PROTOCOL

TITLE:	**A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED PHASE III STUDY OF IPATASERTIB IN COMBINATION WITH PACLITAXEL AS A TREATMENT FOR PATIENTS WITH *PIK3CA/AKT1/PTEN*-ALTERED, LOCALLY ADVANCED OR METASTATIC, TRIPLE-NEGATIVE BREAST CANCER OR HORMONE RECEPTOR–POSITIVE, HER2-NEGATIVE BREAST CANCER**
PROTOCOL NUMBER:	CO40016
VERSION NUMBER:	11 (Cohort C)
EUDRACT NUMBER:	2017-001548-36
IND NUMBER:	133823
NCT NUMBER	NCT03337724
TEST PRODUCTS:	Ipatasertib (RO5532961, GDC-0068) 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
17-Feb-2022 21:49:01	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
11 (Cohort C)	see electronic date stamp on title page
10 (Cohort C)	9 February 2021
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PROTOCOL AMENDMENT, VERSION 11 (COHORT C)
RATIONALE

Protocol CO40016, Version 11 (Cohort C) has primarily been amended to align the protocol with the most recent Investigator's Brochures for Ipatasertib (Version 13) and Atezolizumab (Version 18). 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.
- Language added to allow Tumor Assessments to be performed per standard of care, (Section 3.1.1, Section 4.5.5, Appendix 1, Appendix 2) to reduce burden on patients.
- In Section 5.1.1 (Risks associated with ipatasertib in combination with paclitaxel), added that Investigators should refer to Section 6 of the ipatasertib Investigator's Brochure for a detailed description of anticipated safety risks for ipatasertib.
- 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- The medical term "primary biliary cirrhosis" has been replaced by the term "primary biliary cholangitis" to align with the updated preferred term in MedDRA (Appendix 11).
- Hepatoxicity management guidelines for ipatasertib added to align with ipatasertib Investigator's Brochure Version 13 (Appendix 13).
- Updates have been made to the management guidelines for atezolizumab for the following immune-mediated risks (Appendix 14, Appendix 15):
  - Pulmonary Events
  - Hepatic Events
  - Endocrine Events
  - Infusion-Related Reactions and Cytokine-Release Syndrome
  - Neurologic Disorders
  - Renal Events
  - Myositis
  - Dermatologic Events
- The footnotes of extended treatment interruption and rechallenging patients with atezolizumab after treatment discontinuation in all AE management tables updated to remove the requirement of the Medical Monitor (MM) approval. Instead, the role of the MM for safety-related issues has been updated to being available for advice (Appendix 14, Appendix 15).

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.

TABLE OF CONTENTS

PROTOCOL AMENDMENT ACCEPTANCE FORM 12

PROTOCOL SYNOPSIS 13

1. BACKGROUND 38

1.1 Background on Triple-Negative and Hormone-Receptor–Positive Breast Cancer 38

1.2 Background on Ipatasertib 39

1.3 Background on Atezolizumab 40

1.4 Background on Studies in TNBC Combining Ipatasertib and Atezolizumab 42

1.5 Study Rationale and Benefit-Risk Assessment 42

2. OBJECTIVES AND ENDPOINTS 46

3. STUDY DESIGN 54

3.1 Description of the Study 54

3.1.1 Overview of Study Design 54

3.2 End of Study and Length of Study 60

3.3 Rationale for Study Design 60

3.3.1 Rationale for Patient Population 60

3.3.2 Rationale for the China Extension Phase 62

3.3.3 Rationale for Ipatasertib and Paclitaxel Combination 62

3.3.3.1 Rationale for Immunotherapy in Breast Cancer 63

3.3.3.2 Rationale for Combining Ipatasertib with Atezolizumab 64

3.3.4 Rationale for Starting Dose and Schedule of Ipatasertib 64

3.3.5 Rationale for Treatment with Paclitaxel and Choice of Paclitaxel Regimen 65

3.3.6 Rationale for Atezolizumab Dose and Schedule 66

3.3.7 Rationale for Biomarker Assessments 67

3.3.7.1 Rationale for Using Archival Tissue for Examining *PIK3CA/AKT1/PTEN*-Altered Tumor Status 67

3.3.7.2 Rationale for Collection of Blood Samples for Noninvasive Disease Monitoring 68

3.3.7.3 Rationale for Collection of DNA (Blood) for Exploratory Whole Genome Sequencing 68
3.3.7.4 Rationale for Optional Collection of New Tumor Biopsies at Disease Progression for Exploratory Purposes 70
3.3.8 Rationale for the Pharmacokinetic Evaluation Schedule 70
3.3.9 Rationale for Patient-Reported Outcome Assessments 71
3.3.10 Rationale for Skeletal-Related Events Assessments 72
4. MATERIALS AND METHODS 72
4.1 Patients 72
4.1.1 Inclusion Criteria 72
4.1.2 Exclusion Criteria 77
4.2 Method of Treatment Assignment and Blinding 82
4.3 Study Treatment and Other Treatments Relevant to the Study Design 83
4.3.1 Study Treatment Formulation, Packaging, and Handling 84
4.3.1.1 Ipatasertib and Placebo 84
4.3.1.2 Atezolizumab 84
4.3.1.3 Paclitaxel 84
4.3.2 Study Treatment Dosage, Administration, and Compliance 84
4.3.2.1 Ipatasertib and Placebo 84
4.3.2.2 Atezolizumab 85
4.3.2.3 Paclitaxel 86
4.3.3 Other Treatments: Premedications and Prophylactic Treatment 87
4.3.4 Investigational Medicinal Product Accountability 87
4.3.5 Continued Access to Ipatasertib and Atezolizumab 88
4.4 Concomitant Therapy, Prohibited Food, and Additional Restrictions 89
4.4.1 Permitted Therapy 89

4.4.2 Cautionary Therapy 90
4.4.2.1 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes 91
4.4.2.2 Herbal Therapies 92
4.4.3 Prohibited Therapy 92
4.4.4 Prohibited Food 93
4.4.5 Additional Restrictions 93
4.5 Study Assessments 93
4.5.1 Informed Consent Forms and Screening Log 93
4.5.2 Medical History, Concomitant Medication, and Demographic Data 94
4.5.3 Physical Examinations 94
4.5.4 Vital Signs 95
4.5.5 Tumor and Response Evaluations 95
4.5.6 Laboratory, Biomarker, and Other Biological Samples 97
4.5.7 Electrocardiograms and Cardiac Function Assessment 100
4.5.8 Patient-Reported Outcomes 101
4.5.8.1 EORTC QLQ-C30 102
4.5.8.2 PRO-CTCAE 102
4.5.8.3 EQ-5D-5L 103
4.5.9 Skeletal-Related Events Assessment 103
4.5.10 Mandatory Samples for Whole Genome Sequencing 103
4.5.11 Post-Treatment Follow-Up 104
4.5.12 Optional Samples for Research Biosample Repository 104
4.5.12.1 Overview of the Research Biosample Repository 104
4.5.12.2 Approval by the Institutional Review Board or Ethics Committee 105
4.5.12.3 Sample Collection 105
4.5.12.4 Confidentiality 106
4.5.12.5 Consent to Participate in the Research Biosample Repository 106

4.5.12.6 Withdrawal from the Research Biosample Repository 107
4.5.12.7 Monitoring and Oversight 107
4.6 Treatment, Patient, Study, and Site Discontinuation 108
4.6.1 Study Treatment Discontinuation 108
4.6.2 Patient Discontinuation from Study 108
4.6.3 Study Discontinuation 109
4.6.4 Site Discontinuation 109
5. ASSESSMENT OF SAFETY 109
5.1 Safety Plan 109
5.1.1 Risks Associated with Ipatasertib in Combination with Paclitaxel 110
5.1.2 Risks Associated with Atezolizumab 111
5.1.3 Risks Associated with Combination Use of Atezolizumab and Ipatasertib 111
5.1.4 Risks Associated with Paclitaxel 111
5.1.5 Management of Patients Who Experience Specific Adverse Events 112
5.1.5.1 Dose Modifications 112
5.1.5.2 General Guidelines 112
5.1.5.3 Dosage Modification for Ipatasertib/Placebo and Paclitaxel 114
5.1.5.4 Treatment Interruption 115
5.1.5.5 Adverse Event Management Guidelines 116
5.2 Safety Parameters and Definitions 116
5.2.1 Adverse Events 116
5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor) 117
5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor) 118
5.2.4 Selected Adverse Events 119
5.3 Methods and Timing for Capturing and Assessing Safety Parameters 120
5.3.1 Adverse Event Reporting Period 120

5.3.2 Eliciting Adverse Event Information 120
5.3.3 Assessment of Severity of Adverse Events 121
5.3.4 Assessment of Causality of Adverse Events 121
5.3.5 Procedures for Recording Adverse Events 122
5.3.5.1 Infusion-Related Reactions 123
5.3.5.2 Diagnosis versus Signs and Symptoms 123
5.3.5.3 Adverse Events That Are Secondary to Other Events 123
5.3.5.4 Persistent or Recurrent Adverse Events 124
5.3.5.5 Abnormal Laboratory Values 124
5.3.5.6 Abnormal Vital Sign Values 125
5.3.5.7 Abnormal Liver Function Tests 126
5.3.5.8 Deaths 126
5.3.5.9 Preexisting Medical Conditions 126
5.3.5.10 Lack of Efficacy or Worsening of Breast Cancer 127
5.3.5.11 Hospitalization or Prolonged Hospitalization 127
5.3.5.12 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse 128
5.3.5.13 Patient-Reported Outcome Data 130
5.4 Immediate Reporting Requirements from Investigator to Sponsor 130
5.4.1 Emergency Medical Contacts 131
5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest 131
5.4.2.1 Events That Occur prior to Study Drug Initiation 131
5.4.2.2 Events That Occur after Study Drug Initiation 131
5.4.3 Reporting Requirements for Pregnancies 132
5.4.3.1 Pregnancies in Female Patients 132
5.4.3.2 Pregnancies in Female Partners of Male Patients 132
5.4.3.3 Abortions 133
5.4.3.4 Congenital Anomalies/Birth Defects 133
5.5 Follow-Up of Patients after Adverse Events 133
5.5.1 Investigator Follow-Up 133
5.5.2 Sponsor Follow-Up 134

5.6 Adverse Events That Occur after the Adverse Event Reporting Period 134
5.7 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees 134
6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN 135
6.1 Determination of Sample Size 135
6.2 Summaries of Conduct of Study 137
6.3 Summaries of Treatment Group Comparability 138
6.4 Efficacy Analyses 138
6.4.1 Primary Efficacy Endpoint 138
6.4.2 Secondary Efficacy Endpoints 139
6.4.2.1 Objective Response Rate with Duration of Response 139
6.4.2.2 Clinical Benefit Rate 139
6.4.2.3 Overall Survival 139
6.4.2.4 (Cohort C only) 1-Year PFS and 1-Year OS Rate 140
6.4.3 Exploratory Efficacy Endpoints 140
6.4.3.1 Progression-Free Survival 2 (PFS2) 140
6.4.3.2 Patient Subgroup Analysis in Cohort A 140
6.4.4 Time to First Skeletal-Related Event 140
6.4.5 Patient-Reported Outcome Analyses 140
6.4.5.1 Secondary Patient-Reported Outcome Endpoints 140
6.4.5.2 Exploratory Patient-Reported Outcome Analyses 141
6.5 Safety Analyses 141
6.5.1 Exploratory Safety Analysis 142
6.6 Pharmacokinetic Analyses 142
6.7 Biomarker Analyses 143
6.8 Interim Analyses 143
6.8.1 Planned Interim Safety Analyses 143
6.8.2 Safety monitoring will be performed on a continual basis by the Sponsor for Cohort C. Planned Interim OS Analysis at PFS Primary Analysis 143
6.8.3 Optional Interim Analyses 144

6.9 China Subgroup Analyses 145

7. DATA COLLECTION AND MANAGEMENT 146
7.1 Data Quality Assurance 146
7.2 Electronic Case Report Forms 146
7.3 Source Data Documentation 146
7.4 Use of Computerized Systems 147
7.5 Retention of Records 147

8. ETHICAL CONSIDERATIONS 148
8.1 Compliance with Laws and Regulations 148
8.2 Informed Consent 148
8.3 Institutional Review Board or Ethics Committee 149
8.4 Confidentiality 149
8.5 Financial Disclosure 150

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION 150
9.1 Study Documentation 150
9.2 Protocol Deviations 150
9.3 Site Inspections 151
9.4 Administrative Structure 151
9.5 Publication of Data and Protection of Trade Secrets 151
9.6 Protocol Amendments 152

10. REFERENCES 153

LIST OF TABLES

Table 1 Objectives and Corresponding Endpoints (Applicable for Both Cohort A and Cohort B, Unless Otherwise Stated) 48
Table 2 Objectives and Corresponding Endpoints (Cohort C) 51
Table 3 Administration of First and Subsequent Infusions of Atezolizumab 86
Table 4 Dose Reductions for Ipatasertib/Placebo 115
Table 5 Dose Reductions for Paclitaxel 115
Table 6 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE 121

Table 7 Causal Attribution Guidance 122

LIST OF FIGURES

Figure 1 Study Schema..... 58

LIST OF APPENDICES

Appendix 1 Schedule of Activities: Cohorts A and B..... 161
Appendix 2 Schedule of Activities: Cohort C..... 169
Appendix 3 Schedule of Pharmacokinetic and Immunogenicity Samples: Cohorts A and B..... 176
Appendix 4 Schedule of Pharmacokinetic and Immunogenicity, Samples: Cohort C..... 177
Appendix 5 ASCO/CAP Estrogen Receptor and Progesterone Receptor Guideline Recommendations..... 178
Appendix 6 ASCO/CAP HER2 Test Guideline Recommendations..... 180
Appendix 7 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)..... 188
Appendix 8 EuroQol 5-Dimension Questionnaire, Five-Level Version (EQ-5D-5L)..... 190
Appendix 9 Selected items from the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)..... 192
Appendix 10 Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication..... 194
Appendix 11 Preexisting Autoimmune Diseases and Immune Deficiencies . 205
Appendix 12 Anaphylaxis Precautions..... 206
Appendix 13 Guidelines for Management of Adverse Events for Patients in Cohorts A and B..... 207
Appendix 14 Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel)..... 220
Appendix 15 Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab..... 245

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED PHASE III STUDY OF IPATASERTIB IN COMBINATION WITH PACLITAXEL AS A TREATMENT FOR PATIENTS WITH *PIK3CA/AKT1/PTEN*-ALTERED, LOCALLY ADVANCED OR METASTATIC, TRIPLE-NEGATIVE BREAST CANCER OR HORMONE RECEPTOR–POSITIVE, HER2-NEGATIVE BREAST CANCER**
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MEDICAL MONITOR:	[redacted] M.D
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED PHASE III STUDY OF IPATASERTIB IN COMBINATION WITH PACLITAXEL AS A TREATMENT FOR PATIENTS WITH *PIK3CA/AKT1/PTEN*-ALTERED, LOCALLY ADVANCED OR METASTATIC, TRIPLE-NEGATIVE BREAST CANCER OR HORMONE RECEPTOR–POSITIVE, HER2-NEGATIVE BREAST CANCER**
PROTOCOL NUMBER:	CO40016
VERSION NUMBER:	11 (Cohort C)
EUDRACT NUMBER:	2017-001548-36
IND NUMBER:	133823
NCT NUMBER	NCT03337724
TEST PRODUCTS:	Ipatasertib (RO5532961, GDC-0068) Atezolizumab (RO5541267)
PHASE:	III
INDICATION:	Locally advanced unresectable or metastatic triple-negative breast cancer with *PIK3CA/AKT1/PTEN*-altered tumor and no prior chemotherapy in the advanced setting Locally advanced or metastatic hormone receptor–positive, HER2-negative breast cancer with *PIK3CA/AKT1/PTEN*-altered tumor and no prior chemotherapy in the advanced setting
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

Cohorts A and B will independently evaluate the safety, efficacy, and pharmacokinetics of ipatasertib in combination with paclitaxel (ipatasertib + paclitaxel) compared with placebo plus paclitaxel (placebo + paclitaxel) in patients with *PIK3CA/AKT1/PTEN*-altered tumors. Cohort A will evaluate first-line treatment in patients with locally advanced unresectable or metastatic triple-negative breast cancer (TNBC), and Cohort B will evaluate first-chemotherapy treatment in patients with advanced hormone receptor–positive, HER2-negative (HR+/HER2−) breast cancer who are not appropriate candidates for endocrine therapy (as defined by the Sponsor). Patients will be enrolled based on central or local/commercial determination of PIK3CA/AKT1/PTEN-altered status, with central assessment of *PIK3CA/AKT1/PTEN*-altered status in tumor tissue performed in any patients enrolled using alternative methods and will be allocated to one of the cohorts based on hormone-receptor status. Patients with HER2-positive breast cancer are not eligible. The reason that the Cohorts A and B will be evaluated separately is that TNBC and HR+/HER2− breast cancers have different biologies that manifest clinically in different prognoses and response to treatment, and molecularly with distinctly different molecular profiles with dissimilar oncogenic drivers. The patients in Cohorts A and B have different prevalences and progression-free survival (PFS) and overall survival (OS) expectations, and thus different enrollment and analysis timelines.

Patients who initially screen for Cohort A (with TNBC) but do not qualify (i.e., lack of PIK3CA/AKT1/PTEN alteration validated by central tumor tissue testing using the FMI CTA)

may be eligible for Cohort C. Cohort C is an open-label, non-randomized cohort for patients with locally advanced unresectable or metastatic TNBC that will assess the safety, efficacy, and pharmacokinetics of ipatasertib in combination with paclitaxel and atezolizumab. Due to the differences in mechanism of action and evaluation of clinical benefit following cancer immunotherapy treatments, as well as delayed opening of Cohort C, this cohort will be evaluated separately from Cohorts A and B.

The target patient populations for this study are premenopausal and postmenopausal female and male patients with measurable, locally advanced unresectable or metastatic TNBC and HR+/HER2− breast cancer who have not received chemotherapy in either of these settings. Patients must be appropriate candidates for taxane monotherapy. In particular, patients with HR+/HER2− breast cancer should be suitable for treatment with chemotherapy (e.g., demonstrated insensitivity to endocrine therapy; reference eligibility criteria for Sponsor definition of endocrine-insensitivity). Prior adjuvant or neoadjuvant chemotherapy is allowed, provided it has been concluded at least 12 months before recurrence of (locally advanced unresectable or metastatic) disease.

Patients with *PIK3CA/AKT1/PTEN*-altered tumors will be assigned to Cohort A (TNBC) or Cohort B (HR+/HER2− breast cancer) based on their hormone receptor status (as evaluated locally, or on study, only if local evaluation is not available, with additional slides submitted for this purpose) and randomized with a 2:1 ratio to the experimental versus control arm. Patients with TNBC who are biomarker-negative (i.e., lack of PIK3CA/AKT1/PTEN alteration validated by central tumor tissue testing using the FMI CTA) but otherwise eligible will be assigned to Cohort C to receive ipatasertib in combination with atezolizumab and paclitaxel until this cohort is fully accrued. All primary, secondary, exploratory, and safety objectives will be assessed independently for each cohort (i.e., Cohort A: patients with TNBC with *PIK3CA/AKT1/PTEN*-altered tumors, Cohort B: patients with HR+/HER2− breast cancer with *PIK3CA/AKT1/PTEN*-altered tumors and Cohort C: patients with TNBC whose tumors lack PIK3CA/AKT1/PTEN alteration validated by central tumor tissue testing using the Foundation Medicine Clinical Trial Algorithm).

The primary endpoint is PFS for all cohorts. The primary analysis for each cohort will be independent and triggered by cohort-specific events and will also be independent of the readout of the other cohort. The secondary endpoints for Cohorts A and B will be tested if the primary analysis of the respective PFS reaches statistical significance at the level of 5%.

Specific objectives and corresponding endpoints for each cohort will be analyzed independently following cohort-specific statistical analysis plans, and are outlined in the tables below.

Table 1 Objectives and Corresponding Endpoints (Applicable for Both Cohort A and Cohort B, Unless Otherwise Stated)

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the efficacy of ipatasertib + paclitaxel compared with placebo + paclitaxel	• PFS, defined as the time from randomization to the first occurrence of disease progression, as determined locally by the investigator through the use of RECIST v1.1, or death from any cause, whichever occurs first
Secondary Efficacy Objectives:	
• To evaluate the efficacy of ipatasertib + paclitaxel compared with placebo + paclitaxel	• Objective response rate, defined as a CR or PR on two consecutive occasions $\geq$4 weeks apart, as determined locally by the investigator through the use of RECIST v1.1 • Duration of response, defined as the time from the first occurrence of a documented objective response to disease progression, as determined locally by the investigator through use of RECIST v1.1, or death from any cause, whichever occurs first • Clinical benefit rate, defined as an objective response (CR or PR), or stable disease for at least 24 weeks, as determined locally by the investigator through the use of RECIST v1.1 • OS, defined as the time from randomization to death from any cause

Table 1 Objectives and Corresponding Endpoints (Applicable for Both Cohort A and Cohort B, Unless Otherwise Stated) (cont.)

Objectives	Corresponding Endpoints
Secondary Efficacy Objectives (cont.):	
• To evaluate PROs of GHS/HRQoL associated with ipatasertib + paclitaxel compared with placebo + paclitaxel	• Mean and mean changes from baseline GHS/HRQoL score as measured by the GHS/HRQoL scale (Questions 29 and 30) of the EORTC QLQ-C30, by cycle
• To evaluate PROs of disease-related pain of ipatasertib + paclitaxel compared with placebo + paclitaxel (Cohort B only)	• Time to deterioration in pain, defined as the first minimally important increase of ≥11 points from the baseline pain scale score (Questions 9 and 19) of the EORTC QLQ-C30
Exploratory Efficacy Objectives:	
• To evaluate the efficacy of ipatasertib + paclitaxel compared with placebo + paclitaxel in TNBC (Cohort A only) patients with tumors that have the following: – *PIK3CA/AKT1*-activating mutations – *PTEN* alterations (and no *PIK3CA/AKT1*-activating mutations)	• PFS • Objective response rate • Duration of response • Clinical benefit rate • OS
• To evaluate PROs of function and disease/treatment-related symptoms associated with ipatasertib + paclitaxel compared with placebo + paclitaxel	• Mean and mean changes from baseline scores in functional (i.e., role, physical, cognitive, emotional, and social) and disease/treatment-related symptoms by cycle as assessed by the functional and symptom scales of the EORTC QLQ-C30
• To collect utilities for pharmacoeconomic modeling	• Health states for utility assessment and the VAS as measured by the EQ-5D-5L questionnaire for modeling
• To evaluate the clinical benefit	• PFS2, defined as the time from randomization to first objective disease progression on next-line treatment, or death from any cause, whichever occurs first • Time to first skeletal–related event (SRE), defined as the time from randomization to the occurrence of an SRE. An SRE is either a pathologic fracture, radiation therapy to the bone, surgery to the bone, or spinal cord compression.

Table 1 Objectives and Corresponding Endpoints (Applicable for Both Cohort A and Cohort B, Unless Otherwise Stated) (cont.)

Objectives	Corresponding Endpoints
Exploratory Efficacy Objectives (cont.):	
• To evaluate analgesic use in ipatasertib + paclitaxel and placebo + paclitaxel treatment arms (Cohort B only)	• Change in use of opioid and non-opioid analgesics during treatment, as measured by the intake of analgesic treatments
Safety Objective:	
• To evaluate the safety of ipatasertib + paclitaxel compared with placebo + paclitaxel	• Incidence of adverse events as assessed by the investigator, with severity determined through the use of NCI CTCAE v4.0 • Incidence of prespecified adverse events • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Exploratory Safety Objective:	
• To collect PROs regarding key symptomatic adverse events of ipatasertib + paclitaxel compared with placebo + paclitaxel	• Selected items from the PRO-CTCAE capturing patients' rating of the presence, severity, frequency, and/or interference of diarrhea, nausea, vomiting, decreased appetite, fatigue, neuropathy, mouth sores, and rash symptoms and an additional item regarding bother due to side effects of treatment
Pharmacokinetic Objective:	
• To characterize the pharmacokinetics of ipatasertib and its metabolite (G-037720) when administered in combination with paclitaxel	• Plasma concentration of ipatasertib and G-037720 at specified timepoints for analysis using population PK methodology
Exploratory Pharmacokinetic Objective:	
• To evaluate potential relationships between ipatasertib exposure, efficacy, and safety of ipatasertib + paclitaxel compared with placebo + paclitaxel	• Relationship between ipatasertib PK and efficacy endpoints • Relationship between ipatasertib PK and safety endpoints

Table 1 Objectives and Corresponding Endpoints (Applicable for Both Cohort A and Cohort B, Unless Otherwise Stated) (cont.)

Exploratory Biomarker Objectives:	
• To evaluate predictive or prognostic biomarkers (plasma or tissue) associated with disease activity status or response to treatment • 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 • To evaluate alternative diagnostics testing methods for *PIK3CA/AKT1/PTEN*-altered status	• Relationship between tissue- and blood-based biomarkers and patient clinical features (e.g., baseline features) and outcome (e.g., duration of PFS) • 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 • Associations of breast cancer subtypes defined by molecular signatures with patient outcomes • Association of *BRCA*1/2 genetic alterations and homologous repair deficiency with patient outcomes

BRCA = breast and ovarian cancer susceptibility gene; CR = complete response; EORTC = European Organisation for Research and Treatment of Cancer; GHS = global health status; HRQoL = health-related quality of life; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; PK = pharmacokinetics; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; TNBC = triple-negative breast cancer; VAS = visual analog scale.

Table 2 Objectives and Corresponding Endpoints (Cohort C)

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the efficacy of ipatasertib + paclitaxel + atezolizumab	• PFS, defined as the time from enrollment to the first occurrence of disease progression, as determined locally by the investigator through the use of RECIST v1.1, or death from any cause, whichever occurs first
Secondary Efficacy Objectives:	
• To evaluate the efficacy of ipatasertib + paclitaxel + atezolizumab	▪ Objective response rate, defined as a CR or PR on two consecutive occasions $\geq$4 weeks apart, as determined locally by the investigator through the use of RECIST v1.1 • Duration of response, defined as the time from the first occurrence of a documented objective response to disease progression, as determined locally by the investigator through use of RECIST v1.1, or death from any cause, whichever occurs first • Clinical benefit rate, defined as an objective response (CR or PR), or stable disease for at least 24 weeks, as determined locally by the investigator through the use of RECIST v1.1 • OS, defined as the time from enrollment to death from any cause • 1–year PFS defined as progression-free survival probabilities at 1 year. • 1–year OS defined as overall survival probabilities at 1 year.
• To evaluate PROs of GHS/HRQoL associated with ipatasertib + paclitaxel + atezolizumab	• Mean and mean changes from baseline GHS/HRQoL score as measured by the GHS/HRQoL scale (Questions 29 and 30) of the EORTC QLQ-C30, by cycle
• To evaluate PROs of disease-related pain of ipatasertib + paclitaxel + atezolizumab	• Time to deterioration in pain, defined as the first minimally important increase of >10 points from the baseline pain scale score (Questions 9 and 19) of the EORTC QLQ-C30

Table 2 Objectives and Corresponding Endpoints (Cohort C) (cont.)

Objectives	Corresponding Endpoints
Exploratory Efficacy Objectives: (cont.)	
• To evaluate PROs of function and disease/treatment-related symptoms associated with ipatasertib + paclitaxel + atezolizumab	• Mean and mean changes from baseline scores in functional (i.e., role, physical, emotional, cognitive, and social) and disease/treatment-related symptoms by cycle as assessed by the functional and symptom scales of the EORTC QLQ-C30
• To collect utilities for pharmacoeconomic modeling	• Health states for utility assessment and the VAS as measured by the EQ-5D-5L questionnaire for modeling
• To evaluate the clinical benefit	• PFS2, defined as the time from enrollment to first objective disease progression on next-line treatment, or death from any cause, whichever occurs first • Time to first skeletal–related event (SRE), defined as the time from treatment assignment to the occurrence of an SRE. An SRE is either a pathologic fracture, radiation therapy to the bone, surgery to the bone, or spinal cord compression.
Safety Objective:	
• To evaluate the safety of ipatasertib + paclitaxel + atezolizumab	• Incidence of adverse events as assessed by the investigator, with severity determined through the use of NCI CTCAE v4.0 • Incidence of prespecified adverse events • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Exploratory Safety Objective:	
• To collect PROs regarding key symptomatic adverse events of ipatasertib + paclitaxel + atezolizumab	• Selected items from the PRO-CTCAE capturing patients' rating of the presence, severity, frequency, and/or interference of diarrhea, nausea, vomiting, decreased appetite, fatigue, neuropathy, mouth sores, and rash symptoms and an additional item regarding bother due to side effects of treatment

Table 2 Objectives and Corresponding Endpoints (Cohort C) (cont.)

Objectives	Corresponding Endpoints
Pharmacokinetic Objective:	
• To characterize the pharmacokinetics of atezolizumab, ipatasertib and its metabolite (G-037720) when administered in combination with paclitaxel	• Plasma concentration of ipatasertib and its metabolite, G-037720 at specified timepoints for analysis using population PK methodology • Serum concentration of atezolizumab at specified timepoints
Exploratory Pharmacokinetic Objective:	
• To evaluate potential relationships between ipatasertib and/or atezolizumab exposure, efficacy, and safety of ipatasertib + paclitaxel + atezolizumab	• Relationship between ipatasertib and/or atezolizumab PK and efficacy endpoints • Relationship between ipatasertib and/or atezolizumab PK and safety endpoints
Immunogenicity Objective:	
• To evaluate the immune response to atezolizumab	• Incidence of ADAs to atezolizumab during the study relative to the prevalence of ADAs at baseline
Exploratory Immunogenicity Objective:	
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objectives:	
• To evaluate predictive or prognostic biomarkers (plasma or tissue) associated with disease activity status or response to treatment • 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 • To evaluate alternative diagnostics testing methods for PIK3CA/AKT1/PTEN-altered status	• Relationship between tissue- and blood-based biomarkers and patient clinical features (e.g., baseline features) and outcome (e.g., duration of PFS) • 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 • Associations of breast cancer subtypes defined by molecular signatures with patient outcomes • Association of BRCA1/2 genetic alterations and homologous repair deficiency with patient outcomes

ADA = anti-drug antibody; BRCA = breast and ovarian cancer susceptibility gene; CR = complete response; EORTC = European Organisation for Research and Treatment of Cancer; GHS = global health status; HRQoL = health-related quality of life; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; PK = pharmacokinetics; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; TNBC = triple-negative breast cancer; VAS = visual analog scale.

Study Design

Description of Study

The two-cohort (Cohorts A and B), randomized, double-blind, placebo-controlled portion of this Phase III study is designed to evaluate the efficacy of ipatasertib + paclitaxel versus placebo ± paclitaxel in patients with histologically confirmed, locally advanced unresectable or metastatic TNBC and in patients with locally advanced unresectable or metastatic HR+/HER2- breast adenocarcinoma who are not suitable for endocrine therapy (as defined by Sponsor; see eligibility criteria). Each cohort will be independent with separate analyses, but with a single screening process to identify, allocate, and subsequently stratify on the basis of histologic and diagnostic status. Patients must have measurable disease as defined by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) and a *PIK3CA/AKT1/PTEN*-altered tumor as determined either centrally or using local/commercial molecular testing, by a clinical cancer genomic profiling laboratory (e.g., Foundation Medicine, Inc. [FMI]) or a CLIA [or equivalently accredited] diagnostic laboratory). Tumor *PIK3CA/AKT1/PTEN*-altered status is defined as the presence of *PTEN* alterations or *PIK3CA/AKT1*-activating mutations as determined by any blood- or tissue-based molecular assay (see Disease-Specific Inclusion Criteria for further details). Pathological determination of estrogen receptor (ER), progesterone receptor (PgR), and HER2 status based on local assessment according to American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) guidelines will be applied for cohort assignment by an interactive voice or Web-based response system (IxRS), with subsequent randomization within each cohort based on the appropriate stratification factors for the different cohorts. Patients who have unknown tumor ER, PgR, HER2, or *PIK3CA/AKT1/PTEN*-altered status and for whom determination of status is not possible are not eligible for this study.

If a patient will screen for biomarker eligibility with the tissue-based FMI CTA, time for tumor tissue retrieval, shipping, and turnaround of eligibility results should be taken into account when screening patients (and submitted sample should be sufficient per protocol requirements to have maximum likelihood that a valid result can be obtained).

As the FoundationACT™ (FACT) assay is not able to detect all qualifying alterations that may be identified using the FMI CTA, tissue submission should not be delayed as patients may qualify by the latter, rather than by FACT. FACT testing at FMI may not necessarily be faster than the FMI CTA and, therefore, should only be performed when it is anticipated that there will be a significant delay to acquisition of existing tumor tissue.

If local/commercial testing is available, demonstrating a qualifying alteration, or if this result is obtained, these results may be used to determine biomarker eligibility. However, please note, for patients not enrolled on the basis of the FMI tissue-based CTA (e.g., local/commercial tests or blood-based FACT assay), submission of tumor tissue is still required, but randomization should proceed based on the local result with no requirement to wait for central assessment of biomarker eligibility.

Treatment benefit in patients with *PIK3CA/AKT1/PTEN*-altered tumors will be independently compared in patients with triple-negative receptor status and in patients with HR+/HER2− status.

Approximately 349 patients with TNBC (249 biomarker-positive patients and 100 biomarker negative patients), and 201 biomarker-positive patients with HR+/HER2− breast cancer will be enrolled at approximately 165−195 centers worldwide during the global enrollment phase. Patients will be assigned to either Cohort A (TNBC biomarker-positive), Cohort B (HR+/HER2-biomarker-positive breast cancer), or Cohort C (TNBC biomarker-negative) according to the most recent locally assessed pathologically documented receptor status and PIK3CA/AKT1/PTEN alteration status. Receptor status should be assessed in their recurrent or metastatic tumor where applicable and if safely accessible, per ASCO/CAP guidelines. Patients in Cohorts A and B will be randomly assigned in a 2:1 ratio to the experimental arm (ipatasertib 400 mg + paclitaxel) or control arm (placebo + paclitaxel). Approximately 100 patients with TNBC who screen for Cohort A who are shown not to have a PIK3CA/AKT1/PTEN-altered tumor by centrally tested FMI CTA may be assigned to Cohort C to receive ipatasertib in combination with atezolizumab and paclitaxel, unless the cohort is completely accrued.

Randomization for patients in Cohort A and B will be stratified by the following factors: prior adjuvant/neoadjuvant chemotherapy (yes vs. no), region (Asia-Pacific vs. Europe vs. North

America vs. rest of the world), tumor *PIK3CA/AKT1/PTEN*-alteration status (*PIK3CA/AKT1*-activating mutations vs. *PTEN* alterations with no *PIK3CA/AKT1*-activating mutations; Cohort A only), and prior therapy with a phosphoinositide 3-kinase (PI3K) or mTOR inhibitor (yes vs. no; Cohort B only).

All patients must have a validated *PIK3CA/AKT1/PTEN*-alteration status using a blood- or tissue-based molecular assay and must have consented to provide sufficient archival tissue or newly obtained tumor biopsy tissue for central molecular evaluation to be eligible for enrollment. If the patient already has *PIK3CA/AKT1/PTEN* alteration results available from the FMI commercial tissue-based NGS assay known as FoundationONE CDx™, then the FMI CTA does not need to be re-run; in this situation the lesser amount of tissue specified within the protocol is acceptable for other protocol-mandated secondary and exploratory assessments, upon approval of the Medical Monitor. Given the probability of *PIK3CA/AKT1/PTEN* non-altered status (approximately 80%–85% for TNBC and 50%–60% for HR positive by blood-based NGS assay, such as FACT, and 55%–65% by tissue-based NGS, such as FMI CTA), it remains an option to use the biomarker-specific ICF/screening process first, prior to other study screening procedures for those patients who require central testing of biomarker status. It is advised that even if the patient will be screened for biomarker eligibility on the basis of the FACT (or other blood-based) NGS assay, that tissue be submitted as quickly. In blood, the fraction of available circulating tumor DNA (ctDNA) to sequence is less than that in tumor tissue, and because of this biology, it is expected that the FACT assay will not detect all alterations that can be identified using tissue-based NGS; i.e., even if there is biomarker ineligibility based on the blood-based assay, the patient may still qualify on the basis of the tissue-based assay.

