (Partial List) | Drug Class | Therapeutic Use | Risk Category | Route |
|---|---|---|---|---|---|
| Aclarubicin *(Only on Non US Market)* | Aclacin, Aclacinomycine, Aclacinon, Aclaplastin, Jaclacin | Anti-cancer | Cancer | | Injection |
| Amiodarone | Cordarone, Pacerone, Nexterone | Antiarrhythmic | Arrhythmia | | oral, injection |
| Anagrelide | Agrylin, Xagrid | Phosphodiesterase 3 Inhibitor | Thrombocythemia | | oral |
| Arsenic trioxide | Trisenox | Anti-cancer | Cancer (leukemia) | | injection |
| Astemizole *(Removed from US Market)* | Hismanal | Antihistamine | Allergic rhinitis | | oral |
| Azithromycin | Zithromax, Zmax | Antibiotic | Bacterial infection | | oral, injection |
| Bepridil *(Removed from US Market)* | Vascor | Antianginal | Angina Pectoris (heart pain) | | oral |
| Chloroquine | Aralen | Antimalarial | Malaria | | oral |
| Chlorpromazine | Thorazine, Largactil, Megaphen | Antipsychotic / Antiemetic | Nausea, Schizophrenia, many others | | oral, injection, suppository |
| Cilostazol | Pletal | Phosphodiesterase 3 Inhibitor | Intermittent claudication | | oral |
| Ciprofloxacin | Cipro, Cipro-XR, Neofloxin | Antibiotic | Bacterial infection | | oral, injection |
| Cisapride *(Removed from US Market)* | Propulsid | GI stimulant | Increase GI motility | | oral |
| Citalopram | Celexa, Cipramil | Antidepressant, SSRI | Depression | | oral |
| Clarithromycin | Biaxin, Prevpac | Antibiotic | Bacterial infection | | oral, inhaled |
| Cocaine | Cocaine | Local anesthetic | Anesthesia (topical) | | oral, nasal |
| Disopyramide | Norpace | Antiarrhythmic | Arrhythmia | | oral, injection |
| Dofetilide | Tikosyn | Antiarrhythmic | Arrhythmia | | oral |

## Appendix 15: Drugs with Known Risk of TdP; https://www.crediblemeds.org



| Generic Name | Brand Names (Partial List) | Drug Class | Therapeutic Use | Risk Category | Route |
|---|---|---|---|---|---|
| Domperidone *(Only on Non US Market)* | Motilium, Motillium, Motinorm Costi, Nomit | Antiemetic | Nausea, vomiting | | oral, injection, suppository |
| Donepezil | Aricept | Cholinesterase Inhibitor | Dementia (Alzheimer's Disease) | | oral |
| Dronedarone | Multaq | Antiarrhythmic | Arrhythmia | | oral |
| Droperidol | Inapsine, Droleptan, Dridol, Xomolix | Antipsychotic / Antiemetic | Anesthesia (adjunct), nausea | | injection |
| Erythromycin | E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tilloryth | Antibiotic | Bacterial infection, increase GI motility | | oral, injection |
| Escitalopram | Cipralex, Lexapro, Nexito, Anxiset-E (India), Exodus (Brazil), Esto (Israel), Seroplex, Ellicea, Lexamil, Lexam, Entact (Greece), Losita (Bangladesh), Reposil (Chile), Animaxen (Colombia), Esitalo (Australia), Lexamil (South Africa) | Antidepressant, SSRI | Depression (major), anxiety disorders | | oral |
| Flecainide | Tambocor, Almarytm, Apocard, Ecrinal, Flécaine | Antiarrhythmic | Arrhythmia | | oral |
| Fluconazole | Diflucan, Trican | Antifungal | Fungal infection | | oral, injection |
| Gatifloxacin *(Removed from US Market)* | Tequin | Antibiotic | Bacterial infection | | oral, injection |
| Grepafloxacin *(Removed from US Market)* | Raxar | Antibiotic | Bacterial infection | | oral |
| Halofantrine *(Only on Non US Market)* | Halfan | Antimalarial | Malaria | | oral |
| Haloperidol | Haldol (US & UK), Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol (Germany), Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol | Antipsychotic | Schizophrenia, agitation | | oral, injection |
| Hydroquinidine (Dihydroquinidine) *(Only on Non US Market)* | Serecor | Antiarrhythmic | Arrhythmia | | oral |
| Ibogaine *(Only on Non US Market)* | None | Psychedelic | Narcotic addiction, unproven | | oral |
| Ibutilide | Corvert | Antiarrhythmic | Arrhythmia | | injection |