All patients in Cohorts A and B will receive paclitaxel chemotherapy (80 mg/m^2 IV) on Days 1, 8, and 15 of each 28-day cycle and either ipatasertib at a dose of 400 mg administered orally once a day (QD) on Days 1–21 of each 28-day cycle (experimental arm) or placebo orally QD on Days 1–21 of each 28-day cycle (control arm). In Cohort C, patients will receive paclitaxel chemotherapy (80 mg/m^2 IV) on Days 1, 8, and 15 of each 28-day cycle, ipatasertib at a dose of 400 mg administered orally once a day (QD) on Days 1–21 of each 28-day cycle, and atezolizumab 840 mg IV on Days 1 and 15 of each 28-day cycle. Study treatment will continue until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination. Upon treatment discontinuation, patients will be followed every 3 months for survival, PROs, and new anti-cancer therapy and outcome (therapy/procedures, doses, start and stop date, best responses, most recent tumor assessment date, and progression date). *As of Protocol CO40016 Version 11 (Cohort C), these long-term follow-up assessments are no longer required.*

As of Protocol CO40016 Version 11 (Cohort C), tumor measurement for disease evaluation will be performed *per standard of care*, regardless of whether patients receive study treatment during the treatment cycle. For estimation of PFS, objective response rate (ORR), and duration of response (DOR), 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 8–12 weeks for tumor assessments until documented progression per RECIST v1.1, elective withdrawal from the study, or study completion or termination *(as of Protocol CO40016 Version 11 [Cohort C] this is no longer required)*. Images for tumor assessments for all patients will be prospectively collected to enable retrospective blinded independent central review when needed. As of protocol CO40016 Version 10 (Cohort C), images for tumor assessments will no longer be collected for blinded independent central review.

The pharmacokinetics of ipatasertib and its metabolite G-037720 will be assessed in all patients receiving ipatasertib. Safety will be evaluated on an ongoing basis in this study through the monitoring of all serious and non-serious adverse events and will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0).

An independent Data Monitoring Committee (iDMC) will periodically evaluate the safety of ipatasertib or placebo combined with paclitaxel (Cohorts A and B). The analysis supporting iDMC review will be conducted by an independent Data Coordinating Center (iDCC) and provided to the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter. Safety monitoring will be performed on a continual basis by the Sponsor for Cohort C.

No interim analysis of the primary efficacy endpoint PFS is planned. One interim OS analysis (at the time of the primary analysis for PFS) for each cohort is planned.

Analysis of safety and efficacy for each cohort will be performed independently.

Crossover is not allowed (Cohorts A and B).

Potential China Extension Phase for Cohorts A and B

After completion of the global enrollment phase, as needed, additional patients may be enrolled at China Food and Drug Administration (CFDA)-recognized sites in an extended enrollment phase to ensure a total of up to 90 patients with TNBC and up to 120 patients with HR+/HER2−breast cancer, constituting the analysis population of a China subgroup. For each of Cohort A and Cohort B, patients from the China extension phase will be randomized in a 2:1 ratio to the two treatment arms, the same as during the global enrollment phase. Any Chinese patients enrolled in the China extension phase will undergo the same schedule of assessments and will receive study treatment as in the global study cohorts.

The China subgroup includes all Chinese patients enrolled in the global study cohorts and the China extension phase. The China subgroup analysis will be performed and summarized separately. The Chinese patients enrolled in the global study cohorts will be analyzed together with all other patients enrolled in the global study, and will be reported in the global study clinical study report.

Number of Patients

Approximately 450 patients with *PIK3CA/AKT1/PTEN*-altered tumors are expected to be enrolled in this study (~249 patients with TNBC in Cohort A and ~201 patients with HR+/HER2-breast cancer in Cohort B) during the global enrollment phase. Among the ~249 patients in Cohort A, at least 150 patients with a valid alteration as measured by central FMI testing is required. Additionally, approximately 100 patients with TNBC without PIK3CA/AKT1/PTEN-altered tumors are expected to be enrolled in Cohort C.

After the global enrollment phase is completed, additional Chinese patients may be enrolled in the China extension phase for up to a total of 90 Chinese patients with TNBC in Cohort A and up to a total of 120 Chinese patients with HR+/HER2− breast cancer in Cohort B.

Target Population

Inclusion Criteria

General Inclusion Criteria

Patients must meet the following general criteria for study entry:

- Signed Informed Consent Form(s)
- Woman or man age≥ 18 years at the time of signing the Informed Consent Form
- Eastern Cooperative Oncology Group 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, 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 patient value before starting heparin treatment). Patients receiving coumarin derivatives should have an INR between 2.0 and 3.0 assessed in two consecutive measurements 1 to 4 days apart. Patients should be on a stable anticoagulant regimen.

Serum creatinine < 1.5 × ULN or creatinine clearance ≥ 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 ≤ 150 mg/dL and HbA_{1C} ≤ 7.5%

- Life expectancy of at least 6 months
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib/placebo, 5 months after the last dose of atezolizumab, and 6 months after the last 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 (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

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

  With female partners of childbearing potential, 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 last dose of ipatasertib or 6 months after the last 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 last dose of ipatasertib or 6 months after the last 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 interuterine device, 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.

- 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:

- Histologically documented TNBC or HR+/HER2– 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 on-study, if not available locally) according to the ASCO/CAP guidelines:

  HER2+ is defined as one of the following: immunohistochemistry 3+ or in situ hybridization positive

  ER or PgR positivity is defined as ≥ 1% of tumor cell nuclei immunoreactive to the respective hormonal receptor

  TNBC is defined as HER2–, ER–, and PgR– (required for eligibility for Cohort A)

  HR+/HER2– is defined as HER2– and ER+ and/or PgR+ (required for eligibility for Cohort B)

- Measurable disease according to RECIST v1.1
- Eligible for taxane monotherapy, as per local investigator assessment (e.g., absence of rapid clinical progression, life-threatening visceral metastases, or the need for rapid symptom and/or disease control which may require combination chemotherapy)
- HR+/HER2– breast cancer that is not considered appropriate for endocrine-based therapy **and** that meets one of the following inclusion criteria:
  - Patient has recurrent disease (locoregional or metastatic) during adjuvant endocrine therapy (i.e., ≤5 years of being on therapy).
  - If patient has de novo metastatic disease, patient has progressive disease within 6 months of being on first-line endocrine treatment of metastatic disease.

  Note that prior treatment with CDK4/6 inhibitors or mTOR inhibitors is allowed.
- Submission of a formalin-fixed, paraffin-embedded tumor (FFPE) tissue block or a minimum of 20 freshly cut unstained, serial tumor slides from the most recently collected tumor tissue for central molecular analysis (mandatory NGS testing [*PIK3CA/AKT1/PTEN*-altered 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.

  If a newer specimen is either insufficient or unavailable, the patient may still be eligible if the patient can provide a tissue block (preferred) or a minimum of 20 unstained serial slides from an older archival tumor tissue or is willing to consent to and undergo an additional pretreatment core or excisional biopsy of the non-target lesion (if it is assessable and the biopsy can be safely obtained). In general, a minimum of three core biopsies for NGS testing are required.

  If the patient already has PIK3CA/AKT1/PTEN alteration results available from the FMI commercial tissue-based NGS assay known as FoundationONE CDx™, then the FMI clinical trial assay (CTA) does not need to be rerun; in this situation formalin-fixed, paraffin-embedded tumor (FFPE) tissue block or 10 freshly cut unstained, serial tumor slides from the most recently collected tumor tissue is

acceptable for other protocol-mandated secondary and exploratory assessments, upon approval by the Medical Monitor.

Please note, this tumor tissue sample is required to be submitted as described above for all patients (i.e., if local assessment of PIK3CA/AKT1/PTEN alteration status or central ctDNA is used to assess biomarker eligibility (see below), tumor tissue is still required to assess alteration status centrally.)

- Confirmation of biomarker eligibility, i.e., valid results from either central testing (in tumor tissue as detailed above or blood [using FACT assay]tested at FMI) or local/commercial testing of tumor tissue or blood (using an appropriately validated molecular assay at a diagnostic laboratory [full laboratory report must be available and captured within the patient's source documents to support eligibility]) demonstrating PIK3CA/AKT1/PTEN-altered status defined as the presence of one or more of the following:

  AKT1 missense mutations that result in amino acid substitution at the following residues E17, L52, or Q79

  PIK3CA missense mutations that result in amino acid substitution at the following residues R88, G106, K111, G118, N345, C420, E453, E542, E545, Q546, M1043, H1047, or G1049

  PTEN alterations that meet any of the following criteria:

  Homozygous deletion (copy number of 0)

  Dominant negative short variant (e.g., C124S, G129E, R130X)

  Loss of heterozygosity (LOH) with copy number of 1 without concomitant single-nucleotide variants

  One deleterious short variant (including insertions and deletions; classification criteria provided below) with a concomitant loss of the non-mutant PTEN allele defined by LOH with copy number of 1 or LOH with copy number >1.

  - Any protein truncating mutations, including nonsense mutations and frameshift indels
  - Any mutations in the consensus splice donor and acceptor sequence that disrupts the consensus, including insertions and deletions
  - Any missense or non-frameshift mutation that has been confirmed somatic as described in the COSMIC database
  - If there are two or more deleterious short variants under LOH, the patient will not be eligible for the study.

  Please note, for local/commercial testing using tumor tissue or blood, a valid result from the most recently collected tumor tissue/blood is preferred, however, the patient would still be eligible if a valid result is obtained from older archival tissue/blood sample.

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
- Active infection requiring systemic anti-microbial treatment (including antibiotics, anti-fungals, and anti-viral agents)
- Known HIV infection
- 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.

- 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 course of the study

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

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 28 days after the last dose of ipatasertib/placebo and within 6 months after the last 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 using Fridericia's formula (QTcF) $>$480 milliseconds
- 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)
- Need for chronic corticosteroid therapy of $\geq$10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease

  For Cohort C, no chronic corticosteroid use is permitted at baseline with rare exceptions. Refer to 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 render 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 brain or spinal cord metastases, as determined by computed tomography (CT) or magnetic resonance imaging (MRI) evaluation during screening or prior radiographic assessments

  Patients with leptomeningeal carcinomatosis will be excluded.

- Any previous chemotherapy for inoperable locally advanced or metastatic TNBC or HR+/HER2– adenocarcinoma of the breast

  Patients **may** have received prior neoadjuvant or adjuvant chemotherapy and/or radiation treatment for breast adenocarcinoma, provided all chemotherapy was completed $\geq$12 months prior to recurrence.

Patients with TNBC must not have received any previous systemic therapy for inoperable locally advanced or metastatic TNBC, including chemotherapy, immune checkpoint inhibitors, or targeted agents.

Chemotherapy does not include HER2-targeted therapy, such as trastuzumab, pertuzumab, or neratinib (for cases in which patients had early stage HER2+ breast cancer and are entering the study with HER2− advanced breast cancer). The minimum 12-month, disease-free inclusion requirement begins with the last administration of chemotherapy in the early breast cancer setting.

- Unresolved, clinically significant toxicity from prior therapy, except for alopecia and Grade 1 peripheral neuropathy
- Patients who have received palliative radiation treatment 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 radiation therapy.

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

  For other cancers considered to have a low risk of recurrence, discussion with the Medical Monitor is required.

  In cases where there is a history of early-stage breast cancer with ER/PR/HER2 status differing from the advanced breast cancer for which the patient is entering the study, the above language still applies (i.e., any breast cancer within the 5 years prior to consent is permitted, provided there is no controversy as to the current ER/PR/HER2 status.)

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's 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 that prior PI3K or mTOR inhibitors are allowed.

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

Atezolizumab-Specific Exclusion Criteria (Cohort C Only)

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's syndrome, Guillain-Barré syndrome, or multiple sclerosis (see the protocol for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

  Patients with a history of autoimmune-related 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 <u>all</u> 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 is 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 last 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 course of 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.

Length of Study

The total length of the study, from screening of the first patient to the end of the study (excluding the potential China extension phase), is expected to be approximately 53 months.

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

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal products (IMPs) for this study are ipatasertib, matching placebo, atezolizumab, and, dependent on local regulations, paclitaxel. Paclitaxel is an approved treatment for breast cancer and is considered standard of care in some countries. Loperamide (racecadotril as used in Europe) is a non-IMP in the study. The sequence of drug administration is ipatasertib/placebo, then atezolizumab (only for patients in Cohort C), and then paclitaxel. On non-atezolizumab administration days, the sequence of drug administration is ipatasertib/placebo and then paclitaxel.

Each dose of ipatasertib should be taken with a minimum of 3 ounces (90 mL) of fluid. Ipatasertib 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. Missed or vomited doses will not be made up.

Patients will receive atezolizumab 840 mg administered by IV infusion Q2W (on Days 1 and 15 [±3] days) of each 28-day cycle. Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

The dose of paclitaxel in this study is 80 mg/m^2 administered 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. Calculation of body surface area for the purposes of dosing of paclitaxel should be made according to the prescribing information. If the patient's weight changes by $>$ 10% during the study, the body surface area and drug doses should be recalculated.

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.

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 H_2-receptor blocker (i.e., ranitidine or famotidine) or per institutional practice. H_2-receptor antagonists, such as cimetidine, which are known to inhibit cytochrome P450, are excluded.

Comparator

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. Placebo will be administered at the starting dose of 400 mg orally QD, beginning on 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 placebo prior to the IV infusion of paclitaxel.

Each dose of placebo should be taken with a minimum of 3 ounces (90 mL) of fluid. 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. Missed or vomited doses will not be made up.

Non-Investigational Medicinal Products

Loperamide is a non-investigational medicinal product (non-IMP) in the study. All patients should receive loperamide (2 mg oral twice a day or 4 mg once a day) as prophylaxis for diarrhea in the first cycle if allowed by local guidance. Investigators are encouraged to continue this dosing for the remainder of the study, and the prophylaxis dose may be adjusted as necessary, using their discretion based on clinical judgment and per local guidance.

Statistical Methods

The three cohorts, Cohort A (TNBC biomarker-positive), Cohort B (HR+/HER2– biomarker-positive breast cancer), and Cohort C (TNBC biomarker-negative) are three independent cohorts and will be analyzed separately for the following reasons:

- The three patient populations are distinct patient populations and are expected to have different prevalence and PFS and OS expectations, and thus different enrollment and analysis timelines.
- The readout from one cohort is independent of the readout of the other cohorts.
- This study is essentially three independent trials running under one protocol for operational efficiency.

Therefore, for all analyses described below, these three cohorts will be analyzed separately.

The global population will include all patients enrolled during the global enrollment phase (including patients enrolled at CFDA-recognized sites during that phase), and the China subgroup will include all patients enrolled at CFDA-recognized sites (i.e., during both the global enrollment phase and the extended China enrollment phase). Separate analyses will be performed for the global population and the China subgroup.

Primary Analysis

The primary efficacy endpoint is investigator-assessed PFS, defined as the time from randomization (Cohorts A and B) or enrollment (Cohort C) to the first occurrence of disease progression, as determined by the investigator using RECIST v1.1, or death from any cause, whichever occurs first. Data for patients who do not experience disease progression or death will be censored at the last date of evaluable tumor assessment. For patients who do not have an evaluable tumor assessment after randomization/enrollment, the data will be censored at the date of randomization plus 1 day.

For Cohort A and Cohort B, PFS 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. Sensitivity analyses will be conducted to compare PFS between the treatment arms in patients with PIK3CA/AKT1/PTEN-altered tumors as centrally determined by the FMI CTA.

For each treatment arm in each cohort, Kaplan-Meier methodology will be used to estimate the median PFS, and the Brookmeyer-Crowley method will be used to construct the 95% CI for the median PFS (Brookmeyer and Crowley 1982). Kaplan-Meier curves will be produced as well.

Determination of Sample Size

As described earlier, Cohort A (TNBC biomarker-positive), Cohort B (HR+/HER2– biomarker-positive breast cancer), and Cohort C (TNBC biomarker-negative) are three independent cohorts and will be analyzed separately. Cohort A and Cohort B will be tested independently with 5% type I error control each. Cohort C is a single-arm cohort with no statistical hypothesis testing and will be reported descriptively only.

For unblinding of Cohort A and Cohort B, in the event that the primary PFS analysis timelines for the Cohort A and Cohort B are far apart, after the iDMC's review, the treatment codes of the cohort whose PFS data are mature earlier will be sent to the Sponsor to unblind only that cohort for the primary analysis of PFS. The Sponsor will remain blinded to the treatment assignments of the other cohort. Data from any additional patients enrolled within the China extension phase will not be included in the analysis of the global study.

Global Study

For Cohort A, approximately 249 patients with TNBC with *PIK3CA/AKT1/PTEN*-altered tumors will be enrolled and randomized in a 2:1 ratio to the experimental arm (ipatasertib 400 mg + paclitaxel) and control arm (placebo + paclitaxel). The sample size of 249 patients is determined on the basis of the power calculation for the PFS and OS endpoints.

For Cohort B, approximately 201 HR+/HER2– patients with *PIK3CA/AKT1/PTEN*-altered tumors will be enrolled and randomized in a 2:1 ratio to the experimental arm (ipatasertib 400 mg + paclitaxel) and control arm (placebo + paclitaxel). The sample size of 201 patients is determined on the basis of the power calculation for the primary endpoint, PFS.

For Cohort C, approximately 100 patients with TNBC lacking PIK3CA/AKT1/PTEN-altered tumors will be enrolled and assigned to a single arm of ipatasertib plus atezolizumab plus paclitaxel. The sample size of 100 patients is determined on the basis of having a sufficient number of patients for efficacy signal seeking, as well as adding to current knowledge on the safety profile of this combination, and not delaying the enrollment of patients with TNBC for Cohorts A and C.

Potential China Extension

For the potential China extension phase, if at least 1 patient is enrolled into Cohorts A or B in mainland China, Hong Kong, or Taiwan during the global enrollment phase, additional patients may be enrolled at CFDA-recognized sites in an extended enrollment phase for up to a total of 90 Chinese patients with TNBC with PIK3CA/AKT1/PTEN-altered tumors and up to a total of 120 Chinese patients with HR+/HER2– breast cancer with PIK3CA/AKT1/PTEN-altered tumors; these patients will constitute an analysis population of a China subgroup. The sample size of this China subgroup is determined on the basis of showing consistency in the China subgroup for the primary endpoint and PFS with the global cohort.

Planned Interim Safety Analysis

An external iDMC will be set up to evaluate safety data in Cohorts A and B on a periodic basis. All summaries/analyses by treatment arm for the iDMC's review will be prepared by an external iDCC. 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.

The iDMC will convene a review of summaries of the safety data by cohort and by treatment arm after approximately 50 patients (in total from both cohorts) have competed 1 treatment cycle and approximately every 6 months thereafter until the time of the analysis of the primary efficacy endpoint for both cohorts are complete. In the absence of extenuating circumstances, accrual will not be halted while the 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. In addition, the Sponsor may request ad hoc meetings of the iDMC at any time during the study to review ongoing safety summary data.

Safety monitoring will be performed on a continual basis by the Sponsor for Cohort C.

Planned Interim OS Analysis at PFS Primary Analysis

For Cohort A, interim OS will be analyzed at the time of the primary analysis for PFS, and final OS will be analyzed at the time that approximately 188 OS events occur or around after a minimum follow-up of 36 months after the last patient has been enrolled, whichever is earlier. The Lan-DeMets α-spending function with an O'Brien-Fleming boundary will be used to control the type I error accounting for OS interim and final analyses. With a sample size of 249 patients in Cohort A, it is estimated that there will be approximately 75 OS events at the time of PFS primary analysis, and approximately 188 OS events at the final OS analysis, with corresponding p-value boundaries of (0.000774, 0.049737). The corresponding hazard ratio boundaries are 0.44 and 0.74 at interim and final analysis, respectively. The actual alpha-spending will be adjusted and determined based on the actual information fraction at the interim analysis.

For Cohort B, interim OS will be analyzed at the time of the primary analysis for PFS, and final OS will be at the time that approximately 148 OS events occur or around 5 years after the last patient has been enrolled. The Lan-DeMets α-spending function with an O'Brien-Fleming boundary will be used to control the type I error accounting for OS interim and final analyses. For Cohort B, it is estimated that there will be approximately 81 OS events at the time of PFS primary analysis, and approximately 148 OS events at the final OS analysis, with corresponding p-value boundaries of (0.00489, 0.04842). The corresponding hazard ratio boundaries are 0.52 and 0.71 at interim and final analysis, respectively. The actual alpha-spending will be adjusted and determined based on the actual information fraction at the interim analysis.

Further details can be found in the SAP.

Optional Interim Analyses

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct an optional interim efficacy analysis, prior to the time of the primary analysis for PFS, with each cohort considered independently. For example, availability of clinical trial results for a specific external competitor molecule during the course of this study might (depending on the data) trigger an interim analysis, or the existence of an internal competitor molecule might necessitate an interim analysis to enable decision-making regarding continued development of the two molecules. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

The interim analysis will be conducted by an iDCC and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the SAP, and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC Charter will be updated to document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., stop the study for positive efficacy, stop the study for futility), and the iDMC Charter will also be made available to relevant health authorities.

If there is a potential for the study to be stopped for positive efficacy as a result of the interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained. Specifically, the Lan-DeMets α-spending function that approximates the O'Brien-Fleming boundary will be applied the primary endpoint of PFS to determine the critical value for stopping for positive efficacy at the interim analysis. Additional criteria for recommending that the study be stopped for positive efficacy may be added to the iDMC Charter. If the study continues beyond the interim analysis, the critical value at the final analysis would be adjusted accordingly

to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology.
After the primary analysis for PFS, additional OS interim analyses may be conducted to provide additional OS data, per the recommendation from health authorities. If conducted, the Lan-DeMets α-spending function with an O'Brien-Fleming boundary will be used to control the overall type I error for OS accounting for the additional OS interim analyses.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ASCO	American Society of Clinical Oncology
BRCA	breast and ovarian cancer susceptibility gene
CAP	College of American Pathologists
CFDA	China Food and Drug Administration
CIT	Cancer immunotherapy
CR	complete response
CT	computed tomography
CTA	clinical trial assay
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DOR	duration of response
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
ER	estrogen receptor
ESMO	European Society for Medical Oncology
FACT	FoundationACT™
FDA	Food and Drug Administration
FFPE	formalin fixed, paraffin embedded
FMI	Foundation Medicine, Inc.
FNA	fine-needle aspiration
GHS	global health status
HBcAg	hepatitis B core antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HLH	hemophagocytic lymphohistiocytosis
HR	hormone receptor
HRQoL	health-related quality of life
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug (application)

Abbreviation	Definition
IRB	Institutional Review Board
ITT	intent-to-treat
IxRS	interactive voice or Web-based response system
LOH	loss of heterozygosity
MAS	macrophage activation syndrome
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
NGS	next-generation sequencing
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PgR	progesterone receptor
PI3K	phosphoinositide 3-kinase
PIK3CA	phosphatidylinositol-4, 5–bisphosphate 3-kinase, catalytic subunit, alpha
PK	pharmacokinetic
popPK	population pharmacokinetics
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
QD	once a day
QoL	quality of life
QTcF	QT interval corrected using Fridericia's formula
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	statistical analysis plan
TNBC	triple-negative breast cancer
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON TRIPLE-NEGATIVE AND HORMONE-RECEPTOR–POSITIVE 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 human epidermal growth factor receptor 2 (HER2) expression per American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) guidelines (ASCO/CAP 2010, 2013). Patients with metastatic TNBC exhibit a particularly poor clinical outcome, generally with rapid progression and a median overall survival (OS) rate of approximately 16 months (Rodler et al. 2010; Miles et al. 2013). Although TNBC may respond to chemotherapy, including taxanes, there are no approved first-line regimens or targeted therapies for patients with this specific subtype of breast cancer. 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; NCCN 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; Miles et al. 2017). There is a pressing need for clinically active agents for the triple-negative subtype of metastatic breast cancer.

Hormone receptor–positive, HER2-negative breast cancer (hereafter referred to as HR+/HER2– breast cancer) accounts for over 70% of all breast cancers. Patients with metastatic HR+/HER2– breast cancer are treated with endocrine therapy; premenopausal patients often undergo additional ovarian ablation/suppression. Chemotherapy is indicated in patients with symptomatic visceral disease (visceral crisis) or in patients with disease progression after demonstration of endocrine resistance (Cardoso et al. 2017; NCCN 2017). Patients with visceral disease requiring chemotherapy often exhibit symptoms associated with visceral disease burden, such as dyspnea and pain, and have a median OS of approximately 18–24 months (Harb 2015). Patients with HR+/HER2– breast cancer receiving first-line chemotherapy with paclitaxel have a median PFS of approximately 7–8 months in recent studies (RIBBON-1, Robert et al. 2011; PEGGY, Vuylsteke et al. 2016). As with TNBC, there is no clear standard or defined treatment regimen for patients with metastatic HR+/HER2– breast cancer who have progressed after endocrine therapy; in particular, effective treatment is needed for patients when continued endocrine therapy is not indicated.

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 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 HR+/HER2– 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 with 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 (S6RP), 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/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+/HER2-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 with an expansion cohort of patients with HER2− breast cancer (Study PAM4983g, Arm C) and a randomized Phase II Study (GO29227, LOTUS) comparing ipatasertib + paclitaxel versus placebo + 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+/HER2−: n = 2; TNBC: n = 1), and 4 partial responses included patients who had prior exposure to paclitaxel or investigational PI3K inhibitors (HR+/HER2−: n = 2; TNBC: n = 2).

In the randomized Phase II Study GO29227, one of the objectives was to investigate the added benefit of ipatasertib to paclitaxel in the subgroup of patients with *PIK3CA/AKT1/PTEN*-altered tumors. Results from this study showed improvement in median PFS in the intent-to-treat (ITT) population (hazard ratio = 0.60; 6.2 months in the ipatasertib arm compared with 4.9 months in the control arm); and more pronouncedly in the pre-specified patient population with *PIK3CA/AKT1/PTEN*-altered tumors (hazard ratio = 0.44; 9 months vs. 4.9 months).

Refer to the Ipatasertib Investigator's Brochure for details on nonclinical and clinical studies, including single-agent activities in the Phase I study (PAM4743g).

1.3 BACKGROUND ON ATEZOLIZUMAB

Atezolizumab is a humanized Ig G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity

(Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

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

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.

In metastatic 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. 2018b). No new safety signals were identified.

In IMpassion130, 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.

2018b). 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

Study CO40151 is a Phase Ib study currently 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 first-line advanced TNBC. To date, an early safety analysis has been completed on the initial two safety run-in arms enrolled (n = 6 in one arm using paclitaxel + ipatasertib + atezolizumab; n = 6 in one arm using nab-paclitaxel + ipatasertib + atezolizumab) in Cohort 1, and enrollment continues into the remaining arms in Cohort 1 with continuous safety and efficacy monitoring. The toxicity profile in this study, paired with the very early but promising response rate that does not seem to be dependent on presence of a *PIK3CA/AKT1/PTEN*-alteration, suggests that this is a reasonable combination to be used for Cohort C study treatment in the current study. The CO40151 Study Team, including the Study Medical Monitor and Safety Scientist, monitors patient safety throughout the study. In addition to the ongoing assessment of the incidence, nature and severity of adverse events, serious adverse events, deaths, and laboratory abnormalities performed by the investigators and the Medical Monitor, the Study Team reviews all necessary cumulative data at regular intervals (i.e., approximately three times a year) during the study. Assessment of safety for the safety-run-in cohorts is performed by the Study Team and communicated to investigators prior to opening enrollment for the expansion cohorts.

1.5 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Metastatic breast cancer remains an incurable disease. For patients with locally advanced and metastatic TNBC, clinical outcome is particularly poor, generally with rapid progression and a median OS of approximately 16 months (Rodler et al. 2010; Miles et al. 2013). For patients with HR+/HER2− breast cancer who are not appropriate candidates for endocrine therapy, OS with first-line chemotherapy with weekly single-agent paclitaxel is approximately 28 months (Miles et al. 2013; Miles et al. 2017).

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 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.

Nonclinical and preliminary clinical data also support use of the same biomarker selection to identify patients who may derive greater benefit from ipatasertib and paclitaxel in HR+/HER2− breast cancer. Future studies to evaluate ipatasertib combination therapy in cancers being driven by PI3K/Akt pathway activation are warranted.

This study protocol incorporates two parallel Phase III (Cohorts A and B), multicenter, randomized, double-blind, placebo-controlled trials designed to evaluate ipatasertib in combination with paclitaxel in a biomarker-selected patient population with TNBC and in a biomarker-selected patient population with HR+/HER2− breast cancer. Patients must have *PIK3CA/AKT1/PTEN*-altered tumors as determined by local/commercial or central laboratory blood- or tissue-based molecular assay (e.g., Foundation Medicine, Inc. [FMI] FoundationOne, FoundationONE CDx™, Foundation ACT, or PCR, etc.) and have not received prior chemotherapy in the advanced disease setting. Regardless of the biomarker assay performed to confirm eligibility, it remains an eligibility requirement to submit a tumor tissue block or 20 unstained slides for central testing of the *PIK3CA/AKT1/PTEN* alteration, which may be reduced only in the case of subjects meeting biomarker eligibility on the basis of FoundationONE CDx™. If the patient already has *PIK3CA/AKT1/PTEN* alteration results available from the FMI commercial tissue-based NGS assay known as FoundationONE CDx™, then the FMI clinical trial assay (CTA) does not need to be re-run; in this situation the lesser amount of tissue specified within the eligibility is acceptable for other protocol-mandated secondary and exploratory assessments, upon approval by the Medical Monitor. Because the biology and natural treatment history of these two subtypes of breast cancers are distinct and heterogeneous, independent stratification and analyses will be conducted. Eligible patients will be assigned to Cohort A (TNBC) or Cohort B (HR+/HER2− breast cancer) according to tumor hormone receptor status.

In addition, Cohort C with an open-label, non-randomized treatment regimen within this study investigates the combination of atezolizumab, ipatasertib, and paclitaxel in approximately 100 patients with TNBC who are screened for Cohort A but who do not qualify (i.e., lack of *PIK3CA/AKT1/PTEN* alteration validated by central tumor tissue testing using the Foundation Medicine (FMI) clinical trial algorithm [CTA]).

For each cohort, the primary endpoint is investigator-assessed PFS; secondary endpoints include OS, objective response rate (ORR), duration of response (DOR), and clinical benefit rate. In addition, 1-year landmark PFS and OS will be analyzed in Cohort C. Patient-reported outcomes (PROs) will be both secondary and exploratory endpoints, and, along with the other secondary endpoints, may be supportive of the primary PFS endpoint.

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. While these targets have 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-PD1 therapy in melanoma patients. 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.

The clinical safety profile of ipatasertib 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 supports continued development in metastatic breast cancer. 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 $\geq$200 mg. In Study GO29227, the adverse effects of ipatasertib plus paclitaxel in metastatic TNBC were consistent with previous experiences of ipatasertib and of paclitaxel, most notably ipatasertib-related gastrointestinal toxicities that are manageable and reversible. Common adverse events with a $\geq$10% higher incidence in the ipatasertib arm than in the placebo arm were diarrhea, nausea, asthenia, and peripheral sensory neuropathy. Common Grade $\geq$3 adverse events included diarrhea, neutropenia, neutrophil count decreased, 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. The

onset of diarrhea was most common within the first cycle; 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 (only 3%) discontinuation of ipatasertib treatment due to 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.

In this current study, to improve diarrhea management and patient experiences, anti-diarrhea prophylaxis (loperamide) will be mandated for the first cycle for all patients (where allowed by local guidance) and implemented subsequently as clinically indicated. Patients will be monitored for early signs of diarrhea symptoms, and investigators will be provided with comprehensive management guidelines for study treatment–related symptoms or potential risks. If there are clinical concerns that preclude the use of loperamide prophylaxis in Cycle 1, discussion with the Medical Monitor is required.

The adverse events observed with atezolizumab in combination with chemotherapy and/or targeted therapies are consistent with the known risks of each study treatment. The most commonly reported adverse events with single-agent atezolizumab include fatigue, nausea, decreased appetite, diarrhea, constipation, and cough. Immune-mediated adverse events are consistent with the role of the PD-L1/PD-1 pathway in regulating peripheral tolerance. Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated adverse events will be closely monitored in this study. Immune-mediated adverse events associated with atezolizumab include hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, hypophysitis, myocarditis, meningoencephalitis, nephritis, and myositis. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome. Guidance regarding the management of immune-mediated adverse events is provided in Appendix 15 of the protocol and in Section 6 of the Atezolizumab Investigator's Brochure.

Adverse events of special interest, in addition to overall safety, will be monitored as outlined in this protocol.

In summary, the two study populations eligible for this trial (TNBC and HR+/HER2-) both require chemotherapy for the first time in the advanced setting and are appropriate for receiving paclitaxel monotherapy. Prior Phase II data in patients with advanced TNBC support the addition of ipatasertib to paclitaxel treatment with enhanced benefit in those patients with *PIK3CA/AKT1/PTEN*-altered tumors, as demonstrated by a pronounced improvement in PFS compared to treatment with paclitaxel alone. Preclinical and preliminary clinical data also support the addition of ipatasertib to paclitaxel using the same biomarker selection in patients with HR+/HER2– breast cancer. Similarly,

preclinical and preliminary clinical data support the addition of atezolizumab to the combination of ipatasertib and paclitaxel in patients with TNBC independent of *PIK3CA/AKT1/PTEN* alteration status. As described in more detail above, the combination of ipatasertib and paclitaxel (and atezolizumab) has been generally well tolerated, with comprehensive guidelines for management of anticipated treatment-related symptoms incorporated into this protocol. On the basis of the data available to date, the benefit-risk assessment for administration of ipatasertib alongside paclitaxel is considered positive in both locally advanced unresectable or metastatic TNBC and HR+/HER2− breast cancer patient populations. In addition, benefit-risk of the triplet combination of ipatasertib alongside paclitaxel and atezolizumab is supported by preliminary Phase Ib safety and response data in Study CO40151.

2. OBJECTIVES AND ENDPOINTS

Cohorts A and B will independently evaluate the safety, efficacy, and pharmacokinetics of ipatasertib in combination with paclitaxel (ipatasertib + paclitaxel) compared with placebo plus paclitaxel (placebo + paclitaxel) in patients with *PIK3CA/AKT1/PTEN*-altered tumors. Cohort A will evaluate first-line treatment in patients with locally advanced unresectable or metastatic TNBC, and Cohort B will evaluate first-chemotherapy treatment in patients with advanced HR+/HER2− breast cancer who are not appropriate candidates for endocrine therapy (as defined by the Sponsor; see Section 4.1). Patients will be enrolled based on central or local/commercial determination of *PIK3CA/AKT1/PTEN*-altered status, with central assessment of *PIK3CA/AKT1/PTEN*-altered status in tumor tissue performed in any patients enrolled using alternative methods and will be allocated to one of the cohorts based on hormone-receptor status. Patients with HER2-positive breast cancer are not eligible. The reason that the Cohorts A and B will be evaluated separately is that TNBC and HR+/HER2− breast cancers have different biologies that manifest clinically in different prognoses and response to treatment, and molecularly with distinctly different molecular profiles with dissimilar oncogenic drivers. The patients in Cohorts A and B have different prevalences and PFS and OS expectations, and thus different enrollment and analysis timelines.

Patients who initially screen for Cohort A (with TNBC) but do not qualify (i.e., lack of *PIK3CA/AKT1/PTEN* alteration validated by central tumor tissue testing using the FMI CTA) may be eligible for Cohort C. Cohort C is an open-label, non-randomized cohort for patients with locally advanced unresectable or metastatic TNBC that will assess the safety, efficacy, and pharmacokinetics of ipatasertib in combination with paclitaxel and atezolizumab. Due to the differences in mechanism of action and evaluation of clinical benefit following cancer immunotherapy treatments, as well as delayed opening of Cohort C, this cohort will be evaluated separately from Cohorts A and B.

The target patient populations for this study are premenopausal and postmenopausal female and male patients with measurable, locally advanced unresectable or metastatic

TNBC and HR+/HER2− breast cancer who have not received chemotherapy in either of these settings. Patients must be appropriate candidates for taxane monotherapy. In particular, patients with HR+/HER2− breast cancer should be suitable for treatment with chemotherapy (e.g., demonstrated insensitivity to endocrine therapy; reference eligibility criteria for Sponsor definition of endocrine-insensitivity). Prior adjuvant or neoadjuvant chemotherapy is allowed, provided it has been concluded at least 12 months before recurrence of (locally advanced unresectable or metastatic) disease.

Patients with *PIK3CA/AKT1/PTEN*-altered tumors (as defined in Section 3.1.1 and Section 4.1.1) will be assigned to Cohort A (TNBC) or Cohort B (HR+/HER2− breast cancer) based on their hormone receptor status (as evaluated locally, or on study, only if local evaluation is not available, with additional slides submitted for this purpose) and randomized with a 2:1 ratio to the experimental versus control arm. Patients with TNBC who are biomarker-negative (i.e., lack of *PIK3CA/AKT1/PTEN* alteration validated by central tumor tissue testing using the FMI CTA) but otherwise eligible will be assigned to Cohort C to receive ipatasertib in combination with atezolizumab and paclitaxel until this cohort is fully accrued. All primary, secondary, exploratory, and safety objectives will be assessed independently for each cohort (i.e., Cohort A: patients with TNBC with *PIK3CA/AKT1/PTEN*-altered tumors, Cohort B: patients with HR+/HER2− breast cancer with *PIK3CA/AKT1/PTEN*-altered tumors and Cohort C: patients with TNBC whose tumors lack *PIK3CA/AKT1/PTEN* alteration validated by central tumor tissue testing using the FMI CTA).

The primary endpoint is PFS for all cohorts. The primary analysis for each cohort will be independent and triggered by cohort-specific events and will also be independent of the readout of the other cohort (refer to Section 6). The secondary endpoints for Cohorts A and B will be tested if the primary analysis of the respective PFS reaches statistical significance at the level of 5%.

Specific objectives and corresponding endpoints for each cohort will be analyzed independently following cohort-specific statistical analysis plans, and are outlined in Table 1 and Table 2.

Table 1 Objectives and Corresponding Endpoints (Applicable for Both Cohort A and Cohort B, Unless Otherwise Stated)

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the efficacy of ipatasertib + paclitaxel compared with placebo + paclitaxel	• PFS, defined as the time from randomization to the first occurrence of disease progression, as determined locally by the investigator through the use of RECIST v1.1, or death from any cause, whichever occurs first
Secondary Efficacy Objectives:	
• To evaluate the efficacy of ipatasertib + paclitaxel compared with placebo + paclitaxel	▪ Objective response rate, defined as a CR or PR on two consecutive occasions ≥4 weeks apart, as determined locally by the investigator through the use of RECIST v1.1 • Duration of response, defined as the time from the first occurrence of a documented objective response to disease progression, as determined locally by the investigator through use of RECIST v1.1, or death from any cause, whichever occurs first • Clinical benefit rate, defined as an objective response (CR or PR), or stable disease for at least 24 weeks, as determined locally by the investigator through the use of RECIST v1.1 • OS, defined as the time from randomization to death from any cause
• To evaluate PROs of GHS/HRQoL associated with ipatasertib + paclitaxel compared with placebo + paclitaxel	• Mean and mean changes from baseline GHS/HRQoL score as measured by the GHS/HRQoL scale (Questions 29 and 30) of the EORTC QLQ-C30, by cycle
• To evaluate PROs of disease-related pain of ipatasertib + paclitaxel compared with placebo + paclitaxel (Cohort B only)	• Time to deterioration in pain, defined as the first minimally important increase of ≥11 points from the baseline pain scale score (Questions 9 and 19) of the EORTC QLQ-C30
Exploratory Efficacy Objectives:	
• To evaluate the efficacy of ipatasertib + paclitaxel compared with placebo + paclitaxel in TNBC (Cohort A only) patients with tumors that have the following: – *PIK3CA/AKT1*-activating mutations – *PTEN* alterations (and no *PIK3CA/AKT1*-activating mutations)	• PFS • Objective response rate • Duration of response • Clinical benefit rate • OS

Table 1 Objectives and Corresponding Endpoints (Applicable for Both Cohort A and Cohort B, Unless Otherwise Stated) (cont.)

Objectives	Corresponding Endpoints
Exploratory Efficacy Objectives: (cont.)	
• To evaluate PROs of function and disease/treatment-related symptoms associated with ipatasertib + paclitaxel compared with placebo + paclitaxel	• Mean and mean changes from baseline scores in functional (i.e., role, physical, cognitive, emotional, and social) and disease/treatment-related symptoms by cycle as assessed by the functional and symptom scales of the EORTC QLQ-C30
• To collect utilities for pharmacoeconomic modeling	• Health states for utility assessment and the VAS as measured by the EQ-5D-5L questionnaire for modeling
• To evaluate the clinical benefit	• PFS2, defined as the time from randomization to first objective disease progression on next-line treatment, or death from any cause, whichever occurs first • Time to first skeletal–related event (SRE), defined as the time from randomization to the occurrence of an SRE. An SRE is either a pathologic fracture, radiation therapy to the bone, surgery to the bone, or spinal cord compression.
• To evaluate analgesic use in ipatasertib + paclitaxel and placebo + paclitaxel treatment arms (Cohort B only)	• Change in use of opioid and non-opioid analgesics during treatment, as measured by the intake of analgesic treatments
Safety Objective:	
• To evaluate the safety of ipatasertib + paclitaxel compared with placebo + paclitaxel	• Incidence of adverse events as assessed by the investigator, with severity determined through the use of NCI CTCAE v4.0 • Incidence of prespecified adverse events • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Exploratory Safety Objective:	
• To collect PROs regarding key symptomatic adverse events of ipatasertib + paclitaxel compared with placebo + paclitaxel	• Selected items from the PRO-CTCAE capturing patients' rating of the presence, severity, frequency, and/or interference of diarrhea, nausea, vomiting, decreased appetite, fatigue, neuropathy, mouth sores, and rash symptoms and an additional item regarding bother due to side effects of treatment

Table 1 Objectives and Corresponding Endpoints (Applicable for Both Cohort A and Cohort B, Unless Otherwise Stated) (cont.)

Objectives	Corresponding Endpoints
Pharmacokinetic Objective:	
• To characterize the pharmacokinetics of ipatasertib and its metabolite (G-037720) when administered in combination with paclitaxel	• Plasma concentration of ipatasertib and G-037720 at specified timepoints for analysis using population PK methodology
Exploratory Pharmacokinetic Objective:	
• To evaluate potential relationships between ipatasertib exposure, efficacy, and safety of ipatasertib + paclitaxel compared with placebo + paclitaxel	• Relationship between ipatasertib PK and efficacy endpoints • Relationship between ipatasertib PK and safety endpoints
Exploratory Biomarker Objectives:	
• To evaluate predictive or prognostic biomarkers (plasma or tissue) associated with disease activity status or response to treatment • 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 • To evaluate alternative diagnostics testing methods for *PIK3CA/AKT1/PTEN*-altered status	• Relationship between tissue- and blood-based biomarkers and patient clinical features (e.g., baseline features) and outcome (e.g., duration of PFS) • 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 • Associations of breast cancer subtypes defined by molecular signatures with patient outcomes • Association of *BRCA*1/2 genetic alterations and homologous repair deficiency with patient outcomes

BRCA = breast and ovarian cancer susceptibility gene; CR = complete response; EORTC = European Organisation for Research and Treatment of Cancer; GHS = global health status; HRQoL = health-related quality of life; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; PK = pharmacokinetics; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; TNBC = triple-negative breast cancer; VAS = visual analog scale.

Table 2 Objectives and Corresponding Endpoints (Cohort C)

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the efficacy of ipatasertib + paclitaxel + atezolizumab	• PFS, defined as the time from enrollment to the first occurrence of disease progression, as determined locally by the investigator through the use of RECIST v1.1, or death from any cause, whichever occurs first
Secondary Efficacy Objectives:	
• To evaluate the efficacy of ipatasertib + paclitaxel + atezolizumab	▪ Objective response rate, defined as a CR or PR on two consecutive occasions ≥ 4 weeks apart, as determined locally by the investigator through the use of RECIST v1.1 • Duration of response, defined as the time from the first occurrence of a documented objective response to disease progression, as determined locally by the investigator through use of RECIST v1.1, or death from any cause, whichever occurs first • Clinical benefit rate, defined as an objective response (CR or PR), or stable disease for at least 24 weeks, as determined locally by the investigator through the use of RECIST v1.1 • OS, defined as the time from enrollment to death from any cause • 1−year PFS, defined as progression-free survival probabilities at 1 year. • 1−year OS, defined as overall survival probabilities at 1 year.
• To evaluate PROs of GHS/HRQoL associated with ipatasertib + paclitaxel + atezolizumab	• Mean and mean changes from baseline GHS/HRQoL score as measured by the GHS/HRQoL scale (Questions 29 and 30) of the EORTC QLQ-C30, by cycle

Table 2 Objectives and Corresponding Endpoints (Cohort C) (cont.)

Objectives	Corresponding Endpoints
Exploratory Efficacy Objectives: (cont.)	
• To evaluate PROs of function and disease/treatment-related symptoms associated with ipatasertib + paclitaxel + atezolizumab	• Mean and mean changes from baseline scores in functional (i.e., role, physical, cognitive, emotional, and social) and disease/treatment-related symptoms by cycle as assessed by the functional and symptom scales of the EORTC QLQ-C30
• To collect utilities for pharmacoeconomic modeling	• Health states for utility assessment and the VAS as measured by the EQ-5D-5L questionnaire for modeling
• To evaluate the clinical benefit	• PFS2, defined as the time from enrollment to first objective disease progression on next-line treatment, or death from any cause, whichever occurs first • Time to first skeletal–related event (SRE), defined as the time from treatment assignment to the occurrence of an SRE. An SRE is either a pathologic fracture, radiation therapy to the bone, surgery to the bone, or spinal cord compression.
Safety Objective:	
• To evaluate the safety of ipatasertib + paclitaxel + atezolizumab	• Incidence of adverse events as assessed by the investigator, with severity determined through the use of NCI CTCAE v4.0 • Incidence of prespecified adverse events • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
Exploratory Safety Objective:	
• To collect PROs regarding key symptomatic adverse events of ipatasertib + paclitaxel + atezolizumab	• Selected items from the PRO-CTCAE capturing patients' rating of the presence, severity, frequency, and/or interference of diarrhea, nausea, vomiting, decreased appetite, fatigue, neuropathy, mouth sores, and rash symptoms and an additional item regarding bother due to side effects of treatment

Table 2 Objectives and Corresponding Endpoints (Cohort C) (cont.)

Objectives	Corresponding Endpoints
Pharmacokinetic Objective:	
• To characterize the pharmacokinetics of atezolizumab, ipatasertib and its metabolite (G-037720) when administered in combination with paclitaxel	• Plasma concentration of ipatasertib and its metabolite, G-037720 at specified timepoints for analysis using population PK methodology • Serum concentration of atezolizumab at specified timepoints
Exploratory Pharmacokinetic Objective:	
• To evaluate potential relationships between ipatasertib and/or atezolizumab exposure, efficacy, and safety of ipatasertib + paclitaxel + atezolizumab	• Relationship between ipatasertib and/or atezolizumab PK and efficacy endpoints • Relationship between ipatasertib and/or atezolizumab PK and safety endpoints
Immunogenicity Objective:	
• To evaluate the immune response to atezolizumab	• Incidence of ADAs to atezolizumab during the study relative to the prevalence of ADAs at baseline
Exploratory Immunogenicity Objective:	
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objectives:	
• To evaluate predictive or prognostic biomarkers (plasma or tissue) associated with disease activity status or response to treatment • 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 • To evaluate alternative diagnostics testing methods for *PIK3CA/AKT1/PTEN*-altered status	• Relationship between tissue- and blood-based biomarkers and patient clinical features (e.g., baseline features) and outcome (e.g., duration of PFS) • 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 • Associations of breast cancer subtypes defined by molecular signatures with patient outcomes • Association of BRCA1/2 genetic alterations and homologous repair deficiency with patient outcomes

BRCA = breast and ovarian cancer susceptibility gene; CR = complete response; EORTC = European Organisation for Research and Treatment of Cancer; GHS = global health status; HRQoL = health-related quality of life; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OS = overall survival; PK = pharmacokinetics; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome; PRO-CTCAE = Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors, Version 1.1; TNBC = triple-negative breast cancer; VAS = visual analog scale.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

The two-cohort (Cohorts A and B), randomized, double-blind, placebo-controlled portion of this Phase III study is designed to evaluate the efficacy of ipatasertib + paclitaxel versus placebo + paclitaxel in patients with histologically confirmed, locally advanced unresectable or metastatic TNBC and in patients with locally advanced unresectable or metastatic HR+/HER2− breast adenocarcinoma who are not suitable for endocrine therapy (as defined by Sponsor; see eligibility criteria). Each cohort will be independent with separate analyses, but with a single screening process to identify, allocate, and subsequently stratify on the basis of histologic and diagnostic status. Patients must have measurable disease as defined by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) and a *PIK3CA/AKT1/PTEN*-altered tumor as determined by any blood- or tissue-based molecular diagnostic assay (using a CLIA or equivalently accredited diagnostic laboratory). Tumor *PIK3CA/AKT1/PTEN*-altered status is defined as the presence of *PTEN* alterations or *PIK3CA/AKT1*-activating mutations (see Section 4.1.1, Disease-Specific Inclusion Criteria). Pathological determination of ER, PgR, and HER2 status based on local assessment according to ASCO and CAP guidelines (see Appendix 5 and Appendix 6) will be applied for cohort assignment by an interactive voice or Web-based response system (IxRS), with subsequent randomization within each cohort based on the appropriate stratification factors for the different cohorts. Patients who have unknown tumor ER, PgR, HER2, or *PIK3CA/AKT1/PTEN*-altered status and for whom determination of status is not possible are not eligible for this study.

If a patient will screen for biomarker eligibility with the tissue-based FMI CTA, time for tumor tissue retrieval, shipping, and turnaround of eligibility results should be taken into account when screening patients (and submitted sample should be sufficient per protocol requirements to have maximum likelihood that a valid result can be obtained).

As the FoundationACT™ (FACT) assay is not able to detect all qualifying alterations that may be identified using the FMI CTA, tissue submission should not be delayed as patients may qualify by the latter, rather than by FACT. FACT testing at FMI may not necessarily be faster than the FMI CTA and, therefore, should only be performed when it is anticipated that there will be a significant delay to acquisition of existing tumor tissue.

If local/commercial testing is available, demonstrating a qualifying alteration, or if this result is obtained, these results may be used to determine biomarker eligibility. However, please note, for patients not enrolled on the basis of the FMI tissue-based CTA (e.g., local/commercial tests or blood-based FACT assay), submission of tumor tissue is still required, but randomization should proceed based on the local result with no requirement to wait for central assessment of biomarker eligibility. Treatment benefit in patients with *PIK3CA/AKT1/PTEN*-altered tumors will be independently compared in patients with triple-negative receptor status and in patients with HR+/HER2− status.

Approximately 349 patients with TNBC (249 biomarker-positive patients and 100 biomarker-negative patients), and 201 biomarker-positive patients with HR+/HER2− breast cancer will be enrolled at approximately 165−195 centers worldwide during the global enrollment phase. Patients will be assigned to either Cohort A (TNBC biomarker-positive), Cohort B (HR+/HER2− biomarker-positive breast cancer), or Cohort C (TNBC biomarker-negative) according to the most recent locally assessed pathologically documented receptor status and *PIK3CA/AKT1/PTEN* alteration status. Receptor status should be assessed in their recurrent or metastatic tumor where applicable and if safely accessible, per ASCO/CAP guidelines (see Appendix 5 and Appendix 6 for the 2013 guidelines [includes recent HER2 testing update [Wolff et al. 2018]). Patients in Cohorts A and B will be randomly assigned in a 2:1 ratio to the experimental arm (ipatasertib 400 mg + paclitaxel) or control arm (placebo + paclitaxel). Approximately 100 patients with TNBC who screen for Cohort A who are shown not to have a *PIK3CA/AKT1/PTEN*-altered tumor by centrally tested FMI CTA may be assigned to Cohort C to receive ipatasertib in combination with atezolizumab and paclitaxel, unless the cohort is completely accrued. The study schema is shown in Figure 1.

Randomization for patients in Cohort A and B will be stratified by the following factors: prior adjuvant/neoadjuvant chemotherapy (yes vs. no), region (Asia-Pacific vs. Europe vs. North America vs. rest of the world), tumor *PIK3CA/AKT1/PTEN*-alteration status (*PIK3CA/AKT1*-activating mutations vs. *PTEN* alterations with no *PIK3CA/AKT1*-activating mutations; Cohort A only), and prior therapy with a PI3K or mTOR inhibitor (yes vs. no; Cohort B only).

All patients must have a validated *PIK3CA/AKT1/PTEN*-alteration status using a blood- or tissue-based molecular assay and must have consented to provide sufficient archival tissue or newly obtained tumor biopsy tissue for central molecular evaluation to be eligible for enrollment. If the patient already has *PIK3CA/AKT1/PTEN* alteration results available from the FMI commercial tissue-based NGS assay known as FoundationONE CDx™, then the FMI CTA does not need to be re-run; in this situation the lesser amount of tissue specified within Section 4.1.1 is acceptable for other protocol-mandated secondary and exploratory assessments, upon approval of the Medical Monitor. Given the probability of *PIK3CA/AKT1/PTEN* non-altered status (approximately 80%−85% for TNBC and 50%−60% for HR positive by blood-based NGS assay, such as FACT, and 55%−65% by tissue-based NGS, such as FMI CTA), it remains an option to use the biomarker-specific ICF/screening process first, prior to other study screening procedures for those patients who require central testing of biomarker status. It is advised that even if the patient will be screened for biomarker eligibility on the basis of the FACT (or other blood-based) NGS assay, that tissue be submitted as quickly. In blood, the fraction of available circulating tumor DNA (ctDNA) to sequence is less than that in tumor tissue, and because of this biology, it is expected that the FACT assay will not detect all alterations that can be identified using tissue-based NGS; i.e., even if there is biomarker ineligibility based on the blood-based assay, the patient may still qualify on the basis of the tissue-based assay.

All patients in Cohorts A and B will receive paclitaxel chemotherapy (80 mg/m^2 IV) on Days 1, 8, and 15 of each 28-day cycle and either ipatasertib at a dose of 400 mg administered orally once a day (QD) on Days 1–21 of each 28-day cycle (experimental arm) or placebo orally QD on Days 1–21 of each 28-day cycle (control arm). In Cohort C, patients will receive paclitaxel chemotherapy (80 mg/m^2 IV) on Days 1, 8, and 15 of each 28-day cycle, ipatasertib at a dose of 400 mg administered orally once a day (QD) on Days 1–21 of each 28-day cycle, and atezolizumab 840 mg IV on Days 1 and 15 of each 28-day cycle. Study treatment will continue until disease progression, intolerable toxicity, elective withdrawal from the study, or study completion or termination. Upon treatment discontinuation, patients will be followed every 3 months for survival, PROs (see Section 4.5.8), and new anti-cancer therapy and outcome (therapy/procedures, doses, start and stop date, best responses, most recent tumor assessment date, and progression date). *As of Protocol CO40016 Version 11 (Cohort C), these long-term follow-up assessments are no longer required.*

As of Protocol CO40016 Version 11 (Cohort C), tumor measurement for disease evaluation will be performed *per standard of care*, regardless of whether patients receive study treatment during the treatment cycle. For estimation of PFS, ORR, and DOR, 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 8–12 weeks for tumor assessments until documented progression per RECIST v1.1, elective withdrawal from the study, or study completion or termination *(as of Protocol CO40016 Version 11 [Cohort C] this is no longer required).* Images for tumor assessments for all patients will be prospectively collected to enable retrospective blinded independent central review when needed. As of protocol CO40016 Version 10 (Cohort C), 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. Patients who are not randomized in the study may receive a copy of the FMI NGS (and FACT assay report if performed) research report (if available) for their tumor upon request, unless the patient is enrolled onto Cohort C. A copy of this report(s) may also be available upon request by the investigator for all patients, at the time they discontinue all study treatment or following end of the study, whichever occurs earlier, unless required by law. The research report(s) may be obtained by the investigator, via the Sponsor study team, and will describe results from investigational tests that are not intended to be used to guide future treatment decisions.

The pharmacokinetics of ipatasertib and its metabolite G-037720 will be assessed in all patients receiving ipatasertib. Safety will be evaluated on an ongoing basis in this study through the monitoring of all serious and non-serious adverse events and will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0).

An independent Data Monitoring Committee (iDMC) will periodically evaluate the safety of ipatasertib or placebo combined with paclitaxel (Cohorts A and B). The analysis supporting iDMC review will be conducted by an independent Data Coordinating Center (iDCC) and provided to the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter. Safety monitoring will be performed on a continual basis by the Sponsor for Cohort C.

No interim analysis of the primary efficacy endpoint PFS is planned. One interim OS analysis (at the time of the primary analysis for PFS) for each cohort is planned as described in Section 6.8.2.

Analysis of safety and efficacy for each cohort will be performed independently.

Crossover is not allowed (Cohorts A and B).

A schedule of study assessments is provided in Appendix 1, Appendix 2, Appendix 3, and Appendix 4.

Potential China Extension Phase for Cohorts A and B

After completion of the global enrollment phase, as needed, additional patients may be enrolled at China Food and Drug Administration (CFDA)-recognized sites in an extended enrollment phase to ensure a total of up to 90 patients with TNBC and up to 120 patients with HR+/HER2− breast cancer, constituting the analysis population of a China subgroup. For each of Cohort A and Cohort B, patients from the China extension phase will be randomized in a 2:1 ratio to the two treatment arms, the same as during the global enrollment phase. Any Chinese patients enrolled in the China extension phase will undergo the same schedule of assessments and will receive study treatment as in the global study cohorts.

The China subgroup includes all Chinese patients enrolled in the global study cohorts and the China extension phase. The China subgroup analysis will be performed and summarized separately. The Chinese patients enrolled in the global study cohorts will be analyzed together with all other patients enrolled in the global study, and will be reported in the global study clinical study report.

Figure 1 Study Schema

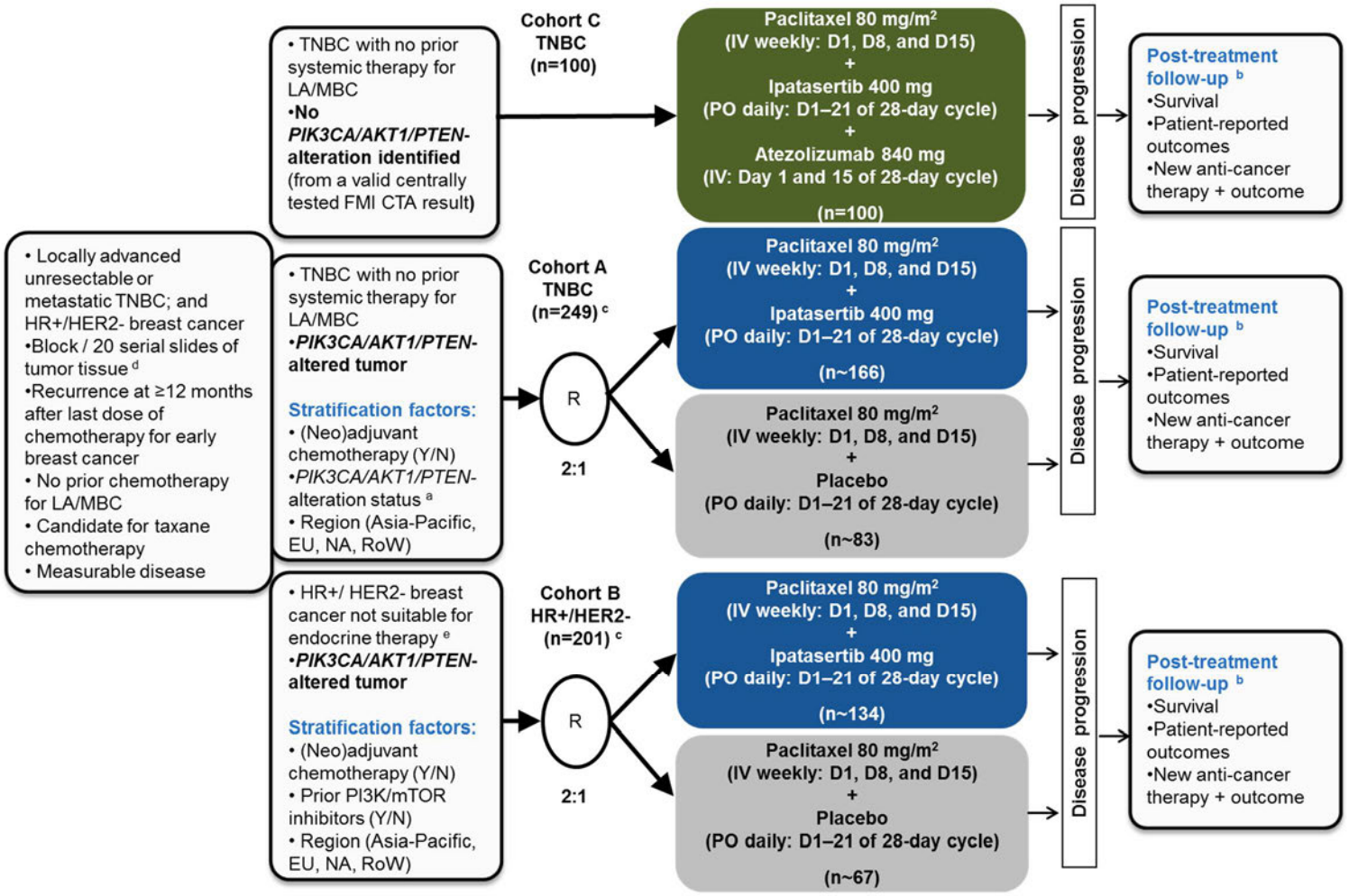

Figure 1 Study Schema (cont.)

BC = breast cancer; D = day; EU=Europe; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; LA = locally advanced unresectable; MBC = metastatic breast cancer; NA= North America; PO = by mouth; R = randomization; RoW= Rest of the World; TNBC = triple-negative breast cancer; Y/N = yes or no.

Note: If allowed locally, prophylaxis loperamide is mandated in Cycle 1, dose adjustment is as necessary, and continuation is per investigator judgment.

[a] *PIK3CA/AKT1* mutant versus *PTEN*-altered (and non-*PIK3CA/AKT1* mutant).

[b] If applicable, patients will return to the clinic every 8–12 weeks for tumor assessments (disease follow-up visit) until disease progression, elective withdrawal from study, or study completion or termination. *As of Protocol CO40016 Version 11 (Cohort C), follow-up tumor assessments are no longer required.*

[c] As needed to potentially support a regulatory submission in China, additional Chinese patients may be subsequently enrolled at CFDA-recognized sites in an extended enrollment phase (China extension phase), for up to a total of 90 Chinese patients with TNBC with *PIK3CA/AKT1/PTEN*-altered tumors and up to 120 Chinese patients with HR+/HER2– breast cancer with *PIK3CA/AKT1/PTEN*-altered tumors, constituting the analysis population of the China subgroup (including Chinese patients enrolled in the global enrollment phase).

[d] A lower number of slides may be required if FoundationONE CDx™ is commercially already run and used for biomarker qualification.

[e] Patients with HR+/HER2– breast cancer who are not suitable candidates for endocrine therapy (as defined by Sponsor; see eligibility criteria) and who meet one of the following criteria: the patient has recurrent disease (locoregional or metastatic) during adjuvant endocrine therapy (i.e., ≤5 years of being on therapy), or if the patient has de novo metastatic disease, patient has progressive disease within 6 months of being on first-line endocrine treatment of metastatic disease.

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.

The total length of the study, from screening of the first patient to the end of the study (excluding the potential China extension phase), is expected to be approximately 53 months.

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

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population

Despite multiple treatment options, advanced breast cancer remains an incurable disease. Although chemotherapy is a mainstay treatment, resistance inevitably develops and benefit is often short-lived. This study evaluates the benefit of the addition of ipatasertib to chemotherapy in two distinct populations that require chemotherapy: 1) locally advanced unresectable or metastatic TNBC with no previous systemic treatment in the advanced setting; and 2) advanced HR+/HER2− breast cancer requiring chemotherapy for the first time in the advanced setting, after development of endocrine resistance (as defined by the Sponsor; see eligibility criteria).

In Study GO29227, patients with TNBC in the ipatasertib + paclitaxel arm showed a more pronounced improvement in PFS in the pre-specified patient population with *PIK3CA/AKT1/PTEN*-altered tumors (hazard ratio = 0.44, 9.0 months vs. 4.9 months) compared with *PIK3CA/AKT1/PTEN* non-altered tumors (hazard ratio = 0.76, 5.3 months vs. 3.7 months) or unselected ITT patients (hazard ratio = 0.60, 6.2 months vs. 4.9 months). Similarly, improvements in PFS in the biomarker-selected patients were observed for ipatasertib + abiraterone in patients with metastatic castration-resistant prostate cancer in the Phase II study GO27983 (refer to the Ipatasertib Investigator's Brochure for details). To prospectively evaluate a clinically meaningful delay in disease progression in patients for whom add-on treatment of ipatasertib to paclitaxel is appropriate, this study will enroll patients with *PIK3CA/AKT1/PTEN*-altered tumors, who are likely to derive greater benefit from the addition of ipatasertib compared with unselected patient populations.

Ipatasertib with paclitaxel has shown encouraging clinical benefit for TNBC from the randomized Phase II study (GO29227 or LOTUS). In addition, CIT has shown promising preliminary clinical data in the treatment of TNBC (Nanda et al. 2016; Schmid et al. 2017), and it has changed the standard of care for other cancers. For those TNBC patients without *PIK3CA/AKT1/PTEN*-altered tumors Cohort C provides patients with the possibility of receiving the combination of ipatasertib with atezolizumab and taxane.

Taxanes, in particular paclitaxel or docetaxel, are increasingly used for adjuvant treatment of HER2− breast cancers worldwide. Many patients are expected to have received adjuvant chemotherapy, including taxanes, leading to a concern regarding rechallenge 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 rechallenge with paclitaxel in the metastatic setting after prior adjuvant taxane exposure, guidelines support the re-use of 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 relapsed within 12 months of completing neoadjuvant/adjuvant chemotherapy treatment (including taxane) will be excluded, thus selecting for patients who are likely to retain sensitivity to paclitaxel in the metastatic setting.

For patients with metastatic HR+/HER2− breast cancer, approved therapy during the endocrine-sensitive phase includes CDK4/6 inhibitors and PI3K/Akt pathway inhibitors such as everolimus. Preliminary data from the Phase Ib study PAM4983g suggest that HR+/HER2− patients may still respond to the combination of ipatasertib + paclitaxel after prior exposure to PI3K/Akt pathway inhibitors (e.g., PI3K inhibitors) (Isakoff et al. 2014); therefore, patients previously treated with a PI3K/mTOR inhibitor will be allowed and stratified at enrollment for Cohort B. However, patients who had received prior investigational Akt inhibitors will be excluded, due to the similarity in the mechanism of action with ipatasertib. The efficacy of ipatasertib for patients previously treated with CDK4/6 inhibitors is unknown, but these patients are not excluded from participation in this study.

Recently, the TNT study demonstrated superiority of carboplatin over docetaxel for the treatment of patients with breast and ovarian cancer susceptibility gene (*BRCA*) mutation-positive breast cancer (Tutt et al. 2015). Thus, in patients with *BRCA*-associated TNBC or endocrine-resistant metastatic breast cancer, 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., *BRCA1/2* germline mutation−positive patients) 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).

3.3.2 Rationale for the China Extension Phase

To characterize the efficacy and safety profile of ipatasertib in combination with paclitaxel in a Chinese population to support a regulatory submission in China, a China extension phase may be included in the study. This study will initially enroll approximately 249 patients with TNBC and 201 patients with HR+/HER2− breast cancer across all sites in a global enrollment phase. If at least 1 patient is enrolled in China (mainland China, Hong Kong, or Taiwan) during the global enrollment phase, additional Chinese patients may be subsequently enrolled at CFDA-recognized sites in an extended enrollment phase as needed, to enroll a total of up to 90 patients with TNBC and up to 120 patients with HR+/HER2− breast cancer, constituting the analysis population of the China subgroup. The China subgroup will include Chinese patients enrolled at sites in mainland China, Hong Kong, or Taiwan during both the global enrollment phase and the China extension phase.

3.3.3 Rationale for Ipatasertib and Paclitaxel Combination

Large-scale comprehensive genomic analyses (Cancer Genome Atlas Network 2012; Lehmann and Pietenpol 2014; Pereira et al. 2016) have characterized the heterogeneous nature of breast cancer and its diverse gene-expression patterns and underlying genomic changes. In breast cancer, Akt is an important node along the PI3K/Akt pathway that controls apoptosis and cell growth (Yap et al. 2008), and this pathway is known to be highly activated in breast cancers (Cancer Genome Atlas Network 2012).

Upregulation of Akt signaling (whether intrinsic or induced following chemotherapy) represents a potentially important survival pathway in response to genotoxic or mitotic stress (Xu et al. 2012). Data from nonclinical models of ipatasertib plus microtubule inhibitors or DNA-damaging chemotherapy agents showed a clear advantage of the combination over respective single-agent treatment (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 breast cancers (Cancer Genome Atlas Network 2012), clinical trials evaluating the preliminary safety and efficacy of the combination of ipatasertib and paclitaxel in breast cancer patients have been conducted.

Paclitaxel chemotherapy is widely used and is often an appropriate choice of chemotherapy in the first-line setting of TNBC or HR+/HER2− breast cancer populations requiring chemotherapy (Cardoso et al. 2017; NCCN 2017). In these populations, the current treatment options provide limited PFS benefit (6–8 months), and long-term treatment is often limited by chemotherapy-associated toxicities. Due to the high prevalence of PI3K/Akt pathway activation and the potential role of inhibition of this pathway to counter chemoresistance, Akt inhibition in combination with paclitaxel has the potential for transformative benefit in breast cancer.

The combination of ipatasertib and paclitaxel has been generally well tolerated. In the randomized, placebo-controlled Phase II study (GO29227) in patients with locally advanced or metastatic TNBC, ipatasertib was administered 400 mg QD on Days 1–21 of each 28-day cycle and paclitaxel 80 mg/m^2 administered weekly on Days 1, 8, and 15 of each 28-day cycle. The most common adverse events in the ipatasertib + paclitaxel arm (incidence of ≥ 10% higher than in the placebo + paclitaxel arm) were diarrhea, nausea, asthenia, and peripheral sensory neuropathy. When grouping the adverse event preferred terms with similar medical concepts for basket term analysis, asthenia/fatigue and peripheral neuropathy were not significantly different between the two arms.