## Appendix 15: Drugs with Known Risk of TdP; https://www.crediblemeds.org



| Generic Name | Brand Names (Partial List) | Drug Class | Therapeutic Use | Risk Category | Route |
|---|---|---|---|---|---|
| Levofloxacin | Levaquin, Tavanic | Antibiotic | Bacterial infection | | oral, injection |
| Levomepromazine (Methotrimeprazine) *(Only on Non US Market)* | Nosinan, Nozinan, Levoprome | Antipsychotic | Schizophrenia | | oral, injection |
| Levomethadyl acetate *(Removed from US Market)* | Orlaam | Opioid agonist | Narcotic dependence | | oral |
| Levosulpiride *(Only on Non US Market)* | Lesuride, Levazeo, Enliva (with rabeprazole) | Antipsychotic | Schizophrenia | | oral, injection |
| Mesoridazine *(Removed from US Market)* | Serentil | Antipsychotic | Schizophrenia | | oral |
| Methadone | Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon | Opioid agonist | Narcotic dependence, pain | | oral, injection |
| Moxifloxacin | Avelox, Avalox, Avelon | Antibiotic | Bacterial infection | | oral, injection |
| Ondansetron | Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax | Antiemetic | Nausea, vomiting | | oral, injection, suppository |
| Oxaliplatin | Eloxatin | Anti-cancer | Cancer | | injection |
| Papaverine HCl (intra-coronary) | none | Vasodilator, Coronary | Diagnostic adjunct | | injection |
| Pentamidine | Pentam | Antifungal | Fungal infection (Pneumocystis pneumonia) | | injection, inhaled |
| Pimozide | Orap | Antipsychotic | Tourette's Disorder | | oral |
| Probucol *(Removed from US Market)* | Lorelco | Antilipemic | Hypercholesterolemia | | oral |
| Procainamide | Pronestyl, Procan | Antiarrhythmic | Arrhythmia | | injection |
| Propofol | Diprivan, Propoven | Anesthetic, general | Anesthesia | | injection |
| Quinidine | Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora | Antiarrhythmic | Arrhythmia | | oral, injection |
| Roxithromycin *(Only on Non US Market)* | Rulide, Xthrocin, Roxi-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roxlmycinv, Roxomycin, Rulid, Tirabicin, Coroxin | Antibiotic | Bacterial infection | | oral |
| Sevoflurane | Ultane, Sojoum | Anesthetic, general | Anesthesia | | inhaled |
| Sotalol | Betapace, Sotalex, Sotacor | Antiarrhythmic | Arrhythmia | | oral |

## Appendix 15: Drugs with Known Risk of TdP; https://www.crediblemeds.org



| Generic Name | Brand Names (Partial List) | Drug Class | Therapeutic Use | Risk Category | Route |
|---|---|---|---|---|---|
| Sparfloxacin *(Removed from US Market)* | Zagam | Antibiotic | Bacterial infection | | oral |
| Sulpiride *(Only on Non US Market)* | Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor | Antipsychotic, atypical | Schizophrenia | | oral, inhaled |
| Sultopride *(Only on Non US Market)* | Barnetil, Barnotil, Topral | Antipsychotic, atypical | Schizophrenia | | oral, injection |
| Terfenadine *(Removed from US Market)* | Seldane | Antihistamine | Allergic rhinitis | | oral |
| Terlipressin *(Only on Non US Market)* | Terlpress, Glypressin, Terlipin, Remestyp, Tresil, Teriss and others | Vasoconstrictor | Septic shock | | injection |
| Terodiline *(Only on Non US Market)* | Micturin, Mictrol (not bethanechol) | Muscle relaxant | Bladder spasm | | oral |
| Thioridazine | Mellaril, Novoridazine, Thioril | Antipsychotic | Schizophrenia | | oral |
| Vandetanib | Caprelsa | Anti-cancer | Cancer (thyroid) | | oral |

**Known Risk of TdP** - Substantial evidence supports the conclusion that these drugs prolong the QT interval AND are clearly associated with a risk of TdP, even when taken as directed in official labeling.

**Possible Risk of TdP** - Substantial evidence supports the conclusion that these drugs can cause QT prolongation BUT there is insufficient evidence at this time that these drugs, when used as directed in official labeling, are associated with a risk of causing TdP.

**Conditional Risk of TdP** - Substantial evidence supports the conclusion that these drugs are associated with a risk of TdP BUT only under certain conditions (e.g. excessive dose, hypokalemia, congenital long QT or by causing a drug-drug interaction that results in excessive QT interval prolongation)

**Drugs to Avoid in Congenital Long QT** - Substantial evidence supports the conclusion that these drugs pose a risk of TdP for patients with congenital long QT. Drugs on this list include those in he above three risk categories and other drugs that do not prolong the QT interval per se but they have a theoretical risk of causing arrhythmia that is based on their known stimulant actions on the heart.

**Note:** Medicines on this list are reviewed on an ongoing basis to assure that the available evidence supports their continued placement on this list. The list changes regularly and we recommend checking the website at crediblemeds.org for the most up-to-date information. There may be many additional brand names that are not listed on this form.

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