Overall, efficacy results from Study GO29227 support the hypothesis that inhibition of Akt signaling may improve the effectiveness of paclitaxel treatment and that patients with PI3K/Akt-activated tumors are more sensitive to ipatasertib. The median PFS in the unselected ITT population demonstrated a hazard ratio of 0.60 (6.2 months in the ipatasertib arm compared with 4.9 months in the control arm) and was more pronounced in the pre-specified patient population with *PIK3CA/AKT1/PTEN*-altered tumors (hazard ratio = 0.44, 9 months vs. 4.9 months).

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

3.3.3.1 Rationale for Immunotherapy in Breast Cancer

CIT has demonstrated significant survival benefits 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 CTLA-4 and PD-L1/PD-1. While these targets have 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.

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

The PD-L1 pathway serves as an immune checkpoint to temporarily dampen immune responses in states of chronic antigen stimulation, such as chronic infection or cancer. PD-L1 is an extracellular protein that down-regulates immune responses through binding

to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and expression is sustained in states of chronic stimulation (Blank et al. 2005; Keir et al. 2008). B7-1 is a molecule expressed on antigen-presenting cells and activated T cells. Binding of PD-L1 to PD-1 and B7-1 inhibits T-cell proliferation and activation, cytokine production, and cytolytic activity, leading to the functional inactivation or exhaustion of T cells (Butte et al. 2007; Yang et al. 2011). Overexpression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen 2007). Therefore, interruption of the PD-L1 pathway represents an attractive strategy for restoring tumor-specific T-cell immunity.

Targeting the PD-L1 pathway with atezolizumab has demonstrated activity in patients with advanced malignancies who have failed standard-of-care therapies. Objective responses have been observed across a broad range of malignancies, including NSCLC, urothelial carcinoma, renal cell carcinoma, melanoma, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma. The combination of atezolizumab and nab-paclitaxel has shown encouraging efficacy (Adams et al. 2016) (see Atezolizumab Investigator's Brochure for detailed efficacy results).

3.3.3.2 Rationale for Combining Ipatasertib with Atezolizumab

Recently, the loss of PTEN, a tumor suppressor that regulates PI3K/ Akt pathway activity, has emerged as a potential mechanism for resistance to checkpoint inhibitor therapy, and inhibition of the PI3K/Akt pathway has shown reversal of T−cell-mediated immunotherapy resistance (Peng et al. 2016; George et al. 2017). Potential impacts of Akt inhibition on immune response include the following: 1) improving recognition of cancer cells by host immune system and rekindling suppressed immune response (Xue et al. 2015); 2) restoring and enhancing physiological functionalities of T cells in the tumor microenvironment, in addition to enhancing expansion of tumor-specific lymphocytes with memory cell phenotype (Crompton et al. 2015); and 3) promoting the generation of superior, stem-like tumor-reactive T cells for adoptive immunotherapy (van der Waart et al. 2014).

Due to encouraging data for TNBC seen in both combinations of ipatasertib with paclitaxel and atezolizumab with nab-paclitaxel, this study tests the hypothesis of improved efficacy with the combination of ipatasertib with atezolizumab and paclitaxel.

3.3.4 Rationale for Starting Dose and Schedule of Ipatasertib

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 pharmacokinetics data from Arm C of Study PAM4983g (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 ipatasertib was better tolerated than 600 mg ipatasertib in this combination.

In the randomized, placebo-controlled Phase II study (GO29227) in patients with locally advanced or metastatic TNBC, the combination of ipatasertib 400 mg administered QD on Days 1–21 of each 28-day cycle and paclitaxel 80 mg/m^2 administered weekly on Days 1, 8, and 15 of each 28-day cycle was generally well tolerated and showed an improvement in PFS (refer to Sections 1.2 and 1.3); 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 pharmacodynamics data from Phase I (PAM4743g, PK/pharmacodynamic analysis) and safety and efficacy data (including exploratory exposure-response analyses, data on file) from randomized Phase II studies of ipatasertib (Study GO29227 and Study GO27983, which evaluated two dose levels of 200 mg and 400 mg of ipatasertib in patients with metastatic castration-resistant prostate cancer) support the selected starting dose of 400 mg 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 + paclitaxel arm of the GO29227 study, despite dose reduction of ipatasertib that occurred in 21.3% of patients due to adverse events, discontinuation of ipatasertib due to any adverse event was 6.1%, and the median cumulative dose intensity of both ipatasertib and paclitaxel were 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 exposures similar to the exposures of ipatasertib Powder-In-Capsule and Phase II tablet formulations used in the Phase I (PAM4743g, PAM4983g) and Phase II (GO29227) studies, respectively.

3.3.5 Rationale for Treatment with Paclitaxel and Choice of Paclitaxel Regimen

Chemotherapy is the primary systemic treatment for patients with advanced TNBC and HR+/HER2– breast cancer for whom endocrine therapy is not suitable (as defined by Sponsor; see eligibility criteria). A variety of chemotherapy choices exist including anthracyclines (doxorubicin, epirubicin, and pegylated liposomal doxorubicin), taxanes (paclitaxel, docetaxel, and albumin-bound paclitaxel), anti-metabolites (capecitabine and gemcitabine), platinums (cisplatin and carboplatin), and non-taxane microtubule inhibitors (eribulin and vinorelbine). Generally, combination chemotherapy is associated with higher ORRs than single-agent chemotherapy; however, because of an increase in toxicity and little survival benefit, sequential use of single agents is usually preferred (Cardoso et al. 2017; NCCN 2017).

Currently, there is no defined standard regimen for paclitaxel in the metastatic setting, as paclitaxel can be administered weekly (80–90 mg/m^2) or every 3 weeks (175 mg/m^2) (Swanton 2006; Cardoso et al. 2017; NCCN 2017). Meta-analysis showed no difference in PFS (6 studies; 1610 patients; hazard ratio of 1.02; 95% CI: 1.08 to 1.32), while OS

was statistically higher among patients receiving weekly paclitaxel (5 studies; 1471 patients; hazard ratio of 0.78; 95% CI: 0.67 to 0.89). Furthermore, the incidence of serious adverse events, neutropenia, neutropenic fever, and peripheral neuropathy were significantly lower in weekly taxane schedules (Mauri et al. 2010). Neurotoxicity, however, is a treatment-limiting toxicity for weekly continuous paclitaxel treatment (Seidman et al. 2008). Among weekly paclitaxel regimens that have been studied, continuous weekly dosing may be associated with more neurotoxicity than dosing on Days 1, 8, and 15 of each 28 day-cycle (Swanton 2006; Miller et al. 2007; Seidman et al. 2008).

In several recent randomized studies of paclitaxel in combination with targeted agents versus paclitaxel control, the median PFS seen in HR+/HER2− patients receiving weekly paclitaxel (90 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle) in the control arm was approximately 7−8 months (E2100, Miller et al. 2007; RIBBON-1, Robert et al. 2011; PEGGY, Vuylsteke et al. 2016) in the first-line chemotherapy setting.

In Study GO29227, paclitaxel was administered in a weekly regimen of 80 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle, which maintains the cumulative dose intensity of paclitaxel when administered every 3 weeks (175 mg/m^2, as recommended by the current prescribing information for paclitaxel IV injection [TAXOL® U.S. Package Insert; Paclitaxel U.K. Summary of Product Characteristics]). The control arm (paclitaxel + placebo) demonstrated a median PFS of 4.93 months (90% CI: 3.58 to 5.36 months), which is similar to the efficacy seen in the TNBC subgroups of several clinical trials using weekly paclitaxel (90 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle) as the control arm (Miller et al. 2007; Miles et al. 2013; Miles et al. 2017).

The current study will use the same paclitaxel dose and schedule in both treatment arms as in Study GO29227. Paclitaxel (80 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle) is considered an appropriate control arm to study the added effect of ipatasertib in both the TNBC and HR+/HER2− populations as specified.

3.3.6 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered at a fixed dose of 840 mg Q2W (840 mg on Days 1 and 15 of each 28-day cycle). The average concentration following the 840-mg Q2W dosage is expected to be equivalent to that of 1200 mg Q3W, the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 mg/kg 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).

3.3.7 Rationale for Biomarker Assessments

Breast cancer is a heterogeneous disease many distinct subtypes as defined by molecular signatures and a diverse array of mutational profiles. In addition to *PIK3CA/AKT1/PTEN*–alteration status, samples will be assessed for additional biomarkers in an effort to identify factors that may correlate with the safety and efficacy of treatment with ipatasertib and/or paclitaxel.

Through the use of NGS, WGS, and/or other methods, the collected DNA from blood samples and tumor tissue from this study will be analyzed to identify germline (e.g., *BRCA1/2*) and somatic alterations 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, or can increase the knowledge and understanding of disease biology.

In addition, all submitted tumor or blood samples at screening (for randomized patients and for patients who are not randomized if approved locally) may be evaluated with the FMI NGS assay and additional diagnostics testing methods to assist future development of alternative diagnostic tests related to *PIK3CA/AKT1/PTEN*-altered status, or when a tissue biopsy is not feasible. It is essential to include samples from randomized patients (with *PIK3CA/AKT1/PTEN*-altered tumors) and patients who are not randomized (to obtain control information from *PIK3CA/AKT1/ PTEN* non-altered tumors).

3.3.7.1 Rationale for Using Archival Tissue for Examining *PIK3CA/AKT1/PTEN*-Altered Tumor Status

Activation of PI3K/Akt signaling frequently occurs in breast cancer through activating mutations in *PIK3CA* or *AKT1* as well as through alterations in *PTEN.* These alterations occur in approximately 35% of triple-negative and 45% of HR+/HER2− breast cancers (Pereira et al. 2016). In the Phase II study GO29227, a pre-specified patient population with *PIK3CA/AKT1/PTEN*-altered tumors as identified using archival or newly obtained biopsy tissue demonstrated a substantial benefit from ipatasertib treatment (hazard ratio = 0.44, 9 months vs. 4.9 months).

These considerations support the use of archival tissue (i.e., sample from primary breast tumor) or a newly obtained biopsy to determine the *PIK3CA/AKT1/PTEN*-altered status of the disease to enrich for a patient population with a higher probability of having a clinically meaningful response to ipatasertib combined with paclitaxel. In the current study, *PIK3CA/AKT1/PTEN*-altered tumor status is required for all patients. Earlier versions of the protocol required central biomarker testing via an NGS assay (e.g., FMI); however, Version 5 of the protocol has been amended to allow randomization (and stratification) of patients based on the presence of a valid *PIK3CA/AKT1/PTEN* alteration, using either central tissue− or blood-based assays or local/commercial tissue− or blood-based assays (using a CLIA or equivalently accredited diagnostic laboratory). Any patients enrolled not using the central tissue-based NGS assay will then have this alteration assessed within the study (using the central tissue-based NGS assay).

Patients with TNBC will be prospectively stratified based on the biomarker results used to determine eligibility because of the relatively high proportion of *PTEN*-inactivating alterations (i.e., stratification by *PIK3CA/AKT1*-activating mutation vs. *PTEN*-inactivating alterations), while patients with HR+/HER2− breast cancer will not be stratified as such, since the majority of *PIK3CA/AKT1/PTEN* alterations in HR-positive disease are activating mutations of *PIK3CA*.

In order to obtain the most accurate reflection of the patient's current disease while minimizing burden, a specimen from the most recently obtained tumor tissue is requested for the central tissue-based assessment.

3.3.7.2 Rationale for Collection of Blood Samples for Noninvasive Disease Monitoring

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/early termination visit to evaluate oncogenic genetic alterations at baseline and to assess for the possible emergence of new alteration after treatment with ipatasertib and 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/AKT1* status between tumor samples and ctDNA may help clarify the prognostic and predictive significance *of PIK3CA/AKT1* mutations in patients with breast cancer treated with ipatasertib and paclitaxel.

In addition, a blood sample for central assessment of biomarker eligibility by ctDNA at FMI may be submitted at screening for assessment using the Foundation ACT (FACT assay). Because the FACT assay is not expected to detect all alterations that can be identified using tissue-based NGS, it is only recommended when timelines for turnaround of tumor tissue are anticipated to preclude the patient from screening for the study.

Furthermore, blood samples from patients in Cohort C will be used to evaluate circulating cytokine levels to better understand the systemic immune response to atezolizumab with ipatasertib and paclitaxel and its relationship with efficacy.

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

Genomics is increasingly informing researcher's understanding of disease pathobiology. Whole genome sequencing (WGS) provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. 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 of important pathways, guiding the development of new targeted agents.

For example, 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 cohort has substantially higher ipatasertib plasma levels than other patients in that cohort, 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.

This sample for WGS will be collected if approved locally.

3.3.7.4 Rationale for Optional Collection of New Tumor Biopsies at Disease Progression for Exploratory Purposes

Tumor tissue may be collected at the time of disease progression for DNA and/or RNA extraction for exploratory NGS or other research on non-inherited biomarkers (including, but not limited to, cancer-related genes and biomarkers associated with common molecular and biological pathways). Understanding the mechanisms of resistance to the combination of ipatasertib and paclitaxel is critical for the development of agents in the PI3K/Akt pathway and may provide an opportunity to develop next-generation inhibitors to prevent resistance.

Progression biopsy tissue samples will aid in determining a resistance mechanism for the combination of ipatasertib and paclitaxel, which may potentially influence future therapies for patients who progress on a PI3K/Akt inhibitor and may be part of a potential substudy. NGS will be performed by a clinical cancer genomic profiling laboratory (e.g., FMI).

For patients who provided an optional biopsy at progression, the investigator may request the FMI NGS report of the new biopsy, which will be provided when available. Results may not be available for samples that do not meet testing criteria.

3.3.8 Rationale for the Pharmacokinetic Evaluation Schedule

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 Appendix 3. Samples will be collected on Days 1 and 15 of Cycle 1 and Day 15 of Cycle 3. The sampling schedule is designed to enable characterization of ipatasertib independently in patients with TNBC (Cohort A) and HR+/HER2− breast cancer (Cohort B) using population PK (popPK) methodology for characterization. In addition, the PK data will allow comparison with single-agent ipatasertib data from the Phase I clinical trial (Study PAM4743g) and with ipatasertib data from other trials to evaluate whether ipatasertib exposures in patients with breast cancers are altered compared with other tumors.

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. Ipatasertib is not expected to alter paclitaxel exposure. 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 was not expected to alter paclitaxel exposure. Therefore, paclitaxel pharmacokinetics will not be evaluated in this study.

In general, monoclonal antibodies do not impact 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 in Cohort C will further 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 Patient-Reported Outcome Assessments

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). The HR+/HER2− breast cancer Cohort (B) may include patients with symptomatic visceral metastases (i.e., visceral crisis). Additionally, a higher proportion of HR+ patients have bone metastases compared to other subtypes. Both of these characteristics are often associated with pain (Irvin et al. 2011; Wood et al. 2016); thus, treatment and disease-related pain may be important components of the patient's treatment experience. Limited data are available characterizing the clinical presentation of disease in this population; however, it is hypothesized that progression of disease would be associated with an increase in pain symptoms. Examining and measuring patients' disease-related pain (Cohort B), treatment-related symptoms, and their interference with daily life is important to capture and will be assessed using validated PRO assessments.

The European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) will be administered to patients to assess disease/treatment-related symptoms, functioning, and health-related quality of life (HRQoL) (see Section 4.5.8.1 and Appendix 7). In addition, selected items from the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) and an additional item regarding bother due to side effects will be collected to assess treatment-related symptoms (see Section 4.5.8.2 and Appendix 9). The European Quality of Life 5-Dimension, 5-Level questionnaire (EQ-5D-5L; see Section 4.5.8.3 and Appendix 8) will be used to derive health states for use in economic models.

The EORTC QLQ-C30, select items of the PRO-CTCAE, and EQ-5D-5L will be assessed at baseline (Day 1 of Cycle 1); at Day 1 of each subsequent cycle; and at the treatment discontinuation visit (see Appendix 1). To minimize burden to patients, only the EQ-5D-5L and select scales of the EORTC QLQ-C30 will be administered over the phone to patients, or completed at the site, after treatment discontinuation and recorded

on paper (see Appendix 1). *As of Protocol CO40016 Version 11 (Cohort C), these long-term follow-up assessments are no longer required.* The selected scales of the EORTC QLQ-C30 to measure disease/treatment-related symptoms are as follows: the global health status/HRQoL (which consists of Questions 29 and 30), pain (Questions 9 and 19), fatigue (Questions 10, 12 and 18), and dyspnea (Question 8). The EQ-5D-5L will be collected to inform pharmacoeconomic modeling and will not be included in the Clinical Study Report.

3.3.10 Rationale for Skeletal-Related Events Assessments

Metastatic breast cancer is often associated with bone involvement, which may potentially lead to skeletal-related complications, possibly impacting a patient's quality of life. To describe the impact of bone involvement in breast cancer, skeletal-related events (SREs) have previously been used as an endpoint, which consists of one or more of the following events to patients:

- Radiation to bone (for pain or impending fracture), pathological fracture, spinal cord compression, or surgery to the bone (Coleman et al. 1985)

SREs will be measured as an exploratory endpoint to describe the incidence of these events in patient populations with TNBC and HR+/HER2– within the study and will describe the impact of treatment with ipatasertib in the locally advanced unresectable/metastatic breast cancer setting (Hortobagyi et al. 1996).

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 450 patients with *PIK3CA/AKT1/PTEN*-altered tumors are expected to be enrolled in this study (~249 patients with TNBC in Cohort A and ~201 patients with HR+/HER2– breast cancer in Cohort B) during the global enrollment phase. Among the ~249 patients in Cohort A, at least 150 patients with a valid alteration as measured by central FMI testing is required. Additionally, approximately 100 patients with TNBC without *PIK3CA/AKT1/PTEN*-altered tumors are expected to be enrolled in Cohort C.

After the global enrollment phase is completed, additional Chinese patients may be enrolled in the China extension phase for up to a total of 90 Chinese patients with TNBC in Cohort A and up to a total of 120 Chinese patients with HR+/HER2- breast cancer in Cohort B.

4.1.1 Inclusion Criteria

Women or men with locally advanced unresectable or metastatic triple-negative or HR+/HER2– adenocarcinoma of the breast who have not received prior systemic chemotherapy in this setting and who are candidates for taxane monotherapy may be eligible for this study. In patients with *BRCA*-associated tumors, platinum chemotherapy as potentially the preferred treatment option (Cardoso et al. 2017), or olaparib (Robson et al.2019), should be taken into consideration when determining if this study may be appropriate for these patients. Similarly, in patients with TNBC with known PD-L1

positive status, atezolizumab plus nab-paclitaxel may be a preferred treatment option where approved, which should also be considered when determining suitability of this study for these patients (Schmid et al. 2018b). Patients may have received prior chemotherapy in the neoadjuvant/adjuvant setting. Locally advanced unresectable disease must not be amenable to resection with curative intent. Patients must have sufficient tumor tissues, have a valid result either from the central molecular assessment of *PIK3CA/AKT1/PTEN*-altered status or from an appropriately validated local laboratory (see specific guidance within disease-specific inclusion criteria), 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)
- Woman or man age ≥ 18 years at the time of signing the Informed Consent Form
- Eastern Cooperative Oncology Group 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, defined by the following:

  Neutrophils (ANC $\geq 1500/\mu L$)

  Hemoglobin ≥ 9 g/dL

  Platelet count $\geq 100{,}000/\mu L$

  Serum albumin ≥ 3 g/dL

  Total bilirubin $\leq 1.5 \times$ the upper limit of normal (ULN), with the following exception:

  – Patients with known Gilbert syndrome who have serum bilirubin $\leq 3 \times$ ULN may be enrolled.

  AST and ALT $\leq 2.5 \times$ ULN, with the following exception:

  – Patients with documented liver or bone metastases may have AST and ALT $\leq 5 \times$ 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 and $2.5 \times$ ULN (or patient value before starting heparin treatment). Patients receiving coumarin derivatives should have an INR between 2.0 and 3.0 assessed in two consecutive measurements 1 to 4 days apart. Patients should be on a stable anticoagulant regimen.

Serum creatinine $< 1.5 \times$ ULN or creatinine clearance ≥ 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 ≤ 150 mg/dL and $HbA_{1C} \leq 7.5\%$

- Life expectancy of at least 6 months
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for at least 28 days after the last dose of ipatasertib/placebo, 5 months after the last dose of atezolizumab, and 6 months after the last 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 (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

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

  With female partners of childbearing potential, 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 last dose of ipatasertib or 6 months after the last 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 last dose of ipatasertib or

6 months after the last 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 interuterine device, 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.

- 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:

- Histologically documented TNBC or HR+/HER2– 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 on-study, if not available locally) according to the ASCO/CAP guidelines (see Appendix 5 and Appendix 6 for the 2013 guidelines [includes recent HER2 testing update [Wolff et al. 2018]):

  – HER2+ is defined as one of the following: immunohistochemistry 3+ or in situ hybridization positive
  – ER or PgR positivity is defined as ≥ 1% of tumor cell nuclei immunoreactive to the respective hormonal receptor
  – TNBC is defined as HER2–, ER–, and PgR– (required for eligibility for Cohort A)
  – HR+/HER2– is defined as HER2– and ER+ and/or PgR+ (required for eligibility for Cohort B)

- Measurable disease according to RECIST v1.1
- Eligible for taxane monotherapy, as per local investigator assessment (e.g., absence of rapid clinical progression, life-threatening visceral metastases, or the need for rapid symptom and/or disease control which may require combination chemotherapy)
- HR+/HER2– breast cancer that is not considered appropriate for endocrine-based therapy **and** that meets one of the following inclusion criteria:

- Patient has recurrent disease (locoregional or metastatic) during adjuvant endocrine therapy (i.e., ≤5 years of being on therapy).
- If patient has de novo metastatic disease, patient has progressive disease within 6 months of being on first-line endocrine treatment of metastatic disease.

Note that prior treatment with CDK4/6 inhibitors or mTOR inhibitors is allowed.

- Submission of a formalin-fixed, paraffin-embedded tumor (FFPE) tissue block or a minimum of 20 freshly cut unstained, serial tumor slides from the most recently collected tumor tissue for central molecular analysis (mandatory NGS testing [*PIK3CA/AKT1/PTEN*-altered 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.

  If a newer specimen is either insufficient or unavailable, the patient may still be eligible if the patient can provide a tissue block (preferred) or a minimum of 20 unstained serial slides from an older archival tumor tissue or is willing to consent to and undergo an additional pretreatment core or excisional biopsy of the non-target lesion (if it is assessable and the biopsy can be safely obtained). In general, a minimum of three core biopsies for NGS testing are required.

  - If the patient already has *PIK3CA/AKT1/PTEN* alteration results available from the FMI commercial tissue-based NGS assay known as FoundationONE CDx™, then the FMI CTA does not need to be re-run; in this situation FFPE tissue block or 10 freshly cut unstained, serial tumor slides from the most recently collected tumor tissue is acceptable for other protocol-mandated secondary and exploratory assessments, upon approval by the Medical Monitor.
  - Please note, this tumor tissue sample is required to be submitted as described above for all patients, i.e., if local assessment of *PIK3CA/AKT1/PTEN* alteration status or central ctDNA is used to confirm biomarker eligibility (see below), tumor tissue is still required to assess alteration status centrally

- Confirmation of biomarker eligibility, i.e., valid results from either central testing (in tumor tissue as detailed above or blood [using FACT assay] tested at FMI) or local testing of tumor tissue or blood (using an appropriately validated molecular assay at a diagnostic laboratory (CLIA or equivalently accredited)—full laboratory report must be available and captured within the patient's source documents to support eligibility), demonstrating *PIK3CA/AKT1/PTEN*-altered status defined as the presence of one or more of the following:

  AKT1 missense mutations that result in amino acid substitution at the following residues E17, L52, or Q79

  PIK3CA missense mutations that result in amino acid substitution at the following residues R88, G106, K111, G118, N345, C420, E453, E542, E545, Q546, M1043, H1047, or G1049

PTEN alterations that meet any of the following criteria:

- Homozygous deletion (copy number of 0)
- Dominant negative short variant (e.g., C124S, G129E, R130X; Papa et al. 2014)
- Loss of heterozygosity (LOH) with copy number of 1 without concomitant single-nucleotide variants

One deleterious short variant (including insertions and deletions; classification criteria provided below) with a concomitant loss of the non-mutant PTEN allele defined by LOH with copy number of 1 or LOH with copy number >1.

- Any protein truncating mutations, including nonsense mutations and frameshift indels
- Any mutations in the consensus splice donor and acceptor sequence that disrupts the consensus, including insertions and deletions
- Any missense or non-frameshift mutation that has been confirmed somatic as described in the COSMIC database
- If there are two or more deleterious short variants under LOH, the patient will not be eligible for the study.

Please note, for local/commercial testing using tumor tissue or blood, a valid result from the most recently collected tumor tissue/blood is preferred, however, the patient would still be eligible if a valid result is obtained from older archival tissue/blood sample.

4.1.2 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
- Active infection requiring systemic anti-microbial treatment (including antibiotics, anti-fungals, and anti-viral agents)
- Known HIV infection
- 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.

- 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 course of the study

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

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 28 days after the last dose of ipatasertib/placebo, 5 months after the last dose of atezolizumab, and 6 months after the last 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 using Fridericia's formula (QTcF) $>$480 milliseconds
- 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)
- Need for chronic corticosteroid therapy of > 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease

  For Cohort C, no chronic corticosteroid use is permitted at baseline with rare exceptions. Refer to 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 render 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 brain or spinal cord metastases, as determined by computed tomography (CT) or magnetic resonance imaging (MRI) evaluation during screening or prior radiographic assessments

Patients with leptomeningeal carcinomatosis will be excluded.

- Any previous chemotherapy for inoperable locally advanced or metastatic TNBC or HR+/HER2– adenocarcinoma of the breast

  Patients **may** have received prior neoadjuvant or adjuvant chemotherapy and/or radiation treatment for breast adenocarcinoma, provided all chemotherapy was completed ≥ 12 months prior to recurrence.

  Patients with TNBC must not have received any previous systemic therapy for inoperable locally advanced or metastatic TNBC, including chemotherapy, immune checkpoint inhibitors, or targeted agents.

  Chemotherapy does not include HER2-targeted therapy, such as trastuzumab, pertuzumab, or neratinib (for cases in which patients had early stage HER2+ breast cancer and are entering the study with HER2– advanced breast cancer). The minimum 12-month, disease-free inclusion requirement begins with the last administration of chemotherapy in the early breast cancer setting.

- Unresolved, clinically significant toxicity from prior therapy, except for alopecia and Grade 1 peripheral neuropathy
- Patients who have received palliative radiation treatment 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 radiation therapy.

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

- Uncontrolled hypercalcemia (> 1.5 mmol/L ionized calcium, > 12 mg/dL calcium, or corrected serum calcium > 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

  For other cancers considered to have a low risk of recurrence, discussion with the Medical Monitor is required.

  In cases where there is a history of early-stage breast cancer with ER/PR/HER2 status differing from the advanced breast cancer for which the patient is entering the study, the above language still applies (i.e., any breast cancer within the 5 years prior to consent is permitted, provided there is no controversy as to the current ER/PR/HER2 status).

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's 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 that prior PI3K or mTOR inhibitors are allowed.

Atezolizumab-Specific Exclusion Criteria (Cohort C Only)

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's syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 11 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

Patients with a history of autoimmune-related 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 is 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 last 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 course of 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

There are 3 cohorts in this study. The first 2 cohorts, A and B, are randomized, double-blind, placebo-controlled cohorts in biomarker-positive populations designed to estimate the effect on PFS of the addition of ipatasertib to paclitaxel compared with placebo plus paclitaxel. The third cohort (C) has a single-arm open-label design to test safety and efficacy of the combination of ipatasertib plus atezolizumab plus paclitaxel in a biomarker-negative population.

To enable independent comparisons, patients will be assigned to either Cohort A (TNBC biomarker-positive), Cohort B (HR+/HER2− biomarker-positive breast cancer), or Cohort C (TNBC biomarker-negative), according to tumor hormone receptor and biomarker status and these cohorts will be analyzed independently.

In Cohorts A and B, patients will be allocated to each of the treatment arms through the use of a stratified permuted block randomization to ensure within-stratum balance of patient characteristics between treatment arms. Randomization will be stratified by the following criteria: prior adjuvant/neoadjuvant chemotherapy (yes vs. no), region (Asia-Pacific vs. Europe vs. North America vs. rest of the world), and tumor *PIK3CA/AKT1/PTEN*-alteration status (*PIK3CA/AKT1*-activating mutations vs. *PTEN* alterations with no *PIK3CA/AKT1*-activating mutations) for Cohort A only, and prior PI3K/mTOR inhibitors (yes vs. no) for Cohort B only. These factors may correlate with different prognoses and differential responses to Akt inhibition, or they may reflect different regional clinical practices.

Placebo tablets are identical in shape and color to the ipatasertib tablets, and they are indistinguishable (see Section 4.3.1.1 for details). 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.

While PK samples must be collected from patients assigned to the comparator control arm to maintain the blinding of treatment assignment, PK assay results for these patients are generally not needed for the safe conduct or proper interpretation of this study. External laboratories responsible for performing study drug PK assays will be unblinded to patients' treatment assignments to identify appropriate samples to be analyzed. In other words, PK samples from patients assigned to the control arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing).

To further protect the integrity of the study, the results of any patient-specific plasma concentration data for ipatasertib will not be made known to either investigators or the contract research organizations, and any interim safety analyses will not be made known to the investigators or Sponsors. In addition, to minimize potential bias in evaluating progression-free survival, the NGS data and status of *PTEN* alteration versus *PIK3CA/AKT1* mutation of the tumor samples for those patients testing diagnostic-positive will not be disclosed to the investigators/patients prior to RECIST progression. The NGS research report (and FACT assay report if performed), when available, may be released to patients who are: not randomized into Cohorts A or B nor enrolled into Cohort C; randomized into Cohorts A or B or enrolled into Cohort C at the time they discontinue all study treatment; or following end of the study, whichever occurs earlier (unless required by law), upon request by the investigator, and is not intended for treatment decisions.

If unblinding of patients in Cohorts A or B is necessary for patient management (e.g., in the case of a serious adverse event for which patient management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. An investigator may be permitted to perform non-emergency unblinding to enable a patient to switch to an approved therapy. However, non-emergency unblinding is not permitted to enable a patient to switch to an experimental therapy. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event or non-emergency unblinding).

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

The Sponsor will be blinded to treatment assignment until the primary analysis of the respective cohort. The iDMC, iDCC, and the Sponsor-independent PK bioanalytical personnel will remain unblinded to the treatment assignment. 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 of the respective cohort.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are ipatasertib, matching placebo, atezolizumab, and, dependent on local regulations, paclitaxel. Paclitaxel is an approved treatment for breast cancer and is considered standard of care in some countries. Loperamide (racecadotril as used in Europe) is a non-IMP in the study.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Ipatasertib and Placebo

Ipatasertib drug product is intended for oral administration and will be supplied 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. For information on the formulation and handling of ipatasertib/placebo, see the Ipatasertib Investigator's Brochure.

The period between re-dispensing and 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

The atezolizumab drug product will be supplied by the Sponsor as a sterile liquid in a single-use, 20-mL glass vial. Although the vial contains approximately 20 mL (1200 mg) of atezolizumab solution, only 14 mL (840 mg) should be administered.

For information on the formulation, handling, storage, and preparation 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. The sequence of drug administration is ipatasertib/placebo, then atezolizumab (only for patients in Cohort C), and then paclitaxel. On non-atezolizumab administration days, the sequence of drug administration is ipatasertib/placebo and then paclitaxel.

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 Section 5.1.5.

4.3.2.1 Ipatasertib and Placebo

Study treatment of experimental versus placebo arm will be assigned by an IxRS. Ipatasertib/placebo will be administered at the starting dose of 400 mg orally QD, beginning on 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 infusion of paclitaxel.

Each dose of ipatasertib/placebo should be taken 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. Missed or vomited doses will not be made up.

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 in the clinic visit. 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 incidence of vomiting within 3 hours post drug administration should also be recorded for the day of PK sampling.

A sufficient amount of ipatasertib/placebo should be provided to the patient to last one treatment cycle. Patients will be instructed to bring their bottles of ipatasertib/placebo and their medication diaries to each study visit.

4.3.2.2 Atezolizumab

Patients will receive atezolizumab 840 mg administered by IV infusion Q2W (on Days 1 and 15 [±3] days) of each 28-day cycle. Administration of atezolizumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 12.

Atezolizumab infusions will be administered per the instructions outlined in Table 3.

Table 3 Administration of First and Subsequent Infusions of Atezolizumab

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

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

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix 15 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure.

No dose modification for atezolizumab is allowed.

4.3.2.3 Paclitaxel

The dose of paclitaxel in this study is 80 mg/m^2 administered 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. Calculation of body surface area for the purposes of dosing of paclitaxel should be made according to the prescribing information. If the patient's weight changes by > 10% during the study, the body surface area and drug doses should be recalculated.

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.

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

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 H_2-receptor blocker (i.e., ranitidine or famotidine) or per institutional practice. H_2-receptor antagonists, such as cimetidine, which are known to inhibit cytochrome P450, should be avoided.

Diarrhea is a common adverse event associated with ipatasertib and/or paclitaxel treatment. In this current study, to improve diarrhea management and patient experiences, loperamide (2 mg twice a day or 4 mg once a day) will be administered daily as prophylaxis for diarrhea in the first cycle if allowed by local guidance. If side effects of loperamide are not tolerated, doses may be reduced at any time. Investigators are encouraged to continue this dosing for the remainder of the study using their discretion based on clinical judgments.

If diarrhea occurs, it should be managed per guidelines in Appendix 13; upon resolution or when study treatment is restarted, loperamide prophylaxis should be considered to resume and continue based on clinical judgments (if allowed by local guidance).

Due to the risk of rash in Cycle 1, patients in Cohort C should receive the following prophylaxis during the first cycle in which all 3 study treatments will be given: On days when patients will receive atezolizumab (typically D1 and D15), patients should receive at least 10 mg/day 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 prednisone (or equivalent dosing of other steroids) on the day of paclitaxel, then the additional 10 mg prophylactic prednisone (or equivalent dosing of other steroids) should not be given on that day to prevent rash. Timing of steroid on days when patients will receive atezolizumab and paclitaxel is at investigator discretion, as per clinical judgment. 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 pre-medication already includes an antihistamine.

4.3.4 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided by the Sponsor, where required by local health authority regulations. The study site will acknowledge receipt of

IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

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

4.3.5 Continued Access to 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 drug or data suggest that the drug is not effective for breast cancer
- The Sponsor has reasonable safety concerns regarding the drug as treatment for breast cancer
- Provision of the 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 Web site:

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, as allowed per local guidelines
- 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 4.4.3).

  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 with, and approved in advance by, the Medical Monitor. The patient may continue ipatasertib treatment after treatment holding has been completed and the patient has sufficiently recovered.
- Premedication with antihistamines, antipyretics, and/or analgesics for each paclitaxel administration
- Premedication with corticosteroids and antihistamines prior to administration of atezolizumab, as outlined in Section 4.3.3
- Prophylaxis use of loperamide (racecadotril as used in Europe) is mandated in the first cycle (if allowed by local guidance, except when the Medical Monitor approves omission, 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. Patients should be educated/reminded to be cognizant of the onset, duration, severity, and frequency of symptoms and the medications administered.
- Granulocyte colony-stimulating factor treatment is permitted for patients receiving paclitaxel. The primary prophylaxis should be administered per the ASCO, EORTC, and European Society for Medical Oncology (ESMO) guidelines; namely, in patients who are ≥60 years of age 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) is allowed.

- 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)
- Inactivated influenza vaccinations
- 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

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

4.4.2 Cautionary Therapy

Patients who require radiation or surgery as part of medical treatment in the absence of radiographic disease progression must exercise caution, and all study treatment should be temporarily held for at least 7 days before and after the procedure (at least 14 days after radiation is recommended). For minor surgeries or single-day radiotherapy, this hold may be shorter, if discussed by the investigator with, and approved in advance by, the Medical Monitor. After the temporary treatment hold is complete, study treatment may be re-initiated when the patient has sufficiently recovered.

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific adverse events (refer to Section 5.1.5 for details). All study treatment should be temporarily held during systemic corticosteroids treatment (except when corticosteroids are given as pre-medication to paclitaxel).

4.4.2.1 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 dosed at 600 mg 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 ~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
- 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 last dose of these drugs.
- 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 lists of medications are 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 investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer 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) is prohibited 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) is prohibited 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 4.4.1 for details).
- Chronic use of a strong CYP3A4/5 inhibitor or inducer, or sensitive CYP3A substrates with a narrow therapeutic window that are deemed not permissible by the Medical Monitor after enrollment (refer to the guidance in Section 4.4.2)
- 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®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin 2) are prohibited 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 immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited 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, is prohibited during the study treatment period and for 10 days after the last dose of study treatment.
- Consumption of St. John's wort, a potent CYP3A4 enzyme inducer, is prohibited for up to 14 days prior to and during the study treatment period, and for 10 days after the last dose of study treatment.

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 study 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, Appendix 2, Appendix 3, and Appendix 4. All activities must be performed and documented for each patient.

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

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 or submission of archival tissues). Patients may be first screened for *PIK3CA/AKT1/PTEN*-altered status by participating in a separate "biomarker-specific" screening consent, or this assessment may be made as part of the full eligibility evaluation and consent for this study. The biomarker-specific screening consent specifically allows for the collection and submission of the tumor tissue sample (and FACT blood sample if desired) for central FMI biomarker-eligibility testing. Patients with confirmed *PIK3CA/AKT1/PTEN*-altered status by central tissue- or blood-based FMI assay must have consented to the full study before performing other study-related procedures. The biomarker-specific screening consent also allows for the collection of the associated exploratory blood biomarker sample. 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 screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable. Patient re-screening may be considered under

exceptional circumstances, after approval by the Medical Monitor. If *PIK3CA/AKT1/PTEN*-altered status has been determined for a patient, a repeat testing of the biomarker-specific screening process is not required at re-screening.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), 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.

Further, to assess the actual intake of analgesic, anti-histamine, and anti-diarrheal medication use taken outside of the clinic/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, anti-histamine, or anti-diarrheal medications, including the recommended dosage and route of administration. Patients should use the diary to record daily ipatasertib/placebo dosing and specifically any anti-diarrheal, anti-histamine, or analgesic medications used (prescribed or over-the-counter) taken on that cycle of treatment. The intake of analgesic, anti-histamine, and loperamide medication will be reported in the Analgesics Medication, Anti-histamine, and Targeted Loperamide Concomitant Medications eCRFs, respectively.

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

4.5.3 Physical Examinations

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

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

4.5.4 Vital Signs

Vital signs will include measurements of pulse rate, systolic and diastolic blood pressure while the patient is in a seated position after resting for at least 5 minutes, respiratory rate and oral, axillary, or tympanic temperature.

On paclitaxel dosing days, vital signs should be recorded prior to dosing and at the end of the infusion. On days when atezolizumab and paclitaxel are both administered, vital signs should also be recorded prior to atezolizumab dosing (and during infusion if clinically indicated), per Table 3.

4.5.5 Tumor and Response Evaluations

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator on the basis of physical examinations (with photography measurements) and imaging (CT, MRI, and bone scans) through use of RECIST v1.1 criteria (see Appendix 10). Images for tumor assessments will be collected to enable retrospective blinded independent central review when needed. As of Protocol CO40016, Version 10 (Cohort C), images for tumor assessments will no longer be collected for blinded independent central review. 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. An objective response should be confirmed by repeat assessments $\geq$4 weeks after initial documentation. 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 before 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 before Day 1, Cycle 1. For patients in Cohort B (HR+/HER2–), screening head scans will be performed only if clinically indicated.

As of Protocol CO40016 Version 11 (Cohort C), tumor assessments should be performed based on a schedule calculated from Cycle 1, Day 1 (study Day 1) with the first assessment during Week 8 and *per standard of care* thereafter, regardless of treatment administration timings or prior early/late tumor assessments. 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 from 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 (approximately every 8–12 weeks) until documented progressive disease per RECIST v1.1, elective withdrawal from the study, or study completion or termination (see schedule of assessments *[*Appendix 1 for Cohorts A and B and Appendix 2 for Cohort C]). *As of Protocol CO40016 Version 11 (Cohort C), these long-term follow-up tumor assessments are no longer required.*

A documented standard-of-care tumor assessment performed within 28 days before Cycle 1, Day 1 (bone or head scans within 6 weeks prior to Cycle 1, Day 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, and 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. However, an MRI scan of the chest may be performed only with the approval of the Medical Monitor. 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.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Laboratory samples should be drawn according to the schedule of activities (see Appendix 1, Appendix 2, Appendix 3, and Appendix 4) 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 to assess the dosing decision. The following tests are essential assessments for Day 1 dosing for every cycle: hemoglobin, absolute neutrophil counts, lymphocytes, and platelet count; glucose, creatinine, potassium, calcium, total bilirubin, ALP (total ALP), AST, ALT; and a pregnancy test. Screening local laboratory assessments obtained within these windows before Day 1 of Cycle 1 do not have to be repeated on Day 1 of Cycle 1.

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

- Hematology: hemoglobin, hematocrit, WBC count with differential (i.e., must be sufficient for the determination of absolute neutrophil counts, lymphocytes), and platelet count
- Fasting serum chemistry: glucose (following ≥8-hour fast, plasma glucose is also acceptable per local practice), plus the chemistry panel including BUN or urea, bicarbonate, creatinine, sodium, potassium, magnesium, calcium, phosphorus, albumin, total bilirubin, ALP (total ALP), AST, ALT, and LDH

  For investigational sites in countries where bicarbonate may not be collected as part of the standard chemistry panel, bicarbonate will not be measured.
- Fasting lipid profile: total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, performed following ≥8-hour fast
- Glycosylated hemoglobin (HbA_{1c})
- Amylase and lipase
- Coagulation: PTT (or aPTT) and INR
- Urinalysis (dipstick allowed): pH, specific gravity, glucose, protein, ketones, and blood; microscopic examination if clinically indicated
- 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 Cycle 1, Day 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/serum 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.

- Screening viral serology: HIV, HBsAg, total hepatitis B core antibody (HBcAb), HCV antibody; additional tests for HBV DNA or HCV RNA will be required to confirm eligibility in patients with a positive antibody result.
- Home glucose monitoring:

  For any patients who initiate home glucose monitoring (see Table 2 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 the Sponsor or a designee for analysis:

- Plasma samples for PK analysis
- Blood samples for exploratory research on biomarkers

  Blood will be collected for ctDNA analysis at screening (either as part of the biomarker-specific screening process or full screening; if screening sample used for FACT biomarker eligibility analysis, this sample for exploratory biomarker research should be collected prior to dosing of Day 1 of Cycle 1), at the time of the first tumor assessment (± 7 days), and at the study drug discontinuation visit. A screening/ Day 1 of Cycle 1sample for all patients will be collected and submitted with the tissue (see Section 3.3.7 for the rationale).
- Blood samples for whole genome sequencing (if approved locally)
- Most recently collected tumor tissue for evaluation of *PIK3CA/AKT1/PTEN*-altered tumor status (using the FMI CTA NGS assay, unless the patient already has an available FoundationONE CDx™ commercial test confirming biomarker eligibility) and for exploratory research on biomarkers

  A representative FFPE tumor specimen in a paraffin block (preferred) or at least 20 slides containing unstained, freshly cut, serial sections should be submitted at least 3 weeks prior to planned study randomization date. (As noted in Section 4.4.1, 10 slides rather than 20, are acceptable in patients already qualifying via a commercial FoundationONE CDx™ result, with Medical Monitor approval.)

  Tumor tissue should be of good quality based on total and viable tumor content. Samples collected via resection, core-needle biopsy (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. FNA (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 submitted tissue is determined to be unsuitable for required testing, a pre-treatment tumor biopsy (preferred, a minimum of three core biopsies is required for NGS evaluation), or older archival tissue may be submitted to obtain a valid result.

- A blood sample for central assessment of biomarker eligibility by ctDNA at FMI may be submitted at screening for assessment using the Foundation ACT (FACT assay, should generally only be performed when it is anticipated that there will be a significant delay to acquisition of existing tumor tissue). If this assessment is used, the blood sample normally collected as part of screening procedures (for exploratory biomarker analysis) may be used to perform the FACT assay, with an additional sample (approximately 20 mL) collected on Day 1 of Cycle 1 for the purposes of exploratory biomarker analysis (see above). Please note, submission of most recently collected tumor tissue (as described above) is still an eligibility requirement but is not in itself required to determine biomarker eligibility if the patient qualifies by FACT assay.
- 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

    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)

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

For patients who are not randomized into Cohorts A or B nor enrolled into Cohort C, if valid results of the FMI NGS assay (and FACT assay report if performed) are available, the investigator may obtain results of this screening assay in the form of a research report from FMI, which is available upon request. A copy of this report(s) may also be available upon request by the investigator for patients randomized into Cohorts A or B or enrolled into Cohort C, at the time they discontinue all study treatment or following end of the study, whichever occurs earlier, unless required by law.

If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The FMI assay has not been cleared or approved by health authorities. The NGS and FACT reports are generated for research purposes and are not provided for the purpose of guiding future treatment decisions. Results may not be available for samples that do not meet testing criteria.

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 4.5.12), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Plasma samples collected for PK analysis may be needed for additional PK characterization and assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood samples collected for WGS will be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the Institutional Review Board/Ethics Committee (IRB/EC)-approved Informed Consent Form and applicable laws (e.g., health authority requirements).
- 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.
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first. For patients who are not randomized into Cohorts A or B or enrolled into Cohort C, the remaining archival tissue blocks (if applicable) will be returned to the site no later than 6 weeks after eligibility determination. The submitted tissues may still be analyzed using FMI NGS assays and may be used for future development of diagnostic tests related to *PIK3CA/AKT1/PTEN*-altered status.

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, including data on germline mutations, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of the analyses, data derived from WGS specimens 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.

4.5.7 Electrocardiograms and Cardiac Function Assessment

A cardiac function assessment by echocardiogram or multiple-gated acquisition 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 may be acceptable (e.g., cardiac MRI), if consistent with local standard practice, but must be approved by the Medical Monitor.

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 postdose 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 should be notified. 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, as described in Sections 5.2.1 and 4.6.1. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.8 Patient-Reported Outcomes

To more fully characterize ipatasertib in combination with paclitaxel compared with single-agent paclitaxel (Cohorts A and B) or ipatasertib plus atezolizumab and paclitaxel (Cohort C) as a first-line treatment in patients with metastatic breast cancer, PRO data will be collected using the following instruments: EORTC QLQ-C30, select items of the PRO-CTCAE, and the EQ-5D-5L.

PRO questionnaires scheduled for administration during a clinic visit must be completed by the patient at the investigational site at the start of the clinic visit prior to all other study assessments and before administration of study treatment. Patients will complete paper versions of the questionnaires, which will be provided by site staff. Interviewer assessment is allowed but can only be conducted by a member of the clinic staff for patients who are unable to complete the measures on their own. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. Appropriate translated versions of the local language of the PRO measures will be available at the site.

To minimize burden to patients**,** only the EQ-5D-5L and select scales of the EORTC QLQ-C30 will be administered over the phone to patients, or completed at the site, after treatment discontinuation (due to any reason; see Appendix 1). The following selected scales of the EORTC QLQ-C30 will measure disease/treatment-related symptoms: the global health status/HRQoL (which consists of Questions 29 and 30), pain (Questions 9 and 19), fatigue (Questions 10, 12 and 18), and dyspnea (Question 8) scales. 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. *As of Protocol CO40016 Version 11 (Cohort C), these long-term follow-up assessments are no longer required.*

4.5.8.1 EORTC QLQ-C30

The EORTC QLQ-C30 (see Appendix 7) is a validated and reliable self-reported measure (Aaronson et al. 1993; Sprangers et al. 1996; Fitzsimmons et al. 1999) consisting of 30 questions that assess 5 aspects of patient functioning (physical, emotional, role, cognitive, and social), 8 symptoms (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea), financial difficulties, and global health status (GHS)/quality of life (QoL) with a recall period of the previous week.

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-items scales by using a linear transformation for standardization of the calculated raw score. The EORTC QLQ-C30 takes approximately 10 minutes to complete.

4.5.8.2 PRO-CTCAE

The PRO-CTCAE (see Appendix 9) is an item bank reflecting 78 symptomatic adverse events rated according to their severity, interference with daily function, frequency, and/or occurrence. The item bank was designed and validated as a repository of stand-alone items (Basch et al. 2014). PRO-CTCAE will be completed per the Schedule of Activities, only when available in the local language of the investigational site.

Symptoms selected for this study include those adverse events experienced at any grade that occurred in ≥20% of patients for either treatment (ipatasertib and/or paclitaxel) in previous studies.

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, 8 symptomatic adverse events were selected from the PRO-CTCAE item bank (i.e., diarrhea, nausea, vomiting, decreased appetite, fatigue, peripheral numbness and tingling, mouth sores, and rash); 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 of the PRO-CTCAE.

4.5.8.3 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. Published weighting systems allow for the creation of a single composite score of the patient's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study to inform pharmacoeconomic evaluations and, as such, will not be included in the Clinical Study Report (see Appendix 8).

4.5.9 Skeletal-Related Events Assessment

For this study, a skeletal-related event (SRE) is defined as either a pathologic fracture, radiation therapy to the bone, surgery to the bone, or a spinal cord compression. The investigator assessment for each adverse event, radiation or surgery relating to the bone or spinal cord, should be reported in the patient chart and in the eCRF. Patients should be monitored for any SREs during the treatment and treatment-free follow-up periods of the study. *As of Protocol CO40016 Version 11 (Cohort C), these long-term follow-up assessments are no longer required.*

4.5.10 Mandatory Samples for Whole Genome Sequencing

At participating sites, blood samples will be collected for DNA extraction to enable WGS to identify germline mutations and somatic mutations 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, or can increase the knowledge and understanding of disease biology. The blood samples may be sent to one or more laboratories for analysis.

Collection and submission of WGS samples is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS sampling, this section of the protocol (Section 4.5.10) will not be applicable at that site.

Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. 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 of important pathways, guiding the development of new targeted agents.

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

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

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

Given the complexity and exploratory nature of the WGS analyses, 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.

4.5.11 Post-Treatment Follow-Up

At post-treatment follow-up visits, survival follow-up information, subsequent treatment and outcome, and PROs will be collected via telephone calls, patient's medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, or study termination by Sponsor. All patients will be followed for post-treatment follow-up information unless the patient requests to be withdrawn from study post-treatment follow-up; this request must be documented in the source file and signed by the investigator.

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 8–12 weeks for tumor assessments (disease follow-up clinic visits; see Appendix 1) until documented progression per RECIST v1.1, elective withdrawal from the study, or study completion or termination. Images for tumor assessments will be collected to enable retrospective blinded independent central review when needed. As of Protocol CO40016, Version 10 (Cohort C), images for tumor assessments will no longer be collected for blinded independent central review.

As of Protocol CO40016 Version 11 (Cohort C), these long-term follow-up assessments are no longer required.

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 biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection,

storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

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

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

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR 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, and breast cancer biology:

- **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 mutations via WGS, whole exome sequencing (WES), NGS, 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 (results may not be available for samples that do not meet testing criteria).

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS, WES, and NGS provide a comprehensive characterization of the genome and exome, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. 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 of important pathways, guiding the development of new targeted agents.

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

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

4.5.12.4 Confidentiality

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

Patient medical information associated with RBR specimens is confidential and may be disclosed 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 specimens, 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 specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and 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 specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not 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 specimens 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 samples from the RBR at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the 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 specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. 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 for any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Withdrawal of consent from the study treatment
- Pregnancy
- Use of an anti-cancer therapy not required per protocol
- Disease progression per investigator's assessment according to RECIST v1.1

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 28 (±3) days (Cohorts A and B) or 30 (±3) days (Cohort C) after the last dose of study drug or prior to initiation of new anti-cancer therapy, whichever is sooner (see Appendix 1 for additional details).

After treatment discontinuation, patients will return to the clinic for disease follow-up (if patient did not discontinue due to disease progression per RECIST v1.1), and information on survival follow-up, PROs, 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 from the study or the Sponsor terminates the study). *As of Protocol CO40016 Version 11 (Cohort C), these long-term follow-up assessments are no longer required.*

4.6.2 Patient Discontinuation from Study

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

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

Every effort should be made to obtain information on patients who withdraw from the study. Patients should be asked to return to the clinic for a study treatment discontinuation visit (if applicable). The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn

from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

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

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for 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. The safety plan for patients in this study is based on clinical experience with ipatasertib in completed and ongoing studies.

The anticipated important safety risks and management plan for ipatasertib, atezolizumab, and paclitaxel are outlined below. The identified risks associated with ipatasertib treatment include gastrointestinal toxicities (diarrhea, nausea, vomiting, and oral mucositis), fatigue/asthenia, rash, erythema multiforme, *dehydration, decreased appetite, ALT/AST increased*, and hyperglycemia. 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 anticancer therapies. Refer to the Atezolizumab Investigator's Brochure for a complete summary of safety information of atezolizumab as a single agent and in combination with chemotherapy and other

anti-cancer therapies. Refer to the Paclitaxel Prescribing Information or Summary of Product Characteristics for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this 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. Vital signs and relevant laboratory values will be monitored at baseline and during the study.

Guidelines for managing adverse events, including prophylaxis (for diarrhea), and criteria for dose modification (interruption, dose reduction or discontinuation) for the management of specific adverse events attributable to ipatasertib/placebo, atezolizumab, and/or paclitaxel, are summarized in Section 5.1.5.5. The instructions provided are intended to serve as a guideline to improve safety and tolerability for patients to continue receiving ongoing treatment. Suggested dose reductions for ipatasertib/placebo and paclitaxel are listed in Table 4 and Table 5. Dose reduction for atezolizumab is not allowed. General guidelines for dose modification are provided in Section 5.1.5.1.

The iDMC will be responsible for ongoing monitoring of patient safety in the double-blinded, randomized Cohorts A and B.

5.1.1 Risks Associated with Ipatasertib in Combination with Paclitaxel

Ipatasertib in combination with paclitaxel has been administered to 61 cancer patients in Study GO29227 (LOTUS). Adverse events related to ipatasertib/placebo whose incidences were higher by ≥10% in patients receiving ipatasertib + paclitaxel versus placebo + paclitaxel were 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) in patients in the ipatasertib + paclitaxel arm vs placebo + paclitaxel arm were diarrhea (14 patients [23.0%], all Grade 3, vs. 0 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.

The incidence of overall neutropenia in the LOTUS Study was similar in both arms (34% in the ipatasertib + paclitaxel arm vs. 39% in the placebo + paclitaxel arm), but Grade ≥3 neutropenia, analyzed by grouped terms of similar medical concept, was higher in the ipatasertib + paclitaxel arm (18% vs. 8%). Thus, for recurrent Grade ≥3 neutropenia, ipatasertib should be reduced by one dose level when treatment is restarted (refer to the management guidelines in Section 5.1.5.5).

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 as a single agent and in combination with chemotherapy.

5.1.2 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs, immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, hypophysitis, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous 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 14 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.3 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.

5.1.4 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, and hematologic toxicity.

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

Adverse events related to paclitaxel in the LOTUS study (GO29227) whose incidences were higher by $\geq$10% in patients receiving ipatasertib + paclitaxel versus placebo + paclitaxel were diarrhea (78.7% vs. 12.9%), nausea (41.0% vs. 24.2%), and peripheral sensory neuropathy (26.2% vs. 16.1%). Refer to the management guidelines in Section 5.1.5.5 for these adverse events.

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.

5.1.5 Management of Patients Who Experience Specific Adverse Events

5.1.5.1 Dose Modifications

Guidelines for dosage modification and treatment interruption or discontinuation are provided below. There will be no dose modifications for atezolizumab in this study; however, treatment may be interrupted/discontinued as needed (see below for details).

Any dose modification should be noted on the corresponding Study Drug Administration eCRF. Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

5.1.5.2 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 (Table 4 and Table 5). 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 in 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/μL
- Platelet count $\geq$ 100,000/μL
- 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 contains exactly 28 days.
- Cohorts A and B; if ipatasertib/placebo treatment is interrupted, paclitaxel treatment may continue if medically appropriate (per investigator discretion).
- Cohorts A and B; if paclitaxel treatment is interrupted, consider delaying the ipatasertib/placebo and paclitaxel treatment concurrently for up to 7 days (i.e., shifting the 7 days-off week for ipatasertib/placebo so that 21 daily doses in 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.
- Cohort C; if ipatasertib treatment is interrupted, atezolizumab and/or paclitaxel treatment may continue if medically appropriate (per investigator discretion).
- Cohort C; if atezolizumab treatment is interrupted, ipatasertib and/or paclitaxel treatment may continue if medically appropriate (per investigator discretion).

- Cohort C; if paclitaxel treatment is interrupted, ipatasertib and/or atezolizumab treatment may continue if medically appropriate (per investigator discretion). If paclitaxel treatment is interrupted, consider delaying ipatasertib treatment concurrently for up to 7 days (i.e., shifting the 7 days-off week for ipatasertib so that 21 daily doses in 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.
- Cohort C; given the complexity of this triple drug combination's schedule, although there are pre-specified windows allowed around dosing days, it is strongly suggested that paclitaxel administration only be on Days 1, 8, and 15, (or Day 22 as a day to compensate for missed paclitaxel on any of the 3 prior days), and that atezolizumab be given on Days 1 or 15. If dosing is not feasible on those days, it is acceptable and encouraged to dose on the next suggested day using above guidance. Sites are encouraged to reach out to the Medical Monitor for any guidance on this matter.
- 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, Day 15, or Day 22). However, laboratory assessments and clinical visits should be scheduled as needed for follow-up of adverse events. In addition, tumor assessment *per standard of care* 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 any concomitant conditions at baseline, dose modifications may apply according to the shift in toxicity grade, if the investigator deems it appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this change may be considered a shift of one grade and may be treated as Grade 1 toxicity for dose-modification purposes if medically appropriate.
- 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.
- Dose reductions or interruptions may not be required for anemia (non-hemolytic) if satisfactorily managed by transfusions.
- If any observed toxicity is attributable to only one drug as assessed by the investigator, the dose of the other drug(s) may not require modification.
- 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, Day 15, or Day 22 laboratory value).
- Patients who require chemotherapy dose reductions and tolerate the reduced dose for more than one cycle (28 days) may be allowed to increase back to a 100% dose

at the treating physician's discretion (no specific guidance is provided for ipatasertib re-escalation, as it is not permitted).

- 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. Dose hold for longer than 4 weeks for a treatment-related adverse event will require permanent discontinuation of the attributable treatment component and per specific adverse event management guidelines in Section 5.1.5.5.

  Cohort C: Atezolizumab may be held for up to 12 weeks. See additional details in Section 5.1.5.4.

  As applicable, patients may continue treatment with remaining study drugs (Cohorts A and B: if paclitaxel has been discontinued, ipatasertib/placebo may be continued alone, after discussion with the Medical Monitor)

5.1.5.3 Dosage Modification for Ipatasertib/Placebo and Paclitaxel

If the patient does not tolerate the 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 below 200 mg/day of ipatasertib/placebo) will be allowed (see Table 4). Dose re-escalation is not permitted for ipatasertib/placebo.

To manage paclitaxel-related toxicity, no more than one dose reduction for paclitaxel will be allowed (Table 5). Paclitaxel doses other than specified in Table 5 will not be allowed.

Table 4 Dose Reductions for Ipatasertib/Placebo

Dose Level [a]	Ipatasertib/Placebo
Starting dose	400 mg
First dose reduction	300 mg
Second dose reduction	200 mg
Third dose reduction	Not permitted

[a] If the patient continues to experience specified drug-related adverse events after the second reduction, the treatment should be discontinued.

Table 5 Dose Reductions for Paclitaxel

Dose Level [a]	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 drug-related adverse events after the dose reduction, the treatment should be discontinued.

5.1.5.4 Treatment Interruption

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.

In Cohorts A and B, if the ipatasertib/placebo is discontinued at any time during the study, patients may continue on study with chemotherapy alone (Cohorts A and B). In Cohort C, if any of the three study treatments are discontinued, the other study treatments may be continued independent of each other (i.e., if the ipatasertib is discontinued at any time during the study, patients may have the option of continuing on study with atezolizumab and chemotherapy or atezolizumab alone or chemotherapy alone).

Ipatasertib/placebo, atezolizumab, and/or paclitaxel treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor approval. If, 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, study drug may be restarted with the approval of the Medical Monitor.

If daily systemic corticosteroids are initiated for treatment of any toxicity or other condition, they must be tapered to ≤ 10 mg/day oral prednisone or equivalent before

ipatasertib or ipatasertib/placebo can be resumed. Steroids used as prophylaxis (i.e., prior to scans, as protocol-directed rash prophylaxis for patients in Cohort C, or prior to paclitaxel or atezolizumab) do not require holding of ipatasertib or ipatasertib/placebo. Steroids used on a single day to manage IRRs or allergic reactions similarly do not require holding of ipatasertib or ipatasertib/placebo.

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to atezolizumab. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks due to atezolizumab-related toxicity (as measured from the first day of interruption of scheduled atezolizumab dosing), the patient will be discontinued from atezolizumab. Given that a slow taper of steroids, as directed above, is required by protocol, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can then be resumed after being withheld for > 12 weeks if the Medical Monitor agrees that the patient is likely to derive clinical benefit. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with Medical Monitor's approval, with acceptable length of interruption to be determined by the Medical Monitor based on discussion with the investigator. Following discussion with the Medical Monitor, the investigator may determine the acceptable length of treatment interruption based on sound medical and clinical judgement, and taking into consideration the overall benefit–risk for the patient.

5.1.5.5 Adverse Event Management Guidelines

Refer to the following appendices for adverse event management guidelines:

- Cohorts A and B: Appendix 13
- Cohort C, Ipatasertib plus Atezolizumab plus Paclitaxel: Appendix 14
- Cohort C, Atezolizumab: Appendix 15

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

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

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

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

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

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

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

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

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

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

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

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Grade ≥3 fasting hyperglycemia
- Grade ≥3 hepatotoxicity
- Grade ≥3 ALT/AST elevations
- Grade ≥2 colitis/enterocolitis
- Grade ≥3 diarrhea
- Grade ≥3 rash
- Grade ≥2 pneumonitis (Cohorts A and B)

The following adverse events of special interest apply to Cohort C only:

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

- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine-release syndrome, influenza-like illness, 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
- Severe cutaneous reactions (e.g., 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
- Peripheral neuropathy (peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy)
- 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)

- Pneumonia (lower respiratory tract infection)
- 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

Investigators will seek information on adverse events at each patient contact. All adverse events identified by the investigator will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (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 drug, all adverse events for patients in Cohorts A and B will be reported until 28 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. For patients in Cohort C, 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 non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

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

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

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 this 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 (SAE) or an adverse event of special interest (AESI), the investigator will determine whether the criteria for an SAE or AESI 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 (v4.0) will be used for assessing adverse event severity. Table 6 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 6 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an

adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 7):

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

Table 7 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug 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 the study drug, 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 the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (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 the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

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.

There is one eCRF page for recording adverse events or serious adverse events.

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

5.3.5.1 Infusion-Related Reactions

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 or placebo.

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 per institutional practice with dexamethasone, diphenhydramine, and one of the following two H_2-receptor blockers: ranitidine or famotidine. Other H_2-receptor antagonists, such as cimetidine, which are known to inhibit cytochrome P450, should be avoided. An H1-receptor antagonist, such as diphenhydramine 50 mg IV, may be given as well.

Patients should be monitored during paclitaxel administration per institutional policies. Patients may receive anti-emetic and other prophylactic treatments (e.g., IV infusions of calcium and magnesium to try to decrease any potential peripheral neuropathy) according to institutional and/or local standards and per manufacturer's instructions.

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

5.3.5.2 Diagnosis versus Signs and Symptoms

If known, a diagnosis 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. Details regarding any increases or decreases in severity of selected adverse events (e.g., diarrhea, Section 5.2.4) will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) 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 $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

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

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of underlying breast cancer should be recorded on the Study Discontinuation eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An 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").

During post-treatment follow-up, deaths attributed to progression of underlying breast cancer should be recorded only on the Study Discontinuation eCRF. 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 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.

Hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration 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 progression of the underlying 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 a non-serious 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.

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, 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.

In addition, all special situations associated with ipatasertib/placebo, atezolizumab, and paclitaxel, 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.

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.

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. 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.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

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

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

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

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for All Sites

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

Mobile Telephone No.: [redacted]

Medical Monitor/Roche Medical Responsible: [redacted], *Ph.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 Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial 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 Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first (Cohorts A and B), or for patients in Cohort C, 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. 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 >28 days (>90 days for patients in Cohort C) after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 28 days after the last dose of ipatasertib/placebo, 5 months after the last dose of atezolizumab, or 6 months after the last dose of paclitaxel, whichever occurs later. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue ipatasertib or placebo 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 28 days after the last dose of ipatasertib/placebo or 6 months after the last 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 drug. 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 embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, 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 adverse event reporting period (defined as 28 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first for patients in Cohorts A and B; defined as 30 days [all adverse events] or 90 days [serious adverse events and adverse events of special interest] after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, for patients in Cohort C), all deaths, regardless of cause, should be reported through use of the Long-Term Post-Treatment Follow-Up eCRF and in the Study Discontinuation eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study drug, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial 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 using the following reference documents:

- Ipatasertib Investigator's Brochure
- Atezolizumab Investigator’s Brochure
- 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

The three cohorts, Cohort A (TNBC biomarker-positive), Cohort B (HR+/HER2– biomarker-positive breast cancer), and Cohort C (TNBC biomarker-negative) are three independent cohorts and will be analyzed separately for the following reasons:

- The three patient populations are distinct patient populations and are expected to have different prevalence and PFS and OS expectations, and thus different enrollment and analysis timelines.
- The readout from one cohort is independent of the readout of the other cohorts.
- This study is essentially three independent trials running under one protocol for operational efficiency.

Therefore, for all analyses described below, these three cohorts will be analyzed separately.

The global population will include all patients enrolled during the global enrollment phase (including patients enrolled at CFDA-recognized sites during that phase), and the China subgroup will include all patients enrolled at CFDA-recognized sites (i.e., during both the global enrollment phase and the extended China enrollment phase). Separate analyses will be performed for the global population and the China subgroup.

In general, data will be described and summarized as warranted by sample sizes. Continuous variables will be summarized using means, standard deviations, medians, and ranges; categorical variables will be summarized using counts and percentages; time-to-event data will be summarized using estimates of the median and associated confidence intervals. Listings will be used in place of tables in the event of small sample sizes.

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.

6.1 DETERMINATION OF SAMPLE SIZE

As described earlier, Cohort A (TNBC biomarker-positive), Cohort B (HR+/HER2– biomarker-positive breast cancer), and Cohort C (TNBC biomarker-negative) are three independent cohorts and will be analyzed separately. Cohort A and Cohort B will be tested independently with 5% type I error control each. Cohort C is a single-arm cohort with no statistical hypothesis testing and will be reported descriptively only.

For unblinding of Cohort A and Cohort B, in the event that the primary PFS analysis timelines for the Cohort A and Cohort B are far apart, after the iDMC's review, the

treatment codes of the cohort whose PFS data are mature earlier will be sent to the Sponsor to unblind only that cohort for the primary analysis of PFS. The Sponsor will remain blinded to the treatment assignments of the other cohort. Data from any additional patients enrolled within the China extension phase will not be included in the analysis of the global study.

Global Study

For Cohort A, approximately 249 patients with TNBC with *PIK3CA/AKT1/PTEN*-altered tumors will be enrolled and randomized in a 2:1 ratio to the experimental arm (ipatasertib 400 mg + paclitaxel) and control arm (placebo + paclitaxel). The sample size of 249 patients is determined on the basis of the power calculation for the PFS and OS endpoints.

The PFS primary analysis in Cohort A is planned to be conducted after approximately 125 PFS events in Cohort A have been observed or Cohort A's last patient in, whichever is later. Data of 125 PFS events allows for 95.5% power to detect an improvement in median PFS from 6 months in the placebo + paclitaxel arm to approximately 12 months in the ipatasertib + paclitaxel arm (hazard ratio = 0.5) at the 5% level of significance (two-sided). The largest hazard ratio deemed to be statistically significant at the 5% level will be approximately 0.69 (with median PFS improvement from 6 months to 8.7-months).

For Cohort A, the key secondary endpoint, OS, will be tested only if the PFS result is statistically significant. The final OS analysis with approximately 188 OS events will provide 80% power to detect a hazard ratio of 0.65 (median OS improvement from 16 to 24.6 months), or 64% power to detect a hazard ratio of 0.7. The largest detectable OS hazard ratio (with a log-rank test) will be approximately 0.74 (with median OS improvement from 16 months to 21.6 months).

Assuming a 2-month site ramp-up period and approximately 120−150 sites, the enrollment duration is projected to be approximately 16 months (from the first patient enrolled). The last PFS event (the 125th PFS event) for the PFS analysis in Cohort A (patients with TNBC) is projected to occur approximately 20 months after the first patient is enrolled. The last death (the 188th OS event) for the final OS analysis in Cohort A (patients with TNBC) is projected to occur approximately 53 months after the first patient is enrolled.

For Cohort B, approximately 201 HR+/HER2– patients with *PIK3CA/AKT1/PTEN*-altered tumors will be enrolled and randomized in a 2:1 ratio to the experimental arm (ipatasertib 400 mg + paclitaxel) and control arm (placebo + paclitaxel). The sample size of 201 patients is determined on the basis of the power calculation for the primary endpoint, PFS.

The PFS primary analysis in Cohort B is planned be conducted when approximately 150 PFS events in the Cohort B patients have been observed. This allows for 80% power to detect an improvement in median PFS from 8.5 months in the placebo + paclitaxel arm to approximately 13.8 months in the ipatasertib + paclitaxel arm (hazard ratio = 0.62) at the 5% level of significance (two-sided). The largest hazard ratio deemed to be statistically significant at the 5% level will be approximately 0.71 (with median PFS improvement from 8.5 months to 11.93 months).

Assuming a 2-month site ramp-up period and approximately 120–150 sites, the enrollment duration is projected to be approximately 10 months (from the first patient enrolled). The last PFS event (the 150th PFS event) for the PFS analysis in Cohort B (patients with HR+/HER2– breast cancer) is projected to occur approximately 30 months after the first patient is enrolled.

The above timeline estimates are based on an assumption of an annual loss-to-follow-up rate for PFS of 5% and an annual loss-to-follow-up rate for OS of 2%.

For Cohort C, approximately 100 patients with TNBC lacking *PIK3CA/AKT1/PTEN*-altered tumors will be enrolled and assigned to a single arm of ipatasertib plus atezolizumab plus paclitaxel. The sample size of 100 patients is determined on the basis of having a sufficient number of patients for efficacy signal seeking, as well as adding to current knowledge on the safety profile of this combination, and not delaying the enrollment of patients with TNBC for Cohorts A and C. There is no formal hypothesis testing planned for this cohort, and the endpoints listed in Section 2 (including PFS, ORR, DOR, 1-year and 2-year landmark PFS and OS) will be reported descriptively.

Potential China Extension

For the potential China extension phase, if at least 1 patient is enrolled into Cohorts A or B in mainland China, Hong Kong, or Taiwan during the global enrollment phase, additional patients may be enrolled at CFDA-recognized sites in an extended enrollment phase for up to a total of 90 Chinese patients with TNBC with *PIK3CA/AKT1/PTEN*-altered tumors and up to a total of 120 Chinese patients with HR+/HER2– breast cancer with *PIK3CA/AKT1/PTEN*-altered tumors; these patients will constitute an analysis population of a China subgroup. The sample size of this China subgroup is determined on the basis of showing consistency in the China subgroup for the primary endpoint and PFS with the global cohort (see Section 6.9).

6.2 SUMMARIES OF CONDUCT OF STUDY

Patient enrollment, study discontinuation, and discontinuation reasons will be summarized by treatment arm for the two cohorts. In addition, major protocol violations, including violations of inclusion and/or exclusion criteria, will be summarized by treatment arm for the two cohorts.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

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

Descriptive summaries of continuous data will present the group mean, standard deviation, median, minimum, and maximum. Descriptive summaries of discrete data will present the category counts as frequencies and percentages.

6.4 EFFICACY ANALYSES

All efficacy analyses will be based on the ITT population (i.e., all randomized patients in Cohorts A and B; all enrolled patients in Cohort C) according to the treatment arm to which patients are allocated. DOR analysis will include all patients with an objective response.

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

A sensitivity analysis of primary and key secondary efficacy objectives on the basis of blinded independent central review assessments will be performed using the same methodology as specified for investigator-assessed endpoints.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is investigator-assessed PFS, defined as the time from randomization (Cohorts A and B) or enrollment (Cohort C) to the first occurrence of disease progression, as determined by the investigator using RECIST v1.1 (see Appendix 10), or death from any cause, whichever occurs first. Data for patients who do not experience disease progression or death will be censored at the last date of evaluable tumor assessment. For patients who do not have an evaluable tumor assessment after randomization/enrollment, the data will be censored at the date of randomization plus 1 day.

For Cohort A and Cohort B, PFS 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. Sensitivity analyses will be conducted to compare PFS between the treatment arms in patients with *PIK3CA/AKT1/PTEN*-altered tumors as centrally determined by the FMI CTA.

For each treatment arm in each cohort, Kaplan-Meier methodology will be used to estimate the median PFS, and the Brookmeyer-Crowley method will be used to

construct the 95% CI for the median PFS (Brookmeyer and Crowley 1982). Kaplan-Meier curves will be produced as well.

6.4.2 Secondary Efficacy Endpoints

The secondary endpoints will be tested in Cohort A and Cohort B separately, and will be tested only if the primary analysis of respective PFS in the corresponding cohort reaches statistical significance at the level of 5%.

6.4.2.1 Objective Response Rate with Duration of Response

Objective response is defined as a complete response (CR) or partial response (PR) on two consecutive occasions ≥4 weeks apart, as determined by the investigator through the use of RECIST v1.1 (Appendix 10). Patients without a post-baseline tumor assessment will be considered as non-responders. ORR is defined as the proportion of patients who have an objective response. For each cohort, an estimate of ORR will be calculated for each treatment arm, and its 95% CI will be calculated using the Blyth-Still-Casella method. 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 described 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.

DOR is defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator through the use of RECIST v1.1, or death from any cause, whichever occurs first. The censoring method for DOR will be the same as that for PFS. For each cohort, 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.

6.4.2.2 Clinical Benefit Rate

Clinical benefit rate is defined as the proportion of patients who have an objective response (CR or PR), or stable disease for at least 24 weeks, as determined by the investigator through the use of RECIST v1.1. For each cohort, clinical benefit rate will be analyzed using methods similar to those used for ORR.

6.4.2.3 Overall Survival

OS is defined as the time from randomization (Cohorts A and B) or enrollment (Cohort C) to death from any cause. Data for patients who are not reported as having died at the time of analysis will be censored at the date when they were last known to be alive. Data for patients who do not have post-baseline information will be censored at the randomization (Cohorts A and B) or enrollment (Cohort C) date plus 1 day. For Cohort A and Cohort B, the analyses will be conducted using the stratified two-sided log-rank test, and the results from the unstratified log-rank test will also be provided. For each cohort,

the OS curve for each treatment arm will be estimated by the Kaplan-Meier methodology, and the survival rates at landmarks (e.g., 1-year and 2-year OS) will be provided when data allow. The hazard ratio for OS and its 95% CI will be estimated by the Cox proportional-hazards models.

For each cohort, sensitivity analyses will be conducted to compare OS between the treatment arms in patients with *PIK3CA/AKT1/PTEN*-altered tumors as centrally determined by the FMI CTA.

6.4.2.4 (Cohort C only) 1-Year PFS and 1-Year OS Rate

For Cohort C, 1-year PFS and 1-year OS rate will be estimated using the Kaplan-Meier method, and their 95% CIs will be provided using Greenwood's formula.

6.4.3 Exploratory Efficacy Endpoints

6.4.3.1 Progression-Free Survival 2 (PFS2)

PFS2 is defined as the time from randomization (or enrollment for Cohort C patients) to first objective disease progression on next-line treatment, or death from any cause, whichever occurs first. Specifically, next-line therapy is defined as the treatment received after the first disease progression. Patients who do not experience disease progression on next-line therapy or death will be censored at the last time known to be alive and without objective disease progression on next-line therapy. Observations from patients who do not have post-baseline information will be censored at the date of randomization plus 1 day. This analysis will be performed as data allows and will be described in the SAP.

6.4.3.2 Patient Subgroup Analysis in Cohort A

For Cohort A (TNBC), all primary and secondary efficacy endpoints will also be explored in two subgroups: patients with tumors that have *PIK3CA/AKT1*-activating mutations; and patients with tumors that have *PTEN*-alterations but no *PIK3CA/AKT1*-activating mutations.

6.4.4 Time to First Skeletal-Related Event

Time to first skeletal–related event (SRE) is defined as the time from randomization (Cohorts A and B) or enrollment (Cohort C) to the first occurrence of an SRE. An SRE is either a pathologic fracture, radiation therapy to bone, surgery to bone, or spinal cord compression. Patients for whom an SRE has not been observed should be censored at the last time known to be alive and without an SRE. This analysis will be performed as data allow and will be described in the SAP.

6.4.5 Patient-Reported Outcome Analyses

6.4.5.1 Secondary Patient-Reported Outcome Endpoints

To evaluate patient-reported HRQoL while on study treatment, descriptive analysis of the mean and mean change from patients' baseline GHS/HRQoL scale score, which consists of Questions 29 and 30 of the EORTC QLQ-C30; Appendix 7) will be assessed

by cycle and independently within each cohort. The GHS/HRQoL data will be scored and analyzed as described in Section 6.4.5.2 (Exploratory PRO Analyses). To evaluate time to deterioration of pain, changes in the pain scale (Questions 9 and 19) of the EORTC QLQ-C30 will be assessed. Time to deterioration is defined as the time from baseline to the first documentation of at least an 11-point increase on the pain scale from baseline. Patients who do not have an observed deterioration at the time of clinical data cut-off will be censored at the last non-missing assessment date. Patients without a post-baseline assessment will be censored at randomization (Cohort B).

An 11-point change is defined as a clinically meaningful difference (Cocks et al. 2012); additional sensitivity analyses using different thresholds, and definitions of change (e.g. confirmed or permanent changes in pain score) will also be conducted.

6.4.5.2 Exploratory Patient-Reported Outcome Analyses

Summary statistics (mean, SD, median, 25th and 75th percentiles, and range) of linear transformed scores will be reported for all scales (symptom, functional domains, and single items) of the EORTC QLQ-C30 questionnaire according to the EORTC scoring manual guidelines (Fayers et al. 2001) for each assessment timepoint. The mean change of the linear transformed scores from baseline (and 95% CI using the normal approximation) will also be reported independently for each cohort. Line charts depicting the mean changes (and 95% confidence intervals) of items and scales over time will be provided for each treatment arm from the baseline assessment. In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a prorated score will be computed consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed, the subscale will be considered as missing.

The EQ-5D-5L (Appendix 8) will be scored according to its manual, and results will be reported separately from the clinical study report.

PRO completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm for each measure in the ITT population. The questionnaire is considered completed if at least one question was completed. The compliance rate will be based on the total number of patients expected to complete the questionnaire at a particular timepoint.

6.5 SAFETY ANALYSES

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

Safety analyses will be conducted by treatment arms and include frequency, nature, and severity of treatment-emergent adverse events, including adverse events leading to death, serious adverse events, and adverse events of special interest. All deaths will be summarized. In addition, adverse events leading to study drug discontinuation and dose

modification will be summarized. Laboratory measurements outside of the normal range will be identified. Selected laboratory data will be summarized by treatment arm and grade compared with baseline. Relevant vital signs will be presented using summary statistics by treatment arm 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 v4.0. Multiple occurrences of the same event will be counted once at the maximum severity.

6.5.1 Exploratory Safety Analysis

For the PRO-CTCAE analysis (Appendix 9), for each treatment arm and dose, the number (percentage) of patients reporting symptoms by “frequency,” ”severity,” “interference,” and “presence” category will be reported at each assessment independently for each cohort. A summary table of the percentage of patients reporting severity of a symptom as “severe” or “very severe” over the course of the study by treatment arm will also be provided. Finally, a longitudinal analysis of change will be employed to understand how symptoms may have changed over the course of treatment.

PRO-CTCAE completion, compliance rates, and reasons for missing data will be summarized at each timepoint by treatment arm for each measure in the safety population. The questionnaire is considered completed if at least one question was completed. The compliance rate will be based on the total number of patients expected to complete the questionnaire at a particular timepoint.

6.6 PHARMACOKINETIC ANALYSES

Ipatasertib and G-037720 concentrations will be measured on Days 1 and 15 of Cycle 1, and on Day 15 of Cycle 3. Atezolizumab, ipatasertib, and G-037720 plasma concentration versus time data, together with information on dosing and patient characteristics, will be pooled and analyzed using a popPK analysis approach independently for each cohort. Plasma samples will also be used to characterize the immunogenicity of atezolizumab. Nonlinear mixed-effect modeling will be used for the estimation of popPK parameters for ipatasertib and G-037720. Covariates such as patient demographics (e.g., age, sex, body size), total protein, serum albumin, liver function tests (e.g., AST, ALT, alkaline phosphatase), and serum creatinine will be tested for significance on PK parameters of interest.

The PK data will be combined with the safety and efficacy (e.g., PFS) data for exposure–response modeling as data permit for each cohort. PK and PK/pharmacodynamic analyses may be reported in separate stand-alone reports. Additional analyses may be explored as warranted by the data.

6.7 BIOMARKER ANALYSES

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.

6.8 INTERIM ANALYSES

6.8.1 Planned Interim Safety Analyses

An external iDMC will be set up to evaluate safety data in Cohorts A and B on a periodic basis. All summaries/analyses by treatment arm for the iDMC's review will be prepared by an external iDCC. 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.

The iDMC will convene a review of summaries of the safety data by cohort and by treatment arm after approximately 50 patients (in total from both cohorts) have competed 1 treatment cycle and approximately every 6 months thereafter until the time of the analysis of the primary efficacy endpoint for both cohorts are complete. In the absence of extenuating circumstances, accrual will not be halted while the 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. In addition, the Sponsor may request ad hoc meetings of the iDMC at any time during the study to review ongoing safety summary data.

6.8.2 Safety monitoring will be performed on a continual basis by the Sponsor for Cohort C. Planned Interim OS Analysis at PFS Primary Analysis

For Cohort A, interim OS will be analyzed at the time of the primary analysis for PFS, and final OS will be analyzed at the time that approximately 188 OS events occur or around 36 months after the last patient has been enrolled, whichever is earlier. The Lan-DeMets α-spending function with an O'Brien-Fleming boundary will be used to control the type I error accounting for OS interim and final analyses. With a sample size of 249 patients in Cohort A, it is estimated that there will be approximately 75 OS events at the time of PFS primary analysis, and approximately 188 OS events at the final OS analysis, with corresponding p-value boundaries of (0.000774, 0.049737). The corresponding hazard ratio boundaries are 0.44 and 0.74 at interim and final analysis, respectively. The actual alpha-spending will be adjusted and determined based on the actual information fraction at the interim analysis.

For Cohort B, interim OS will be analyzed at the time of the primary analysis for PFS, and final OS will be at the time that approximately 148 OS events occur or around 5 years after the last patient has been enrolled, whichever is earlier. The Lan-DeMets α spending function with an O'Brien-Fleming boundary will be used to control the type I error accounting for OS interim and final analyses. For Cohort B, it is estimated that there will be approximately 81 OS events at the time of PFS primary analysis, and approximately 148 OS events at the final OS analysis, with corresponding p-value boundaries of (0.00489, 0.04842). The corresponding hazard ratio boundaries are 0.52 and 0.71 at interim and final analysis, respectively. The actual alpha-spending will be adjusted and determined based on the actual information fraction at the interim analysis.

Further details can be found in the SAP.

6.8.3 Optional Interim Analyses

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct an optional interim efficacy analysis, prior to the time of the primary analysis for PFS, with each cohort considered independently. For example, availability of clinical trial results for a specific external competitor molecule during the course of this study might (depending on the data) trigger an interim analysis, or the existence of an internal competitor molecule might necessitate an interim analysis to enable decision-making regarding continued development of the two molecules. Below are the specifications in place to ensure the study continues to meet the highest standards of integrity when an optional interim analysis is executed.

The interim analysis will be conducted by an iDCC and reviewed by the iDMC. Interactions between the iDMC and Sponsor will be carried out as specified in the iDMC Charter.

The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis, will be documented in the SAP, and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis. The iDMC Charter will be updated to document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., stop the study for positive efficacy, stop the study for futility), and the iDMC Charter will also be made available to relevant health authorities.

If there is a potential for the study to be stopped for positive efficacy as a result of the interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained. Specifically, the Lan-DeMets α-spending function that approximates the O'Brien-Fleming boundary will be applied the primary endpoint of PFS to determine the critical value for stopping for positive efficacy at the interim analysis (DeMets and Lan 1994). Additional criteria for recommending that the study be stopped for positive efficacy may be added to the iDMC Charter. If the study continues beyond the interim

analysis, the critical value at the final analysis would be adjusted accordingly to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology.

After the primary analysis for PFS, additional OS interim analyses may be conducted to provide additional OS data, per the recommendation from health authorities. If conducted, the Lan-DeMets α-spending function with an O'Brien-Fleming boundary will be used to control the overall type I error for OS accounting for the additional OS interim analyses.

6.9 CHINA SUBGROUP ANALYSES

After enrollment for the global study is completed, additional Chinese patients may continue to be recruited into the China extension cohorts. A total of up to 90 Chinese patients with TNBC with *PIK3CA/AKT1/PTEN*-altered tumors and up to 120 Chinese patients with HR+/HER2− breast cancer with *PIK3CA/AKT1/PTEN*-altered tumors from China (mainland China, Hong Kong or Taiwan) may be enrolled, including Chinese patients enrolled within the global study population and the China extension phase, combined. The objective of the China subgroup analyses is to assess the efficacy and safety of ipatasertib + paclitaxel versus placebo + paclitaxel in a patient population from China, including those enrolled originally during the global phase and the China extension phase.

The analysis of PFS among Chinese patients with TNBC will be performed when approximately 50 PFS events have occurred in patients with TNBC from the China subgroup. A total of 50 PFS events in the China subgroup will provide approximately 91% probability of observing at least 50% of the risk reduction in PFS expected to be observed in the global population, assuming that the true PFS hazard ratio in the China subgroup is the same as the target PFS hazard ratio in the global population. The analysis of PFS among Chinese patients with HR+/HER2- breast cancer will be performed when approximately 65 PFS events have occurred in patients with HR+/HER2- breast cancer from the China subgroup. A total of 65 PFS events in the China subgroup will provide approximately 89% probability of observing at least 50% of the risk reduction in PFS expected to be observed in the global population, assuming that the true PFS hazard ratio in the China subgroup is the same as the target PFS hazard ratio in the global population.

Data from patients in the China extension phase will not be included in the analyses of the global phase of the study; instead, data will be combined with data from Chinese patients in the global phase of the study and summarized as the China subgroup analysis in a separate report.

Details regarding PK analysis for the potential China extension phase will also be described in the SAP.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

The Sponsor will produce an EDC Study Specification document that describes the quality 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. The data from the questionnaires 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 on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, 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 IMPs, including eCRFs, electronic or paper PRO data (if applicable), 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 Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the 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 a Child's Informed Assent Form, biomarker-specific consent 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.

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

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

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (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 9.6).

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

8.4 CONFIDENTIALITY

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

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

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

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. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures,

prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

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

Approximately 120–150 sites globally will participate to enroll approximately 450 patients during the global enrollment phase. Enrollment will occur through an IxRS.

After global enrollment is completed (i.e., after approximately 450 patients), as needed, up to 210 Chinese patients may be enrolled in total (between Cohorts A and B; combining Chinese patients enrolled in the global enrollment phase and those enrolled in the China extension phase).

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. 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 (Cohorts A and B) throughout the study. Tumor response and progression will be evaluated by an independent review committee as needed. Membership and procedures for each of these committees will be detailed in a charter.

9.5 PUBLICATION 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. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical 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.

9.6 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Activities: Cohorts A and B

	Screening [a]		Treatment Cycles (28-Day Cycles) [b]															SDDV [c]	Post-Treat. Follow-Up
			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycles ≥ 5				
	Biomarker -Specific Screening	Safety Eligibility or Baseline	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15		
Signed informed consent(s) [d]	x																		
Demographics, medical history, prior cancer treatment	x																		
Tumor tissue sample submission	x [e]																		
Confirmation of biomarker eligibility (local or central testing)	x [ii]																		
Blood sample for biomarkers [f]	x [f]		x [f]						x [f]									x [f]	
Viral serology [g]		x																	
Blood sample for WGS [h]			x																
Complete physical examination		x																x	

Appendix 1
Schedule of Activities: Cohorts A and B (cont.)

	Screening [a]		Treatment Cycles (28-Day Cycles) [b]																
			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycles ≥ 5				
	Biomarker -Specific Screening	Safety Eligibility or Baseline	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	SDDV [c]	Post-Treat. Follow-Up
Limited physical examination			x	x	x	x	x	x	x		x	x		x	x				
Weight		x	x			x			x			x			x				
Height		x																	
Vital signs [i]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
ECOG Performance Status		x	x			x			x			x			x			x	
ECHO or MUGA scan		x [j]																	
12-Lead electrocardiogram [k]		x																x	
Hematology [l]		x	x [m]	x [m]	x [m]	x [m]	x [m]	x [m]	x [m]		x [m]	x [m]		x [m]	x [m]			x	
INR and PTT (or aPTT)		x																x	
Fasting serum chemistry [n]		x	x [m]	x [m]	x [m]	x [m]	x [m]	x [m]	x [m]		x [m]	x [m]		x [m]	x [m]			x	
Fasting lipid profile, amylase, lipase		x							x [o]						x [o]			x	
HbA_{1C}		x							x [o]						x [o]			x	
Urinalysis		x	As clinically indicated															x	
Pregnancy test [p]		x	x [p]			x			x			x			x			x	
Tumor assessments [q]		x	*Per standard of care* [r]															x [s]	x [t]
Bone scan		x [u]	Every 16 weeks based on starting date of C1D1															x [u]	x [t]

Appendix 1
Schedule of Activities: Cohorts A and B (cont.)

	Screening [a]		Treatment Cycles (28-Day Cycles) [b]																
			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycles ≥ 5				
	Biomarker -Specific Screening	Safety Eligibility or Baseline	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	SDDV [c]	Post-Treat. Follow-Up
Head scan (CT or MRI scan)		x [v]																	
Prophylaxis anti-diarrheal (2 mg BID loperamide or equivalent) [w]			If side effects are not tolerated, doses may be reduced. After 1 cycle without any diarrhea, continuation is at physician's discretion. If diarrhea occurs, it should be managed per guidelines in Appendix 13; anti-diarrheal treatment should also be resumed with loperamide prophylaxis as needed.																
Ipatasertib/placebo dispension/ accountability			x [x]			x			x			x			x				
Paclitaxel administration [y]			x [x]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Record cancer-related radiotherapy and surgical procedures [z]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications [aa]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events [bb, z]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [cc]	x [cc]
EORTC QLQ-C30 [dd]			x			x			x			x			x			x	x [ee]
PRO-CTCAE [dd]			x			x			x			x			x			x	
EQ-5D-5L [dd]			x			x			x			x			x			x	x [ee]
PK samples [ff]			x		x						x								
Survival and anti-cancer therapy follow-up [z]																			x [gg]

Appendix 1
Schedule of Activities: Cohorts A and B (cont.)

	Screening [a]		Treatment Cycles (28-Day Cycles) [b]																
			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycles ≥ 5				
	Biomarker -Specific Screening	Safety Eligibility or Baseline	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15	SDDV [c]	Post-Treat. Follow-Up
Tumor tissue sample obtained at time of progression (optional) [hh]																		x [hh]	
Patient diary (medication, dosing log, Kit ID)			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

BID = twice a day; CT = computed tomography; ctDNA = circulating tumor DNA; D = day; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for the Research and Treatment of Cancer; FNA = fine-needle aspiration; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; MUGA = multiple-gated acquisition; MRI = magnetic resonance imaging; NGS = next-generation sequencing; PK = pharmacokinetic; PRO = patient-reported outcome; PRO-CTCAE = Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QD = once a day; RECIST = Response Evaluation Criteria in Solid Tumors; SDDV = study drug discontinuation visit; TNBC = triple-negative breast cancer; Treat. = treatment; WGS = whole genome sequencing.

Notes: Results of standard-of-care tests or examinations performed prior to obtaining informed consent but within the screening safety eligibility/ baseline window specified for each assessment. Screening assessments are to be performed after informed consent and generally within 28 days preceding Day 1 of Cycle 1 unless otherwise noted. The safety eligibility/baseline window does not apply to the biomarker-specific screening process (i.e., submission of tissue/blood sample for biomarker testing). In addition, patients must have adequate hematologic and organ function within 14 days and have a negative pregnancy test (if applicable) prior to the first study treatment on Day 1 of Cycle 1, as defined in Section 4.1.1. All assessments or procedures are to be performed predose unless otherwise specified.

[a] Screening window per individual assessment guidelines detailed, generally within 28 days of Day 1 of Cycle 1 for time-dependent screening safety eligibility/baseline assessments.

[b] 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 or window. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays; however, study cycle day count continues without breaks; i.e., every cycle contains exactly 28 days.

[c] The study drug discontinuation visit should occur approximately 28 days after the last administration of ipatasertib/placebo or paclitaxel, whichever is discontinued last, or prior to initiation of another therapeutic regimen.

Appendix 1
Schedule of Activities: Cohorts A and B (cont.)

[d] Patients may be consented for the biomarker-specific process (if enrolling on the basis of central tissue or blood-based FMI testing) using the biomarker-specific ICF, followed by (if an alteration is present) full study consent and remaining screening procedures prior to enrollment in the study; or, patients may consent using the full study ICF prior to screening and enrollment. Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

[e] Archival tissue (either formalin-fixed paraffin-embedded tumor specimens or a minimum of 20 unstained serial paraffin slides) and an associated pathology report must be confirmed to be available prior to entry into the study. This requirement is required for all patients except those enrolled on the basis of *PIK3CA/AKT1/PTEN* alteration results available from the FMI commercial tissue-based NGS assay known as FoundationONE CDx™, when a formalin fixed, paraffin embedded tumor (FFPE) tissue block or 10 freshly cut unstained, serial tumor slides from the most recently collected tumor tissue is acceptable for other protocol-mandated secondary and exploratory assessments, upon approval by the Medical Monitor. 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 for NGS testing are required. If *PIK3CA/AKT1/PTEN*-altered status has been determined for a patient during study screening procedures, a repeat biomarker-specific screening is not required.

[f] Blood will be collected for ctDNA analysis at screening (either as part of the biomarker-specific screening process or full screening), at the time of the first tumor assessment (±7 days), and at the study drug discontinuation visit. For patients who send a blood sample for FACT assay to determine biomarker eligibility, the initial screening blood sample may be used for this purpose, but an additional blood sample taken on Day 1 of Cycle 1 will be required for exploratory biomarker assessment.

[g] HIV, HBsAg, total hepatitis B core antibody (HBcAb), HCV antibody; additional tests for HBV DNA or HCVRNA will be required to confirm eligibility.

[h] Samples will be collected only at sites with local regulatory authority approval. Sample collection may occur at the same time as other blood sampling if preferred (i.e., within 48 hours prior to dosing at the same time as laboratory samples or postdose at the same time as the PK sample).

[i] Includes pulse rate, respiratory rate, systolic and diastolic blood pressure while patient is in a seated position after resting for 5 minutes, and temperature (oral, axillary, or tympanic). On paclitaxel dosing days, vital signs should be recorded prior to dosing and at the end of the infusion. From Cycle 5 onward, if paclitaxel treatment has been discontinued, the patient is not required to return to the clinic for Days 8 and 15 vital sign assessments. A telephone call for adverse events and concomitant medication assessment may be performed as clinically indicated.

[j] Performed within 12 weeks prior to Day 1 of Cycle 1. Under exceptional circumstances cardiac function assessment by methods other than echocardiogram (ECHO) or multiple-gated acquisition (MUGA) may be acceptable, if this is consistent with local standard practice (e.g., cardiac MRI), but must be approved by the Medical Monitor.

[k] A single 12-lead ECG measurement at screening and at SDDV visit, and as clinically indicated (refer to Section 4.5.7).

[l] Includes WBC count, WBC differential count (including absolute neutrophil counts, lymphocytes), hemoglobin, hematocrit, and platelet count.

[m] Laboratory samples should be drawn within 48 hours prior to study drug administration at the clinic; results should be available to assess dosing; with at least 8-hour fasting for glucose measurement as indicated (refer to Section 4.5.6). Glucose logs for any home glucose monitoring performed should also be reviewed at clinic visits prior to dosing, and only values which result in intervention recorded within the eCRF.

Appendix 1
Schedule of Activities: Cohorts A and B (cont.)

[n] Includes sodium, potassium, bicarbonate, glucose (fasting), BUN/urea, creatinine, calcium, phosphorus, magnesium, total bilirubin, albumin, LDH, ALT, AST, and ALP. For investigational sites in countries where bicarbonate may not be collected as part of the standard chemistry panel, bicarbonate will not be measured. For investigational sites where local practice includes measuring only fasting plasma glucose levels, these local assessments may be acceptable to confirm eligibility and should be provided consistently across the study for intra-patient comparability. Grade ≥3 non-hematologic toxicity should be monitored at least weekly.

[o] Fasting lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides), amylase, lipase, and HbA1c will be assessed at screening, every 3 cycles starting on Day 1 of Cycle 3, and at SDDV visit.

[p] For women of childbearing potential. A serum pregnancy test is to be performed at screening. A negative serum pregnancy test must be obtained either within 96 hours prior to C1D1 study treatment administration, or within 7 days of C1D1 (in this case, confirmed by a negative urine pregnancy test prior to C1D1 dosing). In addition, pregnancy tests (serum or urine) are to be performed within 96 hours of Day 1 of each following treatment cycle prior to dosing, 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. For all other women, documentation must be present in medical history confirming that patient is not of childbearing potential.

[q] 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. As of Protocol CO40016, Version 10 (Cohort C), images for tumor assessments will no longer be collected for blinded independent central review.

[r] *As of Protocol CO40016 Version 11 (Cohort C),* tumor assessments (TAs) should be calculated from C1D1 (study Day 1) and completed *per standard of care*. 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. As of Protocol CO40016, Version 10 (Cohort C), images for tumor assessments will no longer be collected for blinded independent central review.

[s] At SDDV visit, tumor assessments should be performed only if not performed within the previous 6 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 to assess disease response approximately every 8–12 weeks until documented progressive disease per RECIST v1.1 *(as of Protocol CO40016 Version 11 [Cohort C] this is no longer required).* Images for tumor assessments will be collected to enable retrospective blinded independent central review when needed. As of Protocol CO40016, Version 10 (Cohort C), images for tumor assessments will no longer be collected for blinded independent central review.

[t] If a patient discontinues from the study for any reason other than disease progression per RECIST v1.1, a disease follow-up clinical visit approximately every 8–12 weeks will be required for tumor assessments until documented progressive disease per RECIST v1.1 *(as of Protocol CO40016 Version 11 [Cohort C] this is no longer required).* Images for tumor assessments will be collected prospectively to enable retrospective blinded independent central review when needed. As of Protocol CO40016, Version 10 (Cohort C), images for tumor assessments will no longer be collected for blinded independent central review.

Appendix 1
Schedule of Activities: Cohorts A and B (cont.)

[u] 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 by CT scan, MRI or X-ray to ascertain the presence of bone destruction versus a healing reaction. For patients with known or suspected bone metastasis, bone scans should be performed with every other tumor assessment starting from Week 16, adhering to the same 7-day window. If these patients discontinue from the study treatment for any reason other than disease progression, they should continue to be followed as clinically indicated, or for approximately every 4 months at "disease follow-up" until documented progressive disease per RECIST v1.1. *As of Protocol CO40016 Version 11 (Cohort C), this long-term follow-up assessment is no longer required.* If it is not possible to acquire a technetium bone scan, NaF-PET scans may be considered an alternative, with approval from the Medical Monitor.

[v] Performed within 6 weeks prior to Day 1 of Cycle 1. Mandatory for Cohort A (TNBC), and as clinically indicated for Cohort B (HR+/HER2−).

[w] Administer prophylactic loperamide dose of 2 mg BID or 4 mg QD, if allowed by local guidance. Refer to Appendix 13 for further diarrhea management guidance.

[x] Patients should receive their first dose of study drug on the day of randomization, if possible. If this is not possible, the first dose should occur no later than 3 days after randomization. For patients in Cohort A *and Cohort B*, who are unblinded and in the placebo + paclitaxel arm, placebo no longer needs to be dispensed and therefore accounted for.

[y] If the patient's weight changes by > 10% from baseline during the study, the body surface area and drug doses of paclitaxel should be recalculated.

[z] A skeletal-related event (SRE) is defined as either a pathologic fracture, radiation therapy to the bone, surgery to the bone, or spinal cord compression. Any cancer-related radiation or surgery to the bone (on–study treatment and during post-treatment follow-up), or adverse events with diagnosis of pathologic fracture or spinal cord compression, should be assessed according to the SRE criteria and reported with this assessment on the relevant eCRF page.

[aa] At screening and Day 1 of Cycle 1, record all concomitant medications taken between 14 days prior to screening and Day 1 of Cycle 1; at subsequent time points, record new concomitant medications and any changes to the daily dosing. Actual intake of anti-diarrheal, pain medication, or pre-medications at each dosage change should be recorded.

[bb] 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 28 days after the last dose of study treatment. After this period, investigators should report any serious adverse events 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.

[cc] 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 28 days after the last dose of study drug). An additional adverse event follow-up visit may be scheduled (even after the SDDV); follow-up by telephone for adverse event resolution date as applicable.

[dd] 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 on Day 1 of each cycle and at the SDDV visit. PRO-CTCAE questionnaires will be completed when available in the local language of the investigational site.

Appendix 1
Schedule of Activities: Cohorts A and B (cont.)

[ee] The global health status/HRQoL (which consists of Questions 29 and 30), pain (Questions 9 and 19), fatigue (Questions 10, 12 and 18) and dyspnea (Question 8) from the EORTC QLQ-C30 and the EQ-5D-5L will be administered during post-treatment follow-up calls (or visits). 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 via 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. *As of Protocol CO40016 Version 11 (Cohort C), these long-term follow-up assessments are no longer required.*

[ff] See Appendix 3 for schedule of PK assessments.

[gg] Information about survival, subsequent anti-cancer therapies and associated response, progression date, and most recent tumor assessment date will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (± 1 month) until death, loss to follow up, or study termination by the Sponsor, unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. *As of Protocol CO40016 Version 11 (Cohort C), these long-term follow-up assessments are no longer required.*

[hh] Tumor biopsy collection is optional for study participation. For patients who sign an Optional Research Biosample Repository Informed Consent Form 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.

[ii] Biomarker eligibility (i.e., presence of *PIK3CA/AKT1/PTEN* alteration) may be determined using central testing at FMI (from tumor tissue sample provided [CTA] or blood samples provided for ctDNA analysis [FACT assay]) or local/commercial testing using an appropriately validated molecular-based assay at an accredited diagnostic laboratory (CLIA accredited or equivalent). If local/commercial assessment of *PIK3CA/AKT1/PTEN* alteration status or central ctDNA is used to confirm biomarker eligibility, tumor tissue is still required to confirm alteration status centrally, with the exception of the commercial FoundationONE CDx™ assay, which would allow for a reduced tissue requirement (see Section 4.1.1), randomization should proceed based on the local result with no requirement to wait for central confirmation of biomarker eligibility. For all local/commercial molecular testing results used to determine biomarker eligibility a full laboratory report must be available and captured within the patient's source documents to support enrollment, key details of the test and result used to confirm biomarker eligibility should be entered into the eCRF.

Appendix 2
Schedule of Activities: Cohort C

	Screening (Day –28 to Day –1)		Treatment Cycles (28-Day Cycles) [a]												SDDV [b]	Post-Treat. Follow-Up
			Cycles 1 and 2			Cycle 3			Cycle 4			Cycles ≥ 5				
			D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15		
	Biomarker -Specific Screening	Safety Eligibility or Baseline														
Signed informed consent(s) [c]	x															
Viral serology [d]		x														
Demographics, medical history, prior cancer treatment		x														
Tumor tissue sample submission at screening	x [e]															
Blood sample for WGS [f]			x													
Blood sample for biomarkers			x	x [ii]												
Complete physical examination [g]		x													x	
Limited physical examination			x	x	x	x		x	x		x	x			x	
Weight		x	x			x			x			x			x	
Height		x														
Vital signs [h]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
ECOG Performance Status		x	x			x			x			x			x	
ECHO or MUGA scan		x [i]														
12-Lead ECG [j]		x													x	
Hematology [k]		x	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x	
INR and PTT (or aPTT)		x													x	
Fasting serum chemistry [m]		x	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x	

Appendix 2
Schedule of Activities: Cohort C (cont.)

	Screening (Day –28 to Day –1)		Treatment Cycles (28-Day Cycles) [a]												SDDV [b]	Post-Treat. Follow-Up
			Cycles 1 and 2			Cycle 3			Cycle 4			Cycles ≥ 5				
			D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15		
TSH, free T3 (or total T3), free T4 [n]		x	x						x			x [n]			x	
Fasting lipid profile, amylase, lipase		x				x [o]						x[o]			x	
HbA_{1C} [o]		x	x			x			x			x			x	
Urinalysis		x	As clinically indicated												x	
Pregnancy test [p]		x	x [p]			x			x			x			x	
Tumor assessments [q]		x				x [r]						x [r]			x [s]	x[s]
Bone scan		x [t]	See footnote "t"												x [t]	x [t]
Head scan (CT or MRI scan)		x [u]														
Prophylaxis with 10 mg prednisone (or equivalent) for 2–4 consecutive days [hh]			x		x											
Daily antihistamine prophylaxis [hh]			x	x	x											
Prophylaxis anti-diarrheal (2 mg BID loperamide 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)			If side effects are not tolerated, doses may be reduced. After 1 cycle without any diarrhea, continuation is at physician's discretion. If diarrhea occurs, it should be managed per guidelines in Appendix 14; anti-diarrheal treatment should also be resumed with loperamide prophylaxis as needed.													
Ipatasertib dispension/accountability			x [v]			x			x			x				
Atezolizumab administration			x [v]		x	x		x	x		x	x		x		
Paclitaxel administration [w]			x [v]	x	x	x	x	x	x	x	x	x	x	x		

Appendix 2
Schedule of Activities: Cohort C (cont.)

	Screening (Day −28 to Day −1)		Treatment Cycles (28-Day Cycles) [a]												SDDV [b]	Post-Treat. Follow-Up
			Cycles 1 and 2			Cycle 3			Cycle 4			Cycles ≥5				
			D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15		
Record cancer-related medications and surgical procedures		x													x	x
Concomitant medications [x]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events [y]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [z]	x [z]
EORTC QLQ-C30 [dd, ee]			x			x			x			x			x	x [ee]
PRO-CTCAE [dd]			x			x			x			x			x	
EQ-5D-5L [dd, ee]			x			x			x			x			x	x [ee]
PK and ADA samples [aa]			x		x [bb]	x		x	x			x [ff]			x [cc]	
Tumor tissue sample obtained at time of progression (optional) [gg]															x [gg]	
Patient diary (medication, dosing log, Kit ID)			x	x	x	x	x	x	x	x	x	x	x	x	x	

ADA = anti-drug antibody; BID = twice a day; CT = computed tomography; D = day; Discon. = discontinuation; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FNA = fine-needle aspiration; HbA_{1C} = glycosylated hemoglobin; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; NGS = next-generation sequencing; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; T3 = triiodothyronine; T4 = thyroxine; Treat. = treatment; 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. 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. Study assessments may be delayed or moved ahead of the window to accommodate holidays, vacations, and unforeseen delays; however, study cycle day count continues without breaks.

[b] The study drug discontinuation visit should occur approximately 30 days after the last administration of ipatasertib, atezolizumab, paclitaxel, whichever is discontinued last, or prior to initiation of another therapeutic regimen.

Appendix 2
Schedule of Activities: Cohort C (cont.)

[c] The Informed Consent Form for Cohort C may be signed only when a patient who initially screens for Cohort A (with TNBC) does not qualify for Cohort A (i.e., lack of *PIK3CA/AKT1/PTEN* alteration validated by central tumor tissue testing using the Foundation Medicine Clinical Trial Algorithm).

[d] HIV, HBsAg, total HBcAb, HCV antibody. 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 20 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 for NGS testing are required.

[f] Samples will be collected on Day 1 of Cycle 1 only and only at sites with local regulatory authority approval.

[g] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[h] Includes pulse rate, respiratory rate, systolic and diastolic blood pressure while patient is in a seated position after resting for 5 minutes, and temperature (oral, axillary, or tympanic). On paclitaxel dosing days, vital signs should be recorded prior to dosing and at the end of the infusion. On days when atezolizumab and paclitaxel are both administered vital sign should also be recorded prior to atezolizumab dosing (and during infusion if clinically indicated). From Cycle 5 onward, if paclitaxel treatment has been discontinued, the patient is not required to return to the clinic for Day 8 and Day 15 vital sign assessments. However, if atezolizumab administration continues on these days then patient continue to have vital signs monitored when they present for atezolizumab infusions. A telephone call for adverse events and concomitant medication assessment may be performed as clinically indicated.

[i] Performed within 12 weeks prior to Day 1 of Cycle 1. If the left ventricular ejection fraction (LVEF) 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), if this is consistent with local standard practice.

[j] A single 12-lead ECG measurement at screening and at the treatment discontinuation visit, and as clinically indicated (refer to Section 4.5.7).

[k] Includes WBC count, WBC differential count (including ANCs, lymphocytes), hemoglobin, hematocrit, and platelet count. Hematology assessments to be conducted per local guidelines prior to each chemotherapy dosing.

[l] Laboratory samples should be drawn within 48 hours prior to study drug administration at the clinic; results should be available to assess dosing; with at least 8-hour fasting for glucose measurement as indicated.

[m] Includes sodium, potassium, bicarbonate, glucose (fasting), BUN/urea, creatinine, calcium, phosphorus, magnesium, total bilirubin, albumin, LDH, ALT, AST, and ALP. For investigational sites in countries where bicarbonate may not be collected as part of the standard chemistry panel, bicarbonate will not be measured. Grade ≥3 non-hematologic toxicity should be monitored at least weekly. Chemistry evaluation to be conducted per local guidelines.

[n] 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.).

Appendix 2
Schedule of Activities: Cohort C (cont.)

[o] Fasting lipid profile, amylase, and lipase will be assessed at screening, every 3 cycles starting on Day 1 of Cycle 3, and at treatment discontinuation visit. HbA_{1C} will be assessed at the beginning of each cycle, with the exception of Cycle 1 (the screening value may be used in place of Cycle 1 testing).

[p] For women of childbearing potential. A serum pregnancy test is to be performed at screening and within 96 hours of Day 1, Cycle 1. In addition, pregnancy tests (serum or urine) are to be performed within 48 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. For all other women, documentation must be present in medical history confirming that patient is not of childbearing potential.

[q] 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 collected to enable retrospective independent central review when needed. As of Protocol CO40016, Version 10 (Cohort C), images for tumor assessments will no longer be collected for blinded independent central review.

[r] *As of Protocol CO40016 Version 11 (Cohort C),* tumor assessments (TAs) should be calculated from C1D1 (study Day 1) and completed *per standard of care*. 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. As of Protocol CO40016, Version 10 (Cohort C), images for tumor assessments will no longer be collected for blinded independent central review.

[s] At treatment discontinuation visit, tumor assessments should be performed only if not performed within the previous 6 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 to assess disease response approximately every 8–12 weeks until documented progressive disease per RECIST v1.1, elective withdrawal from the study, or study completion or termination *(as of Protocol CO40016 Version 11 [Cohort C] this is no longer required)*. Images for tumor assessments will be collected to enable retrospective blinded independent central review when needed. As of Protocol CO40016, Version 10 (Cohort C), images for tumor assessments will no longer be collected for blinded independent central review.

[t] 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 by CT scan, MRI 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 it is not possible to acquire a technetium bone scan, NaF-PET scans may be considered an alternative, with approval from the Medical Monitor. If a patient discontinues from the study for any reason other than disease progression per RECIST v1.1, patients with bone metastases should continue to have bone scans during the follow-up phase, approximately every 16 weeks. *As of Protocol CO40016 Version 11 (Cohort C), these long-term follow-up assessments are no longer required.*

[u] Performed within 6 weeks prior to Day 1 of Cycle 1.

[v] 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 to days in which the patient will receive both atezolizumab and paclitaxel.

Appendix 2
Schedule of Activities: Cohort C (cont.)

[w] If the patient's weight changes by > 10% from baseline during the study, the body surface area and drug doses of paclitaxel should be recalculated.

[x] At screening and 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 anti-diarrheal, pain medication, or premedications at each dosage change should be recorded.

[y] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. 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 until 90 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. 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.

[z] 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 last dose of study drug for all adverse events, and 90 days for serious adverse events and adverse events of special interest). 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.

[aa] See Appendix 4 for a schedule of PK assessments.

[bb] This sampling of PK and ADA does not need to be conducted on Cycle 2, Day 15.

[cc] Discontinuation sample of PK and ADA must be within 30 days of the last dose.

[dd] 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 on Day 1 of each cycle and at the SDDV visit. PRO-CTCAE questionnaires will be completed when available in the local language of the investigational site.

[ee] The global health status/HRQoL (which consists of Questions 29 and 30), pain (Questions 9 and 19), fatigue (Questions 10, 12, and 18) and dyspnea (Question 8) from the EORTC QLQ-C30 and the EQ-5D-5L will be administered during post-treatment follow-up calls (or visits). 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 via 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. *As of Protocol CO40016 Version 11 (Cohort C), these long-term follow-up assessments are no longer required.*

[ff] For Cycles 8, 12, and 16.

[gg] Tumor biopsy collection is optional for study participation. For patients who sign an Optional Research Biosample Repository Informed Consent Form 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 Activities: Cohort C (cont.)

[hh] First cycle (or first 28 days of triplet combination dosing) only: On days when patients will receive atezolizumab (typically 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 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. 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 pre-medications already includes an antihistamine.

[ii] Applicable to Cycle 1 only.

Appendix 3
Schedule of Pharmacokinetic and Immunogenicity Samples: Cohorts A and B

Visit	Timepoint	Sample Type
Cycle 1, Day 1	1–3 hours post-ipatasertib/placebo	Plasma sample for ipatasertib/placebo and G-037720
Cycle 1, Day 15 [a]	Predose [b]	Plasma sample for ipatasertib/placebo and G-037720
Cycle 1, Day 15 [a]	1–3 hours post-ipatasertib/placebo	Plasma sample for ipatasertib/placebo and G-037720
Cycle 3, Day 15 [a]	Predose [b]	Plasma sample for ipatasertib/placebo and G-037720
Cycle 3, Day 15 [a]	2–4 hours post-ipatasertib/placebo	Plasma sample for ipatasertib/placebo and G-037720

PK = pharmacokinetic.

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 post drug administration should also be recorded for the day of PK sampling.

PK sampling timepoint should be accurately reported.

[a] Other than the Cycle 1, Day 1 visit, if 3 or more consecutive doses of ipatasertib/placebo were 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 done any day after Day 12 of the relevant cycle corresponding with a planned ipatasertib/placebo dosing day.

[b] Predose = 0 to 3 hours prior to dosing with ipatasertib/placebo on the day of the visit.

Appendix 4
Schedule of Pharmacokinetic and Immunogenicity, Samples: Cohort C

Visit	Time	Sample
Day 1 of Cycle 1	Prior to start of first atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
	30 (±10) minutes after end of atezolizumab infusion	• Atezolizumab PK (serum)
	1–3 hours post-ipatasertib/placebo	• Plasma sample for ipatasertib and G-037720
Day 15 of Cycle 1	Prior to start of atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
	Prior to ipatasertib dose	• Plasma sample for ipatasertib and G-037720
	1–3 hours after ipatasertib dose	• Plasma sample for ipatasertib and G-037720
Day 1 of Cycle 2	Prior to start of atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 3	Prior to start of atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 15 of Cycle 3	Prior to ipatasertib dose	• Plasma sample for ipatasertib and G-037720
	2–4 hours after ipatasertib	• Plasma sample for ipatasertib and G-037720
Day 1 of Cycle 4	Prior to start of atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 8	Prior to start of atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycles 12 and 16	Prior to start of atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)

ADA = anti-drug antibody; PK = pharmacokinetic.

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 post ipatasertib administration should also be recorded for the day of PK sampling. PK sampling timepoint should be accurately reported. Other than the Cycle 1, Day 1 visit, if 3 or more consecutive doses of ipatasertib/placebo were 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 done any day after Day 12 of the relevant cycle corresponding with a planned ipatasertib/placebo dosing day. Prior to start of atezolizumab and ipatasertib dose = 0 to 3 hours prior to dosing of the drug(s) on the day of the visit.

Appendix 5
ASCO/CAP Estrogen Receptor and Progesterone Receptor Guideline Recommendations

COLLEGE of AMERICAN PATHOLOGISTS

ASCO GUIDELINES

Summary of ASCO/CAP ER and PgR Guideline Recommendations

Optimal algorithm for ER/PgR testing

Recommendation:

Positive for ER or PgR if finding of ≥ 1% of tumor cell nuclei are immunoreactive.

Negative for ER or PgR if finding of < 1% of tumor cell nuclei are immunoreactive in the presence of evidence that the sample can express ER or PgR (positive intrinsic controls are seen).

Uninterpretable for ER or PgR if finding that no tumor nuclei are immunoreactive and that internal epithelial elements present in the sample or separately submitted from the same sample lack any nuclear staining.

Comments:

These definitions depend on laboratory documentation of the following:

1. Proof of initial validation in which positive ER or PgR categories are 90% concordant and negative ER or PgR categories are 95% concordant with a clinically validated ER or PgR assay.
2. Ongoing internal QA procedures, including use of external controls of variable ER and PgR activity with each run of assay, regular assay reassessment, and competency assessment of technicians and pathologists.
3. Participation in external proficiency testing according to the proficiency testing program guidelines.
4. Biennial accreditation by valid accrediting agency.

Optimal testing conditions

Recommendation:

Large, preferably multiple core biopsies of tumor are preferred for testing if they are representative of the tumor (grade and type) at resection.

Comments:

Specimen should be rejected and testing repeated on a separate sample if any of the following conditions exist:

1. External controls are not as expected (scores recorded daily show variation).
2. Artifacts involve most of sample.

Specimen may also be rejected and testing repeated on another sample if:

1. Slide has no staining of included normal epithelial elements and/or normal positive control on same slide.
2. Specimen has been decalcified using strong acids.
3. Specimen shows an ER-negative/PgR-positive phenotype (to rule out a false-negative ER assay or a false-positive PgR assay).
4. Sample has prolonged cold ischemia time or fixation duration, < 6 hours or > 72 hours and is negative on testing in the absence of internal control elements.

Recommendation:

Interpretation follows guideline recommendation.

Comments:

Positive ER or PgR requires that ≥ 1% of tumor cells are immunoreactive. Both average intensity and extent of staining are reported. Image analysis is a desirable method of quantifying percentage of tumor cells that are immunoreactive.

H score, Allred score, or Quick score may be provided.

Negative ER or PgR requires < 1% of tumor cells with ER or PgR staining. Interpreters have method to maintain consistency and competency documented regularly.

Accession slip and report must include guideline-detailed elements.

Recommendation:

Accession slip and report must include guideline-detailed elements.

Hammond MEH, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *Arch Pathol Lab Med*. 2010;134:907–922.

Appendix 5
ASCO/CAP Estrogen Receptor and Progesterone Receptor Guideline Recommendations (cont.)

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.

The complete guideline recommendations can be downloaded from: https://www.cap.org/protocols-and-guidelines/cap-guidelines/current-cap-guidelines/guideline-recommendations-for-immunohistochemical-testing-of-estrogen-and-progesterone-receptors-in-breast-cancer

Appendix 6
ASCO/CAP HER2 Test Guideline Recommendations

COLLEGE of AMERICAN PATHOLOGISTS

ASCO GUIDELINES

ASCO–CAP HER2 Test Guideline Recommendations

Summary of Guideline 2007 and 2013 Recommendations

Topic	2007 Recommendation	2013 Recommendation
Specimens to be tested	All primary breast cancer specimens and metastases should have at least one HER2 test performed	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.
Optimal algorithm for HER2 testing	Positive for HER2 is either IHC HER2 3 + (defined as uniform intense membrane staining of > 30% of invasive tumor cells) or FISH amplified (ratio of *HER2* to CEP17 of > 2.2 or average *HER2* gene copy number > six signals/ nucleus for those test systems without an internal control probe	Must report **HER2 test result as positive for HER2 if:** [a,b] • IHC 3+ based on circumferential membrane staining that is complete, intense [c,d] • ISH positive based on: Single-probe average *HER2* copy number ≥6.0 signals/cell.[c,e] Dual-probe *HER2*/CEP17 ratio ≥2.0;[c,e] with an average *HER2* copy number ≥4.0 signals/cell Dual-probe *HER2*/CEP17 ratio ≥2.0;[c,e] with an average *HER2* copy number <4.0 signals/cell[b] Dual-probe *HER2*/CEP17 ratio < 2.0;[c,e] with an average *HER2* copy number ≥6.0 signals/cell
	Equivocal for HER2 is defined as: IHC 2+ or FISH *HER2*/CEP17 ratio of 1.8-2.2 or average *HER2* gene copy number 4-6 *HER2* signals/nucleus for test systems without an internal control probe	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: [a,b] • IHC 2+ based on circumferential membrane staining that is incomplete and/or weak/moderate[f] and within >10% of the invasive tumor cells;[d] *or* complete and circumferential membrane staining that is intense and within ≤10% of the invasive tumor cells [d] • ISH equivocal based on: Single-probe ISH average *HER2* copy number ≥4.0 and <6.0 signals/cell[e,f] Dual-probe *HER2*/CEP17 ratio <2.0 with an average *HER2* copy number ≥4.0 and <6.0 signals/cell[e,f]

Abbreviations: HER2, human epidermal growth factor receptor; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; ISH, in situ hybridization; QA, quality assurance; NBF, neutral buffered formalin; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists

Wolff AC, Hammond ME, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update.

Appendix 6
ASCO/CAP HER2 Test Guideline Recommendations (cont.)

COLLEGE of AMERICAN PATHOLOGISTS

ASCO GUIDELINES

Topic	2007 Recommendation	2013 Recommendation
	Negative for HER2 is defined as: • IHC HER2 0: no staining • IHC HER2 1+: Weak incomplete membrane staining in any proportion of tumor cells or weak, complete membrane staining in <10% of cells • FISH *HER2*/CEP17 ratio of < 1.8 or average *HER2* gene copy number of < 4 signals/nucleus for test systems without an internal control probe	Must report a **HER2 test result as negative** if a single test (or both tests) performed show:[a,b] • IHC 1+ as defined by incomplete membrane staining that is faint/barely perceptible and within >10% of the invasive tumor cells[d] • IHC 0 as defined by no staining observed[d] or membrane staining that is incomplete and is faint/barely perceptible and within ≤10% of the invasive tumor cells[d] • ISH negative based on: Single-probe average *HER2* copy number <4.0 signals/cell Dual-probe *HER2*/CEP17 ratio <2.0 with an average *HER2* copy number <4.0 signals/cell
	Indeterminate for HER2	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: • Inadequate specimen handling • Artifacts (crush or edge artifacts) that make interpretation difficult • Analytic testing failure Another specimen should be requested for testing to determine HER2 status. Reason for indeterminate testing should be noted in a comment in the report.
ISH rejection criteria	Test is rejected and repeated if: • Controls are not as expected • Observer cannot find and count at least two areas of invasive tumor • > 25% of signals are unscorable due to weak signals • > 10% of signals occur over cytoplasm • Nuclear resolution is poor • Autofluorescence is strong	Same and report **HER2 test result as Indeterminate** as per parameters described above.

Appendix 6
ASCO/CAP HER2 Test Guideline Recommendations (cont.)

COLLEGE of AMERICAN PATHOLOGISTS

ASCO GUIDELINES

Topic	2007 Recommendation	2013 Recommendation
ISH interpretation	Interpretation performed by counting at least 20 cells; a pathologist must confirm that counting involved invasive tumor criteria followed	The pathologist should scan the entire ISH slide prior to counting at least 20 cells or use IHC to define the areas of potential *HER2* amplification. If there is a second population of cells with increased *HER2* signals/cell and this cell population consists of more than 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. 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.
Acceptable [IHC and ISH] tests[g]		Should preferentially use an FDA-approved IHC, brightfield ISH, or FISH assay.[g,h]
IHC rejection criteria	Test is rejected and repeated or tested by FISH if: • Controls are not as expected • Artifacts involve most of sample • Sample has strong membrane staining of normal breast ducts (internal controls)	Same
IHC interpretation criteria	Positive HER2 result requires homogeneous, dark circumferential (chicken wire) pattern in > 30% of invasive tumor. Interpreters have method to maintain consistency and competency	Should interpret IHC test using a threshold of more than 10% of tumor cells that must show homogeneous, dark circumferential (chicken wire) pattern to call result 3+, HER2 positive.
Reporting requirements for all assay types	Report must include guideline-detailed elements	Same except for changes to reporting requirement and algorithms defined in this table. (Data Supplements 9 and 10)
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 6–48 hours; cytology specimens must be fixed in formalin. Samples should be sliced at 5-mm to10-mm intervals after appropriate gross inspection and margins designation and placed in sufficient volume of neutral buffered formalin	Duration of fixation has been changed **from 6–48 hours to 6–72 hours.** Any exceptions to this process must be included in report.

Appendix 6
ASCO/CAP HER2 Test Guideline Recommendations (cont.)

COLLEGE of AMERICAN PATHOLOGISTS

ASCO GUIDELINES

Topic	2007 Recommendation	2013 Recommendation
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	Same
Optimal internal validation procedure	Validation of test must be done before test is offered	Same Data Supplement 12 lists examples of various external quality assurance schemes.
Optimal initial test validation	Initial test validation requires 25–100 samples tested by alternative validated method in the same laboratory or by validated method in another laboratory	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 who are routinely participating in external proficiency testing for HER2 tests, such as the program offered by the CAP (Data Supplement 12).
	Proof of initial testing validation in which positive and negative HER2 categories are 90% concordant with alternative validated method or same validated method for HER2	Laboratories are responsible for ensuring the reliability and accuracy of their testing results, by compliance with accredi-tation and proficiency testing requirements for HER2 testing assays. Specific concordance requirements are not required. (Data Supplement 11)
Optimal monitoring of test concordance between methods	Concordance testing must be done prior to initiation of testing, optimally as the form of testing validation. If concordance is below 95% for any testing category, that category of test result of either FISH or IHC must be automatically flexed to alternative method before final interpretation.	See text following under "Optimal Laboratory Accreditation"
Optimal internal QA procedures		Should review and document external and internal controls with each test and each batch of tests.
	Ongoing quality control and equipment maintenance	Same.
	Initial and ongoing laboratory per-sonnel training and competency assessment	Same.
	Use of standardized operating procedures including routine use of control materials	Same.
	Revalidation of procedure if changed	Same.
	Ongoing competency assessment and education of pathologists	Should perform ongoing competency assessment and document the actions taken as a part of the laboratory record.

Appendix 6
ASCO/CAP HER2 Test Guideline Recommendations (cont.)

COLLEGE of AMERICAN PATHOLOGISTS

ASCO GUIDELINES

Topic	2007 Recommendation	2013 Recommendation
Optimal external proficiency assessment	Participation in and successful completion of external proficiency testing program with at least two testing events (mailings) a year	Same.
	Satisfactory performance requires at least 90% correct responses on graded challenges for either test • Unsatisfactory performance will require laboratory to respond according to accreditation agency program requirements	Same.
Optimal laboratory accreditation	Onsite inspection every other year with annual requirement for self-inspection • Reviews laboratory validation, procedures, QA results and processes, results and reports • Unsatisfactory performance results in suspension of laboratory testing for HER2 for that method	Same (Data Supplement 11).

Notes

[a] If a reflex test (same specimen/same tissue) ordered after an initial equivocal HER2 test result does not render a positive or negative HER2 test result, the pathologist should review histopathologic features, confer if possible with the oncologist regarding additional HER2 testing, and document it in the pathology report. The pathologist may pursue additional HER2 testing without conferring with the oncologist. This should be accomplished using: (1) the alternative test (IHC and ISH) on the same specimen, (2) either test on another block (same specimen), or (3) either test on another specimen (eg, core biopsy, surgical resection, lymph node, and/or metastatic site). Because the decision to recommend HER2-targeted therapy requires a HER2-positive test result, additional HER2 testing should be attempted in equivocal specimens to attempt to obtain a positive or negative HER2 test result and most accurately determine the HER2 status of the tumor specimen.

[b] See Data Supplement 2E for additional information on rare scenarios.

[c] Observed in a homogeneous and contiguous population and within >10% of the invasive tumor cells.

[d] Readily appreciated using a low-power objective.

[e] By counting at least 20 cells within the area.

[f] Observed in a homogeneous and contiguous population.

[g] Alternatively, a laboratory accredited by the CAP or another accrediting entity may choose to use an LDT, in which case its analytical performance must be documented in the same clinical laboratory that will use the assay, and documentation of analytical validity of the assay must be available.

[h] A list of HER2 assays approved by the FDA as in vitro companion diagnostic devices to aid in the assessment of patients for whom trastuzumab treatment is being considered can be found in the Medical Devices section of the US FDA website (http://www. accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?start_search=1&search_term=HER2&approval_date_from=&approval_date_to=07/14/2013&sort=approvaldatedesc&pagenum=10; last checked July 14, 2013). The product package insert for trastuzumab and pertuzumab prepared by the FDA indicates that "HER2 testing should be performed using FDA-approved tests by laboratories with ßdemonstrated proficiency".

9/2013

The most current guideline recommendations can be downloaded from: https://www.cap.org/protocols-and-guidelines/cap-guidelines/current-cap-guidelines/recommendations-for-human-epidermal-growth-factor-2-testing-in-breast-cancer

Appendix 6
ASCO/CAP HER2 Test Guideline Recommendations (cont.)

HER2 Testing Update (Wolff et al. 2018)

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: IHC 3+ based on circumferential membrane staining that is complete, intense ISH positive based on: Single-probe average *HER2* copy number ≥ 6.0 signals/cell Dual-probe *HER2*/CEP17 ratio of ≥ 2.0; with an average *HER2* copy number ≥ 4.0 signals/cell Dual-probe *HER2*/CEP17 ratio of ≥ 2.0; with an average *HER2* copy number < 4.0; Dual-probe *HER2*/CEP17 ratio of < 2.0 with an average *HER2* copy number ≥ 6.0 signals/cell 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: 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 ISH equivocal based on: Single-probe ISH average *HER2* copy number ≥ 4.0 and ≤ 6.0 signals/cell Dual-probe *HER2*/CEP17 ratio of < 2.0 with an average *HER2* copy number ≥ 4.0 and ≤ 6.0 signals/cell Must report HER2 test result as negative if a single test (or both tests) performed show: IHC 1+ as defined by incomplete membrane staining that is faint or barely perceptible and within > 10% of the invasive tumor cells 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 ISH negative based on: Single-probe average *HER2* copy number < 4.0 signals/cell Dual-probe *HER2*/CEP17 ratio of < 2.0 with an average *HER2* copy number of 4.0 signals/cell 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: Inadequate specimen handling Artifacts (crush or edge artifacts) that make interpretation difficult Analytic testing failure Another specimen should be requested for testing to determine HER2 status. 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." 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 . . ." 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): a. If the IHC result is 3+, diagnosis is HER2 positive 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: 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. 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* c. If the IHC result is 0 or 1+, diagnosis is HER2 negative with a comment.* 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): a. If the IHC result is 3+, diagnosis is HER2 positive 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: 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 If the *HER2*/CEP17 ratio remains < 2.0 with ≥ 6.0 *HER2* signals/cell, diagnosis is HER2 positive c. If the IHC result is 0 or 1+, diagnosis is HER2 negative with a comment* 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): a. If the IHC result is 3+, diagnosis is HER2 positive 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 6
ASCO/CAP HER2 Test Guideline Recommendations (cont.)

HER2 Testing Update (Wolff et al. 2018)

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 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* 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: Controls are not as expected Observer cannot find and count at least two areas of invasive tumor > 25% of signals are unscorable due to weak signals > 10% of signals occur over cytoplasm Nuclear resolution is poor Autofluorescence is strong 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. 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. 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. 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: Controls are not as expected Artifacts involve most of sample 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. 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. 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)

Appendix 6
ASCO/CAP HER2 Test Guideline Recommendations (cont.)

HER2 Testing Update (Wolff et al. 2018)

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. Ongoing quality control and equipment maintenance Initial and ongoing laboratory personnel training and competency assessment Use of standardized operating procedures including routine use of control materials Revalidation of procedure if changed 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 Satisfactory performance requires at least 90% correct responses on graded challenges for either test 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 Reviews laboratory validation, procedures, QA results and processes, results, and reports 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 7
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

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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

Appendix 7
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) (cont.)

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 8
EuroQol 5-Dimension Questionnaire, Five-Level Version (EQ-5D-5L)

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

MOBILITY

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

SELF-CARE

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

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

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

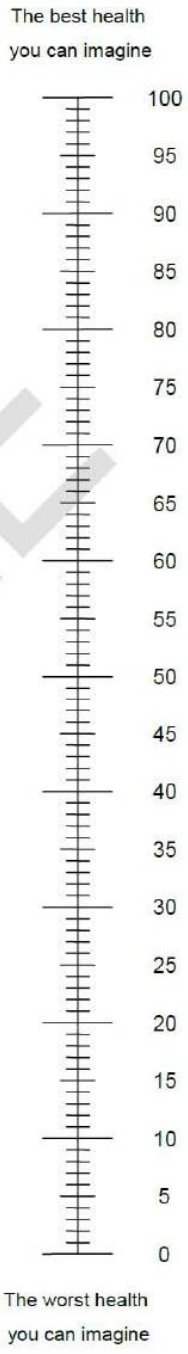
ANXIETY / DEPRESSION

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

Appendix 8
EuroQol 5-Dimension Questionnaire, Five-Level Version (EQ-5D-5L) (cont.)

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

YOUR HEALTH TODAY = ☐



Appendix 9
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

Appendix 9
Selected items from the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) (cont.)

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 10
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication

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

Measurability of Tumor at Baseline

Definitions

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

a. Measurable Tumor Lesions

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

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

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

b. Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 but < 15 mm), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal

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

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

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

c. Special Considerations Regarding Lesion Measurability

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

Bone Lesions:

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

Cystic Lesions:

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

Lesions with Prior Local Treatment:

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

Target Lesions: Specifications by Methods of Measurements

a. Measurement of Lesions

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

Appendix 10
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

b. Method of Assessment

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

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

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

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

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

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

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

Appendix 10
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

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

Baseline Documentation of Target and Non-Target Lesions

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

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

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 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.

Appendix 10
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

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

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

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

Response Criteria

a. Evaluation of Target Lesions

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

- Complete response (CR): disappearance of all target lesions
  - Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline
  - In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
  - The appearance of one or more new lesions is also considered progression.
- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

b. Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero

even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

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

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

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

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

c. Evaluation of Non-Target Lesions

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

- CR: disappearance of all non-target lesions and (if applicable) normalization of tumor marker level
  - All lymph nodes must be non-pathological in size (< 10 mm short axis).

- Non-CR/Non-PD: persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: unequivocal progression of existing non-target lesions
  - The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

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

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden on the basis of the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease; that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. Although it would be ideal to have objective criteria apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

e. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion

Appendix 10
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

should be unequivocal—that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

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

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

Evaluation of Response

a. Time Point Response (Overall Response)

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

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

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

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

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

Appendix 10
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

Table 2 Time Point Response: Patients with Non-Target Lesions Only

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

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

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

b. Missing Assessments and Not-Evaluable Designation

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

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

Appendix 10
Response Evaluation Criteria in Solid Tumors (RECIST): Modified Excerpt from Original Publication (cont.)

Table 3 Best Overall Response When Confirmation Is Required

Overall Response at First Time Point	Overall Response at Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

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

[a] If a CR is truly met at the first time point, any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

c. Special Notes on Response Assessment

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

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective

progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

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

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

Appendix 11
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 • Addison disease • Ankylosing spondylitis • Anti-phospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • Diabetes mellitus type 1 • Dysautonomia • Epidermolysis bullosa acquisita • Gestational pemphigoid • Giant cell arteritis • Goodpasture syndrome • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease - chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary *cholangitis* • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren's syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease • Wegener granulomatosis

Appendix 12
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, IV, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- IV 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 and IV fluids as required by patient status and directed by the physician in charge.
4. Continue to observe the patient and document observations.

Appendix 13
Guidelines for Management of Adverse Events for Patients in Cohorts A and B

Guidelines for management of specific adverse events are provided in the subsections below.

DIARRHEA MANAGEMENT GUIDELINES

Specific guidelines for managing diarrhea to improve safety and tolerability are provided in Table 1. In this study, all patients should receive loperamide (2 mg oral twice a day or 4 mg once a day) as prophylaxis for diarrhea in the first cycle if allowed by local guidance. Investigators are encouraged to continue this dosing for the remainder of the study, and the prophylaxis dose may be adjusted as necessary, using their discretion based on clinical judgment and per local guidance.

Treatment modifications for diarrhea (any grade), when it occurs, should be instituted as early as possible. Guidelines for treatment of diarrhea following the prophylactic dose of loperamide (where allowed) includes use of loperamide 2 mg every 4 hours or 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 Lomotil® (diphenoxylate and atropine), codeine, or octreotide. Duration of diarrhea may be minimized by taking ipatasertib/placebo with food, avoiding lactose-containing foods, and hydrating with 8–10 glasses per day (~12 oz/glass) of electrolyte-containing clear liquid, such as broth or low-calorie drinks.

For diarrhea that persists for more than 5 days, despite treatment with anti-diarrheal agent(s) and/or withholding dosing of ipatasertib/placebo, gastroenterologists should be consulted to rule out the risk of colitis and infection (e.g., obtaining CT images or a stool culture for infectious workup [*Clostridium difficile*, enteric bacteria, cytomegalovirus]). Patients should be educated on the symptoms and importance of early reporting of diarrhea to receive instructions of 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.

Dose intensity of paclitaxel should be maintained as tolerated. Dose reductions of ipatasertib/placebo will be by one level at a time (i.e., 400 to 300 mg; 300 to 200 mg) as outlined in Section 5.1.5.3 and Table 4. If Grade ≥2 diarrhea persists following dose reductions of ipatasertib/placebo to 200 mg daily and with maximum treatment for diarrhea, ipatasertib/placebo should be discontinued. Paclitaxel dose reduction or discontinuation should be considered if diarrhea persists even after ipatasertib/placebo discontinuation.

Appendix 13
Guidelines for Management of Adverse Events for Patients in Cohorts A and B (cont.)

Table 1 Diarrhea Management Guidelines

Severity of Diarrhea [a]	Management Guideline
Prevention	• All patients are mandated to receive loperamide (2 mg BID or 4 mg QD) as prophylaxis for diarrhea in the first cycle, if allowed by local guidance. If there are clinical concerns that preclude the use of loperamide prophylaxis in Cycle 1, discussion with the Medical Monitor is required. Loperamide dose adjustment may be made per investigator discretion after discussion with the Medical Monitor. • After the first cycle, investigators are encouraged to continue this dosing for the remainder of the study using their discretion as clinically indicated.
Grade 1 Increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline	• Continue study drugs at the current dose level. • Manage with loperamide 4 mg initially and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea free interval. • Dietary modifications, such as avoiding any lactose-containing foods and eating small meals. • Hydration with 8–10 glasses per day (~12 oz/glass) of clear liquid, such as broth or low-calorie drinks with electrolytes. • Upon resolution, loperamide prophylaxis can be considered and continues as clinically indicated, if allowed by local guidance.

Appendix 13
Guidelines for Management of Adverse Events for Patients in Cohorts A and B (cont.)

Table 1 Diarrhea Management Guidelines (cont.)

Severity of Diarrhea [a]	Management Guideline
Grade 2 Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared with baseline	• Rule out infectious etiology. • Manage with loperamide as early as possible 4 mg initially and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea free interval. • Dietary modifications, such as avoiding any lactose-containing foods and eating small meals. • Hydration with 8−10 glasses per day (~12 oz/glass) of clear liquid, such as broth or low-calorie drinks with electrolytes. • For non-infectious diarrhea lasting more than 48 hours despite optimal loperamide treatment, manage with second-line anti-diarrheal agents, including, but not limited to Lomotil®, codeine, or octreotide, or as per institutional guidelines. • 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. • Reduce ipatasertib/placebo by one (or one additional) dose level (see Section 5.1.5.3) for recurrent Grade 2 diarrhea. • When study treatment is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated, if allowed by local guidance.
Grade 3 Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	• Rule out infectious etiology. • Treat per Grade 2 management guidelines and supportive care. • Interrupt ipatasertib/placebo and paclitaxel until diarrhea improves to Grade 1 or better. Ipatasertib/placebo should be reduced by one dose level (see Section 5.1.5.3) when treatment is restarted. Consider resuming paclitaxel at the same dose. • For recurrent Grade 3 diarrhea, reduce ipatasertib/placebo dose by one additional dose level (see Section 5.1.5.3). Consider reducing paclitaxel by one dose level when treatment is restarted (see Section 5.1.5.3). • When study treatment is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated, if allowed by local guidance.

Table 1 Diarrhea Management Guidelines (cont.)

Severity of Diarrhea [a]	Management Guideline
Grade 4 Life-threatening consequences; urgent intervention indicated	• Rule out infectious etiology. • Treat per Grade 2 management guidelines and supportive care. • Permanently discontinue ipatasertib/placebo. • 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 Section 5.1.5.3).

ADL = activities of daily living; BID = twice a day; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; QD = once a day.

[a] Diarrhea, as defined by NCI CTCAE v4.0, a disorder characterized by frequent and watery bowel movements.

FASTING HYPERGLYCEMIA

Fasting is defined as abstaining from food and drink (with the exception of water) for at least 8 hours.

Dose modification guidelines for fasting hyperglycemia attributable to study treatment are outlined below (see Table 2) and are intended to provide guidance for fasting glucose measurements assessed in the clinic. Decisions regarding study treatment should be made on fasting levels drawn in the clinic whenever possible.

Home glucose measurements may be used to trigger contact between patient and investigative site team and may lead to an unscheduled clinic visit to assess fasting glucose. Guidance for when to call the investigator/site staff (or designated endocrinologist, if applicable) should be provided to patients for hypoglycemia (e.g., glucose value under 70 mg/dL) and hyperglycemia (e.g., glucose value over 300 mg/dL). Alternative thresholds may be selected as clinically indicated per investigator discretion or institutional guidance and noted in the source documents. For any patients performing home glucose monitoring, the blood glucose log should be reviewed at each clinic visit (and source data retained), entry of results into the patient's eCRF will be limited to values which result in intervention.

In the event of ipatasertib/placebo interruption, anti-diabetic medications may need to be held or reduced (per investigator judgement) and glucose should be monitored closely to minimize the risk of hypoglycemia.

Appendix 13
Guidelines for Management of Adverse Events for Patients in Cohorts A and B (cont.)

Table 2 Fasting Hyperglycemia Management Guidelines

Severity of Fasting Hyperglycemia	Management Guideline
Grade 1: fasting glucose value > ULN to 160 mg/dL (8.9 mmol/L) [a]	• Monitor fasting glucose per protocol • Consider initiating home glucose monitoring
Grade 2: fasting glucose value > 160 to 250 mg/dL (> 8.9–13.9 mmol/L) [a]	• Interruption of ipatasertib/placebo until fasting hyperglycemia resolves to Grade 1 or better. • Initiate home glucose monitoring • Start oral anti-diabetic medications (e.g., metformin). • 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 4). • 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.
Grade 3: glucose value 250 to 500 mg/dL (> 13.9–27.8 mmol/L) [a]	• Interrupt ipatasertib/placebo dosing until fasting hyperglycemia resolves to Grade 1 or better. • Initiate home glucose monitoring • Treat hyperglycemia as medically appropriate. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • If the patient is already on an oral anti-diabetic medication, ipatasertib/placebo should be reduced by one dose level when treatment is restarted. • 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. • If Grade ≥ 3 fasting hyperglycemia recurs, the dose of ipatasertib/placebo should be reduced by one dose level when treatment is restarted.
Grade 4: glucose value > 500 mg/dL (> 27.8 mmol/L); life-threatening consequences [a]	• Interrupt ipatasertib/placebo dosing until resolution to Grade 1 or better. • Treat hyperglycemia as medically appropriate. • Initiate home glucose monitoring • Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • Assess for volume depletion and appropriate intravenous or oral hydration. • Reduce ipatasertib/placebo by one dose level if and when treatment is restarted. • If Grade 4 hyperglycemia recurs, permanently discontinue ipatasertib/placebo.

ULN=upper limit of normal.

[a] For all grades, the patient should receive education on a diabetic diet.

NEUTROPENIA AND/OR THROMBOCYTOPENIA

Addition of hematopoietic growth factors is allowed. If a dose delay is required as a result of neutropenia at any grade, patients should receive prophylactic granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor per institutional standards. Patients should be counseled as to the risk of fever and infection and to the importance of contacting their treating physician immediately if these conditions occur so that they can be promptly and appropriately managed. Dosage modification guidelines for neutropenia and/or thrombocytopenia attributable to ipatasertib/placebo and/or paclitaxel are outlined in Table 3.

Table 3 Neutropenia and Thrombocytopenia Management Guidelines

Severity of Neutropenia and/or Thrombocytopenia	Management Guideline
Grade 2	• Ipatasertib/placebo may be continued at the original dose. Paclitaxel may be held and can then be administered at the previous dose, when ANC has recovered to ≥1500/μL and when the platelet count has recovered to ≥100,000/μL. If clinically appropriate based on the investigator's medical judgment, paclitaxel 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. If the hematologic criteria do not recover to Grade 1 or better within the 14-day window of treating for ongoing Grade 2 neutropenia, the subsequent paclitaxel dose(s) must be held until recovery of hematological criteria to Grade 1 or better.

Grade 3	• Ipatasertib/placebo and paclitaxel should both be held 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 hematological toxicities.
	  ○ 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.
	  ○ Recurrent episode: Ipatasertib/placebo and paclitaxel should be reduced by one dose level when treatment is restarted. If patient has had more than three Grade 3 neutropenia episodes on study, despite the above dose reduction to 65 mg/m^2, the paclitaxel dose should be permanently discontinued, but the patient may continue to receive ipatasertib/placebo following discussion with the Medical Monitor.
	• 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 paclitaxel but may continue ipatasertib/placebo following discussion with the Medical Monitor.

Table 3 Neutropenia and Thrombocytopenia Management Guidelines (cont.)

Severity of Neutropenia and/or Thrombocytopenia	Management Guideline
Febrile neutropenia and Grade 4 neutropenia	• Paclitaxel and ipatasertib/placebo should be held 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 hematological toxicities. First episode: Ipatasertib/placebo and paclitaxel should be reduced by one dose level when treatment is restarted. Recurrent episode: Ipatasertib/placebo and paclitaxel should be discontinued. • 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 paclitaxel and ipatasertib/placebo treatment.

ANC = absolute neutrophil count; G-CSF= Granulocyte-colony stimulating factor.

NAUSEA AND/OR VOMITING

Dose reductions for nausea and/or vomiting should occur only if the symptoms persist despite a minimum of two treatments with adequate (combination) anti-emetic treatment(s), including ondansetron and other anti-emetics (i.e., prochlorperazine or metoclopramide per institutional guidelines; see Table 4). For persistent nausea and/or vomiting attributable to ipatasertib/placebo, dosage modification guidelines are outlined in Section 5.1.5.3, Table 4, and Table 4).

Table 4 Nausea and Vomiting Management Guidelines

Severity of Nausea and /or Vomiting	Management Guideline
Grade 1	• Provide supportive care as needed.
Grade 2	• Provide maximum supportive care as needed per local guidelines, with a minimum of two anti-emetics, including ondansetron.
Grade ≥ 3	• Interrupt ipatasertib/placebo and paclitaxel until nausea or vomiting resolves to Grade 2 or better. • Provide maximum supportive care per local guidelines, with a minimum of two anti-emetics, including ondansetron. • If Grade ≥ 3 nausea or vomiting recurs, ipatasertib/placebo should be reduced by one dose level (see Section 5.1.5.3) when treatment is restarted. Paclitaxel dose may be reduced by one level if recurrent Grade 3 nausea or vomiting occurs after dose reduction of ipatasertib/placebo has occurred (see Section 5.1.5.3).

RASH

Ipatasertib/placebo should be permanently discontinued for rash associated with Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, or other suspected severe hypersensitivity or allergic reaction. Dosage modification and symptom management guidelines for skin toxicity attributable to study treatment are shown in Table 5 (see Section 5.1.5.3 and Table 4 for dose modifications).

Table 5 Rash Management Guidelines

Severity of Rash	Management Guideline
Grade 1	• Continue study drugs. • Consider topical corticosteroids.
Grade 2	• Interrupt ipatasertib/placebo treatment until resolution to Grade 1 or better or the toxicity is no longer clinically significant. • Treat rash with topical corticosteroids. • Consider treatment of rash with oral corticosteroids.
Grade 3	• Interrupt ipatasertib/placebo treatment until resolution to Grade 1 or better or the toxicity is no longer clinically significant. • Treat rash with topical and systemic corticosteroids. • Consider dermatological consultation. • If the skin toxicity resolves to Grade 1 or better or is no longer clinically significant within 28 days, following completion of the steroid taper, ipatasertib/placebo may be resumed at one dose level below the previous dose (see Section 5.1.5.3). • If recovery of the skin toxicity to Grade 1 or better does not occur or skin toxicity remains clinically significant continuously for 4 weeks, or Grade 3 rash recurs, permanently discontinue ipatasertib/placebo.
Grade 4	• Administration of systemic steroids (oral or intravenous) is recommended. Consider dermatological consultation and skin biopsy. Ipatasertib/placebo should be permanently discontinued.

PNEUMONITIS

Pneumonitis is not known to be causally related to any of the study drugs; however, it has been observed with other drugs treating pathways similar to ipatasertib. Every effort should be made to determine the etiology of dyspnea and changes in pulmonary function (see Table 6).

Appendix 13
Guidelines for Management of Adverse Events for Patients in Cohorts A and B (cont.)

Table 6 Pneumonitis Management Guidelines

Severity of Pneumonitis	Management Guideline
Grade 1	• Continue study drugs. • Perform CT scan and PFTs. Repeat CT scan every 8 weeks until a return to baseline.
Grade 2	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Interrupt ipatasertib/placebo and paclitaxel treatment until improvement to Grade 1 or better. Consider resuming ipatasertib/placebo and paclitaxel at same dose level or one dose level below (see Section 5.1.5.3) per investigator's assessment. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. • For recurrent Grade 2 pneumonitis, ipatasertib/placebo must be resumed at one dose level below the previous dose (see Section 5.1.5.3). Consider resuming paclitaxel at same dose or one dose below (see Section 5.1.5.3) per investigator's assessment. • Discontinue ipatasertib/placebo if recovery to Grade 1 or better is not evident within 28 days. Paclitaxel dose should be resumed at one dose level below previous dose (see Section 5.1.5.3) or discontinued per investigator's assessment.
Grade 3	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Interrupt ipatasertib/placebo and paclitaxel treatment until improvement to Grade 1 or better. Resume ipatasertib/placebo and paclitaxel at one dose level below previous dose (see Section 5.1.5.3) per investigator's assessment. If recovery to Grade 1 or better is not evident within 28 days, discontinue study treatments. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended. • For recurrent non-infectious Grade 3 pneumonitis events, ipatasertib/placebo and paclitaxel should be permanently discontinued.
Grade 4	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Permanently discontinue ipatasertib/placebo and paclitaxel. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended.

CT = computed tomography; PFT = pulmonary function test.

MUCOSITIS

Mouthwash such as magic mouth wash (if inaccessible, warm salt or bicarbonate water) should be used as supportive care per institution guidelines. Brushing teeth after meals, keeping lips moisturized with non-Vaseline® products, and avoiding alcohol, spicy food, and smoking have all been shown to reduce pain and infection related to mucositis. Ranitidine or omeprazole may be helpful if patients have epigastric pain. Dosage modification guidelines for mucositis attributable to study treatment are outlined in Table 7.

Table 7 Mucositis Management Guidelines

Severity of Mucositis	Management Guidelines
Grade 1 or 2	• Manage with maximum supportive care. • If Grade ≥ 2 mucositis recurs in subsequent 4 week cycles, despite maximal supportive care, the dose of ipatasertib/placebo should be reduced by one dose level (see Section 5.1.5.3). The dose of paclitaxel may be maintained or reduced by one level for subsequent cycles per investigator's discretion (see Section 5.1.5.3).
Grade ≥ 3	• Hold ipatasertib/placebo and paclitaxel until recovery to Grade 2 or better. If the mucositis resolves to Grade 2 or better during the current cycle, the dose of ipatasertib/placebo should be reduced by one dose level (see Section 5.1.5.3). The dose of paclitaxel may be maintained or reduced by one dose level for subsequent cycles per investigator's discretion (see Section 5.1.5.3). • If recovery of mucositis to Grade 2 or better does not occur within a maximum of 4 weeks, the patient will permanently discontinue paclitaxel and ipatasertib/placebo.

HEPATOTOXICITY

Permanently discontinue ipatasertib for any patients who develop a concurrent elevation of ALT and/or AST greater than 3 ×ULN and total bilirubin greater than 2 ×ULN and/or clinical jaundice in the absence of biliary obstruction or other causes responsible for the concurrent elevation, including patients having abnormal liver function tests that meet Hy's law criteria. Dosage modification and symptom management guidelines for hepatotoxicity, attributable to study treatment are shown below (see Table 8).

Appendix 13
Guidelines for Management of Adverse Events for Patients in Cohorts A and B (cont.)

Table 8 *Hepatotoxicity Management Guidelines*

Severity of LFT Elevation	*Management Guideline*
Grade 1 *AST or ALT > baseline – 3 × ULN if baseline was normal;* *1.5–3.0 × baseline if baseline was abnormal* *or* *T bilirubin > baseline – 1.5 × ULN was normal; 1.0–1.5 × baseline if baseline was abnormal*	• *Continue study drugs.*
Grade 2 *AST or ALT > 3–5 × ULN if baseline was normal; 3–5 × baseline if baseline was abnormal* *or* *T bilirubin > 1.5–3.0 × ULN if baseline was normal;* *1.5–3.0 × baseline if baseline was abnormal*	• *Continue study drugs.* • *The frequency of liver function test monitoring should be increased as clinically indicated if the investigator judges that the laboratory abnormalities are potentially related to study medication.*
Grade 3 *AST or ALT > 5–20 × ULN if baseline was normal; 5–20 × baseline if baseline was abnormal* *or* *T bilirubin > 3–10 × ULN if baseline was normal; 3–10 × baseline if baseline was abnormal*	• *Immediately interrupt* ipatasertib. • *On return of LFTs to baseline or to AST and ALT ≤ 2.5 × ULN and total bilirubin ≤ 1.5 × ULN levels, restart ipatasertib/ at previous dose* • *Following treatment resumption, monitor serum transaminases and bilirubin at a minimum every 2 weeks for 3 months and monthly thereafter.* • *If another Grade 3 event occurs, interrupt ipatasertib. On return of LFTs to baseline or AST and ALT ≤2.5 × ULN and total bilirubin ≤1.5 × ULN levels, restart ipatasertib, reducing the dose by one level* • *Further Grade 3 occurrences must result in permanent discontinuation of ipatasertib.*
Grade 4 *AST or ALT > 20 × ULN if baseline was normal; > 20 × baseline if baseline was abnormal* *or* *T bilirubin > 10 × ULN if baseline was normal; > 10 × baseline if baseline was abnormal*	• *Permanently discontinue ipatasertib.*

LFT =liver function test; QD =once daily; T=total; ULN =upper limit of normal.

PERIPHERAL NEUROPATHY

If Grade ≥3 peripheral neuropathy attributable to paclitaxel develops in patients, paclitaxel should be held until the neuropathy recovers to Grade 2 or better, or resolution such that the peripheral neuropathy is no longer clinically significant. During this time, patients may continue ipatasertib/placebo at the discretion of the investigator. If the peripheral neuropathy recovers to Grade 2 or better within 4 weeks or resolution such that the peripheral neuropathy is no longer clinically significant, dosing of paclitaxel may resume reduced by one dose level (see Section 5.1.5.3). If recovery of the peripheral neuropathy to Grade 2 or better does not occur within a maximum of 4 weeks, the patient will permanently discontinue paclitaxel but may continue the ipatasertib/placebo.

HYPERSENSITIVITY

If a hypersensitivity reaction due to infusion of paclitaxel develops in patients, treatment for the hypersensitivity reaction, including the possibility of rechallenging with the attributable chemotherapy agent, in presence of premedication for paclitaxel should be administered as per institutional guidelines or at the discretion of the investigator. The patient may continue the other study treatment components not associated with the toxicity (i.e., ipatasertib/placebo).

OTHER NON-HEMATOLOGIC TOXICITIES

If other Grade ≥3 non hematologic toxicities not described above develop in patients, treatment with ipatasertib/placebo and/or paclitaxel may be held, depending on the attribution of the toxicity, at the discretion of the investigator. During this time, treatment may continue with the other non-attributable treatment agent (i.e., either ipatasertib/placebo or paclitaxel). Grade ≥3 non-hematologic toxicity should be monitored at least weekly.

If the toxicity resolves to Grade 1 or better within 2 weeks, treatment may resume with the attributable agent.

If the toxicity resolves to Grade 1 or better in 2–4 weeks, the dose of the attributable drug should be reduced by one level per the suggested guidelines in Section 5.1.5.3.

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 attributable agent with dose reduction, or the attributable agent may be permanently discontinued, at the discretion of the investigator and after discussion with the Medical Monitor.

For Grade ≥3 toxicities associated primarily with laboratory abnormalities only (e.g., elevation of ALT, AST, lipase, or amylase, or decreases in phosphorus without clinical or other evidence of pancreatitis or other hepatic dysfunction), study treatment

may continue without interruption and/or dose reduction at the discretion of the investigator per institutional practice.

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel)

Guidelines for the management of patients who experience specific adverse events are provided in Appendix 15 and Table 1, as outlined below:

- Table 1 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 1. For these potential overlapping toxicities, guidelines in Table 1 should be followed instead of guidelines in Appendix 15.
- Table 1 provides guidelines for the management of patients who experience adverse events associated with ipatasertib. It is recommended that atezolizumab and/or ipatasertib be withheld or discontinued per the guidelines in Table 1.
- Appendix 15 provides guidelines for the management of patients who experience atezolizumab-associated IRRs and immune-mediated adverse events. It is recommended that atezolizumab be withheld or discontinued per the guidelines in Appendix 15 and that ipatasertib be withheld or discontinued per the guidelines in Table 1.

For cases in which management guidelines are not covered in Table 1 or Appendix 15, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus Atezolizumab Plus Paclitaxel

Event	*Action to Be Taken*
Infusion-related reactions and anaphylaxis	• *Follow guidelines for atezolizumab in Appendix 15.* • *Withhold ipatasertib/placebo.* • *For anaphylaxis precautions, see Appendix 12.* • *For severe hypersensitivity reactions, permanently discontinue atezolizumab 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. • After the first cycle, continue this dosing for the remainder of the study as clinically indicated. • Thoroughly evaluate all events of diarrhea or colitis for more common etiologies other than drug-induced effects. • For diarrhea that persists for more than 5 days, despite treatment with anti-diarrheal 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.) • 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. Administer anti-diarrheal agents and other supportive care per institutional guidelines or per suggested supportive care outlined below: <u>Medication</u> 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, 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.

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus Atezolizumab Plus Paclitaxel (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
General guidance (cont.)	Medication (cont.) – 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. – 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 4. If Grade ≥2 diarrhea persists following dose reductions of ipatasertib/placebo to 200 mg daily and with maximum treatment for diarrhea, discontinue ipatasertib/placebo. Oral Supplementation – Initiate potassium and/or magnesium if serum levels are less than the lower limit of normal. – Consider rehydration therapy with oral electrolyte solution for Grade ≥1 diarrhea or vomiting. Dietary Modifications – Instruct patient to eat small meals and eliminate lactose-containing products from diet. – Suggest diet of bananas, rice, apples, and toast, while avoiding fiber from vegetables and other fruits. – Encourage adequate hydration with salt-containing liquids (e.g., broth, sports drinks such as Gatorade®).
Diarrhea, Grade 1	• Continue atezolizumab and ipatasertib/placebo. • Initiate supportive care and monitor patient closely. • Investigate etiology, referring patient to gastrointestinal specialist for evaluation of possible colitis if appropriate. • Upon resolution, loperamide prophylaxis can be considered and continued as clinically indicated, if allowed by local guidance. Please note, loperamide prophylaxis is to be taken throughout at least the first cycle.

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus Atezolizumab Plus Paclitaxel (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea, Grade 2	• Withhold atezolizumab and ipatasertib/placebo. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at a fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. a, b, c • 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. • Reduce ipatasertib/placebo by one (or one additional) dose level (see Table 4) for recurrent Grade 2 diarrhea. • 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 may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator.* The Medical Monitor *is available to advise as needed.*

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

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

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus Atezolizumab Plus Paclitaxel (cont.)

Event	Action to Be Taken
Diarrhea, Grade 3	• Withhold ipatasertib/placebo, atezolizumab, and paclitaxel. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at a fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor[a, b, c] • Interrupt ipatasertib/placebo and paclitaxel until diarrhea improves to Grade 1 or better. Ipatasertib/placebo should be reduced by one dose level (see Table 4) when treatment is restarted. Consider resuming paclitaxel at the same dose. • For recurrent Grade 3 diarrhea, reduce ipatasertib/placebo dose by one additional dose level (see Table 4). Consider reducing paclitaxel by one dose level when treatment is restarted (see Table 5). • 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 may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator*. The Medical Monitor *is available to advise as needed.*

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

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

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus Atezolizumab Plus Paclitaxel (cont.)

Event	Action to Be Taken
Diarrhea, Grade 4	• Permanently discontinue atezolizumab and ipatasertib/placebo and contact Medical Monitor. [c] • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Rule out bowel perforation. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis, including biopsy if appropriate. • 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 5).

GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug.

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

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

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

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus Atezolizumab Plus Paclitaxel (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Colitis, Grade 1	• Continue atezolizumab and ipatasertib/placebo. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy if symptoms persist for > 5 days.
Colitis, Grade 2	• Withhold atezolizumab and ipatasertib/placebo. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • For recurrent events or events that persist > 5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at a fixed dose. If not, permanently discontinue atezolizumab and ipatasertib/placebo and contact Medical Monitor. [a, b, c] • 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 may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator.* The Medical Monitor *is available to advise as needed.*

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

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

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus Atezolizumab Plus Paclitaxel (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Colitis, Grade 3	• Withhold atezolizumab and ipatasertib/placebo. • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at a fixed dose. If not, permanently discontinue atezolizumab and ipatasertib/placebo and contact Medical Monitor. [a, b, c] • 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 and ipatasertib/placebo and contact Medical Monitor. [c] • Initiate supportive care and monitor patient closely. • Discontinue medications that may exacerbate colitis (e.g., NSAIDs). • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk*

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

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus Atezolizumab Plus Paclitaxel (cont.)

Event	Action to Be Taken
Endocrine disorders	
Asymptomatic hypothyroidism	• Follow guidelines for atezolizumab in Appendix 15. • Continue ipatasertib/placebo.
Symptomatic hypothyroidism	• Follow guidelines for atezolizumab in Appendix 15. • Continue ipatasertib/placebo.
Asymptomatic hyperthyroidism	• Thyroid-stimulating hormone ≥ 0.1 mU/L and < 0.5 mU/L: • Follow guidelines for atezolizumab in Appendix 15. • Continue ipatasertib/placebo. • Thyroid-stimulating hormone < 0.1 mU/L: • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Follow guidelines for atezolizumab in Appendix 15. • Continue ipatasertib/placebo. • 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 4). If not, permanently discontinue ipatasertib/placebo.

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus Atezolizumab Plus Paclitaxel (cont.)

Event	Action to Be Taken
Endocrine disorders (cont.)	
Symptomatic adrenal insufficiency, Grade 2, 3, or 4	• Follow guidelines for atezolizumab in Appendix 15. • Continue ipatasertib/placebo.
Hyperglycemia, general guidance	• Thoroughly evaluate all events of hyperglycemia for more common etiologies other than drug-induced effects. • Investigate for diabetes. If patient has Type 1 diabetes, treat as Grade 3 event. • In workup, include confirmation of fasting blood glucose, urinary glucose and ketones, arterial blood gas, serum bicarbonate, hemoglobin A1C, C-peptide levels, anti-islet antibodies, and anti-GAD65 antibody. • Treat hyperglycemia per institutional guidelines with fluid replacement, insulin, and correction of electrolyte abnormalities.
Hyperglycemia Grade 1, fasting glucose value > ULN to 160 mg/dL (8.9 mmol/L)	• Continue atezolizumab and ipatasertib/placebo. • Provide patient with education on a diabetic diet and consider home glucose monitoring. • Consider oral anti-diabetic medications (e.g., metformin) or insulin replacement, guided by etiology of hyperglycemia.
Hyperglycemia Grade 2, fasting glucose value > 160–250 mg/dL (> 8.9–13.9 mmol/L)	• Withhold atezolizumab and ipatasertib/placebo dosing until fasting glucose value resolves to Grade ≤ 1. (Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines.) • Encourage a diabetic diet and initiate home glucose monitoring. • Start oral anti-diabetic medications (e.g., metformin) or insulin replacement, guided by etiology of hyperglycemia. • 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 4). • 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.

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus Atezolizumab Plus Paclitaxel (cont.)

Event	Action to Be Taken
Endocrine disorders (cont.)	
Hyperglycemia Grade 3, glucose value >250–500 mg/dL (>13.9–27.8 mmol/L)	• Withhold atezolizumab and ipatasertib/placebo dosing until fasting glucose value resolves to Grade ≤ 1 and contact Medical Monitor. • 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). • Encourage a diabetic diet and initiate home glucose monitoring. • If the patient is already on an oral anti-diabetic medication, ipatasertib/placebo should be reduced by one dose level when treatment is restarted. • 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. • If hyperglycemia Grade 3 recurs, the dose of ipatasertib/placebo should be reduced by one dose level (see Table 1) when treatment is restarted. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hyperglycemia Grade 4, glucose value >500 mg/dL (>27.8 mmol/L); life-threatening consequences	• Withhold atezolizumab and ipatasertib/placebo dosing until fasting glucose value resolves to Grade ≤ 1. • 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). • Assess for volume depletion and appropriate intravenous or oral hydration. • Encourage a diabetic diet and initiate home glucose monitoring. • Upon recovery of fasting glucose to Grade ≤ 1, reduce ipatasertib/placebo by one dose level (see Table 4) when treatment is restarted. • Resume atezolizumab when symptoms resolve and glucose levels are stable. • If hyperglycemia Grade 4 recurs, permanently discontinue ipatasertib/placebo and atezolizumab and contact Medical Monitor.

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus 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. • Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab.
Pulmonary event, Grade 1	• Continue atezolizumab and ipatasertib/placebo. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • *For Grade 1 pneumonitis, consider withholding atezolizumab.*
Pulmonary event, Grade 2	• Withhold atezolizumab and ipatasertib/placebo. • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • If bronchoscopy is consistent with immune-mediated etiology, Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at a fixed dose. If not, permanently discontinue atezolizumab and ipatasertib/placebo and contact Medical Monitor. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume ipatasertib/placebo at current dose. • For recurrent events, treat as a Grade 3 or 4 event.

BAL = bronchoscopic alveolar lavage.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to 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.*

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus Atezolizumab Plus Paclitaxel (cont.)

Event	Action to Be Taken
Pulmonary events (cont.)	
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and ipatasertib/placebo and contact Medical Monitor. [c] • Refer patient to pulmonary and infectious disease specialists and consider Bronchoscopy or BAL. • If bronchoscopy is consistent with immune-mediated etiology *initiate treatment with corticosteroids 1−2 mg/kg/day oral prednisone or equivalent.* • If pulmonary event does not improve within 48 hours or worsens, consider adding an immunosuppressive agent. • 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 and ipatasertib/placebo. • 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 may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator and *in alignment with the protocol requirements for the duration of treatment and documented by the investigator.* The Medical Monitor *is available to advise as needed*.

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

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

[d] The LFT panel should include AST, ALT, alkaline phosphatase, and total bilirubin.

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus 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 and ipatasertib/placebo. • Monitor LFTs [d, f] every 48–72 hours until decreasing and then weekly until return to baseline. • Consider patient referral to a hepatologist e and liver biopsy. ***Suspected immune-mediated* events of > 5 days' duration:** • *Withhold* atezolizumab *for up to 12 weeks after event onset.* • *Initiate* treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If atezolizumab is withheld and event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks, resume atezolizumab at a fixed dose. If not, permanently discontinue atezolizumab and ipatasertib/placebo and contact Medical Monitor. [a, b, c]

BAL = bronchoscopic alveolar lavage; LFT = liver function test; ULN = upper limit of normal.

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

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

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

[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 judgement 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 judgement until a threshold of ALT/AST 5 × ULN.

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus 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 and ipatasertib/placebo. • Monitor LFTs d every 48–72 hours until decreasing and then weekly until return to baseline. • Consider patient referral to hepatologist e and liver biopsy. **Suspected immune-mediated events:** • Withhold atezolizumab. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks, resume atezolizumab at a fixed dose. If not, permanently discontinue atezolizumab and ipatasertib/placebo and contact Medical Monitor. a ,b, c
AST/ALT > ULN to ≤ 3 × ULN with total bilirubin > 2 × ULN	• Investigate causes for elevated bilirubin and initiate treatment as indicated per institutional guidelines. • Use best medical judgment when determining whether to continue study treatment.

LFT = liver function test; ULN = upper limit of normal.

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

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

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

[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).

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus Atezolizumab Plus Paclitaxel (cont.)

Event	Action to Be Taken
Hepatic events (cont.)	
AST/ALT > 3 × to < 10 × ULN with total bilirubin > 2× ULN	• Withhold atezolizumab and ipatasertib/placebo. • Monitor LFTs d every 48–72 hours until decreasing and then monitor weekly. • Refer patient to hepatologist e and consider liver biopsy. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 12 weeks, resume atezolizumab at a fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c] • 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 4). If not, permanently discontinue ipatasertib/placebo. • Permanently discontinue atezolizumab and ipatasertib/placebo for life-threatening hepatic events and contact the Medical Monitor.

LFT = liver function test; ULN = upper limit of normal.

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

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

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

[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).

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C
(Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Event	Action to Be Taken
Hepatic events (cont.)	
AST/ALT > 10 × ULN	• Permanently discontinue atezolizumab and ipatasertib/placebo and contact Medical Monitor. [c] • Monitor LFTs d every 48–72 hours until decreasing and then monitor weekly. • Refer patient to hepatologist e and consider liver biopsy. • Consider administering 1–2 mg/kg/day oral prednisone or equivalent. • If corticosteroids are initiated and event does not improve within 48 hours, consider adding an immunosuppressive agent or escalating the corticosteroid dose. • 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 may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *based on an assessment of benefit–risk* by the investigator *and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.* The Medical Monitor *is available to advise as needed.*

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

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

[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).

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus 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. • 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. • For the first 28-day cycle of triplet study drug combination: On days when patients will receive atezolizumab (typically, Days 1 and 15), patients should receive at least 10 mg 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 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. Timing of steroid on days when patients will receive atezolizumab and paclitaxel is at Investigator discretion, as per clinical judgement. • 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. • 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 (see Appendix 15).
Dermatologic event, Grade 1	• Consider referring patient to a dermatologist. • Continue atezolizumab and ipatasertib/placebo. • Initiate supportive care (e.g., topical corticosteroids and continue antihistamine administration). • Consider treatment with 10 mg/day oral prednisone/or equivalent.
Dermatologic event, Grade 2	• Consider referring patient to dermatologist for evaluation and perform a biopsy, if appropriate. • Continue topical corticosteroids and antihistamine administration • Consider treatment with 10 mg/day oral prednisone or equivalent; treatment with a higher steroid dose may be necessary as clinically indicated. • *If unresponsive to topical corticosteroids, consider* oral prednisone

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C
(Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

	• 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. • Atezolizumab: If steroid dose is ≤ 10 mg/day, atezolizumab should be continued.

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus Atezolizumab Plus Paclitaxel (cont.)

Event	Action to Be Taken
Dermatologic toxicity (cont.)	
Dermatologic event, Grade 3	• Withhold atezolizumab and ipatasertib/placebo. • Refer patient to dermatologist. Perform a biopsy if appropriate. • If no prior steroid treatment has been initiated, consider treatment with 10 mg/day oral prednisone or equivalent. • If prior oral steroid treatment or no improvement within 48 hours, consider, increasing prednisone or equivalent dose to 1–2 mg/kg/day. • Atezolizumab: if event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at a fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. Only restart atezolizumab (if steroid dose is ≤10 mg/day). [a, b, c] • 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 and ipatasertib/placebo and contact Medical Monitor.

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

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

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

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus Atezolizumab Plus Paclitaxel (cont.)

Event	Action to Be Taken
Neutropenia	
Grade 2	• Ipatasertib/placebo may be continued at the original dose. • Withhold the taxane until ANC has recovered to ≥1500/mL. – 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. • 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. • 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. – 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. – 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. • 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.

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus 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. – First episode: Ipatasertib/placebo and taxane should be reduced by one dose level when treatment is restarted. – Recurrent episode: Ipatasertib/placebo and taxane should be discontinued. Atezolizumab maybe continued after discussion with the Medical Monitor • 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. • If the toxicity resolves to Grade 1 or better within 2 weeks, treatment may resume with ipatasertib/placebo at the prior dose level. • 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 4. • 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.

Appendix 14
Adverse Event Management Guidelines for Patients in Cohort C (Ipatasertib Plus Atezolizumab Plus Paclitaxel) (cont.)

Table 1 Management Guidelines for Selected Adverse Events for Ipatasertib/Placebo (for Ipatasertib) Plus Atezolizumab Plus Paclitaxel (cont.)

Event	Action to Be Taken
Atezolizumab-related toxicities not described in Appendix 15	
Grade ≥ 3	• Follow guidelines for atezolizumab in Appendix 15 • Withhold ipatasertib/placebo until resolution to Grade 1. • If the toxicity resolves to Grade 1 or better within 2 weeks, treatment with ipatasertib/placebo may resume at the prior dose level. • 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 4. • 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 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-mediated event. 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. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Appendix 14.

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 14.

GASTROINTESTINAL EVENTS

Immune-mediated related colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Appendix 14.

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 14.

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

Appendix 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 1 Management Guidelines for Endocrine Events

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

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

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

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

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

Table 1 Management Guidelines for Endocrine Events (cont.)

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

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

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

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

Table 1 Management Guidelines for Endocrine Events (cont.)

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

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

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

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

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

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 2.

Table 2 Management Guidelines for Ocular Events

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

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

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

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

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

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

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

Appendix 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

INFUSION-RELATED REACTIONS AND CYTOKINE-RELEASE SYNDROME

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

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

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T-cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee et al. 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz et al. 2017; Adashek and Feldman 2019), including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in Table 4.

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

Table 4 Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome (cont.)

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

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: These management guidelines have been adapted from NCCN guidelines for management of CAR T-cell–related toxicities (Version 2.2019).

[a] Grading system for these management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature ≥ 38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by the investigator (or an appropriate delegate). The Medical Monitor *is available to advise as needed.* For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after *assessing* the benefit–risk ratio.

[f] Refer to Riegler et al. (2019).

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 5.

Appendix 15
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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: • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent. Asymptomatic with amylase and/or lipase > 2.0–5.0 × ULN: • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to* re-challenge *patients* with atezolizumab *should be based on investigator's assessment of benefit–risk and* documented by 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 for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

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

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

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

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 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. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • *If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.*
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to 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 6 Management Guidelines for Dermatologic Events (cont.)

Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to 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.*

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 7.

Table 7 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-mediated neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology *and refer patient to neurologist.* • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • *Refer patient to neurologist.* • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.

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

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

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

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 and contact Medical Monitor. [a] • Refer patient to neurologist. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

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

RENAL EVENTS

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. 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. • Monitor kidney function, including creatinine *and urine protein*, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

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

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

IMMUNE-MEDIATED MYOSITIS

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. *Patients with possible myositis should be referred to a rheumatologist*

or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 10.

Table 10 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be *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 10 Management Guidelines for Immune-Mediated Myositis (cont.)

Immune-mediatedmyositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

Table 10 Management Guidelines for Immune-Mediated Myositis (cont.)

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

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

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

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE 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 ≥ 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 $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.0 \times 10^9$/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)

- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli et al. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin >684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count ≤181 $\times 10^9$/L (181,000/μL)
  - AST ≥48 U/L
  - Triglycerides >1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in Table 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. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. • If event does not respond to treatment within 24 hours, contact Medical Monitor and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

HLH =hemophagocytic lymphohistiocytosis; MAS =macrophage activation syndrome.

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