PROTOCOL

TITLE:	**A PHASE Ib, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF IPATASERTIB IN COMBINATION WITH ATEZOLIZUMAB AND PACLITAXEL OR NAB-PACLITAXEL IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC TRIPLE-NEGATIVE BREAST CANCER**
PROTOCOL NUMBER:	CO40151
VERSION NUMBER:	6
EUDRACT NUMBER:	2017-001957-15
IND NUMBER:	133823
NCT NUMBER:	NCT03800836
TEST PRODUCTS:	Atezolizumab (RO5541267), Ipatasertib (RO5532961)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 10 June 2017
DATES AMENDED:	Version 2: 2 March 2018 Version 3: 27 July 2018 Version 4: 6 March 2019 Version 5: *25 October 2019* *Version 5 (United Kingdom): 8 February 2020* *Version 6: See electronic date stamp below.*

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
26-Jan-2021 10:40:21	Company Signatory	[redacted]

PROTOCOL AMENDMENT, VERSION 6
RATIONALE

Protocol CO40151 has primarily been amended to align the protocol with the most recent Atezolizumab Investigator's Brochure (Version 17). Changes to the protocol, along with a rationale for each change, are summarized below:

- Section 1.3 has been updated to indicate that Atezolizumab is also approved for the treatment of hepatocellular carcinoma, and melanoma.
- It has been clarified that patients will not be allowed to make up missed doses of ipatasertib and atezolizumab study drugs and should resume dosing at their next scheduled dose. If clinically possible, patients should receive 4 doses of doxorubicin and cyclophosphamide and 12 doses of weekly paclitaxel prior to surgery, as per local standard of care (Section 3.1.7).
- Two changes specifically for Cohort 3 in response to Medicines and Healthcare Products Regulatory Agency feedback in the Version 5 (United Kingdom) have also been added to the global study protocol. These two changes are as follows:
  - Text has been modified to state that live, attenuated vaccines are prohibited with cyclophosphamide treatment: Live, attenuated vaccines are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab or cyclophosphamide, and for 5 months after the last dose of atezolizumab or 3 months after the last dose of cyclophosphamide, whichever occurs later (Section 4.4.3).
  - An ECG will be assessed during screening, at each doxorubicin administration (Days 1 and 15 of Cycles 1–2), at the study completion/early terminiation visit, and as clinically indicated. Screening ECG assessments obtained $\leq$ 48 hours before Day 1 of Cycle 1 do not have to be repeated on Day 1 of Cycle 1 (Section 4.5.8 and Appendix 3).
- Section 4.5.7 has been updated to allow investigators to obtain NGS report from baseline and/or at the time of disease progression, after the patient has discontinued study treatment.
- List of identified risks for atezolizumab has been revised to include severe cutaneous adverse reactions (Section 5.1.2).
- Guidelines for management of atezolizumab-associated dermatologic adverse events have been revised to provide guidance on severe cutaneous adverse reactions of Stevens-Johnson syndrome and toxic epidermal necrolysis (Section 5.1.9.4, Table 6, and Appendix 13).
- To address a request by the French National Agency for the Safety of Medicines and Health Products (ANSM), hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS) have replaced systemic inflammatory response syndrome on the list of atezolizumab-associated adverse events of special interest (Section 5.2.3).

- Language has been added to clarify that if a patient experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF (Section 5.3.5).
- Language has been added to clarify that adverse events associated with a special situation that also qualify as adverse events of special interest should be reported within 24 hours (Section 5.3.5.12).
- Language has been updated to indicate that 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 during the adverse event reporting period (Section 5.5.1).
- The list of study records and documents to be retained by Prinicipal Investigator has been amended to include images (Section 7.5).
- A new section has been added to describe the implementation of a system to manage the quality of the study (Section 9.3).
- The name of a Roche policy on data sharing has been corrected (Section 9.6).
- It has been clarified that hematology and fasting serum chemistry laboratory assessments are not required on Days 8 and 22 during Cycles 1–2 because no chemotherapy infusions are being given on these days. Other assessments such as vital signs, weight, and assessment of adverse events, concomitant medications, and review of the patient diary are still required on Days 8 and 22 during Cycles 1–2 as indicated in the protocol. It has also been clarified that screening local laboratory assessments obtained ≤48 hours before Day 1 of Cycle 1 do not have to be repeated on Day 1 of Cycle 1 (Appendix 3).
- Appendix 11 has been revised to indicate that 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 management guidelines for Grade 1 Immune-mediated myocarditis have been removed since it is considered standard of care for patients that are suspected of presenting signs or symptoms suggestive of myocarditis (Appendix 13). The guidelines are also summarized in Section 6.7.6 of the IB.
- To address a request by the French ANSM, the management guidelines for infusion-related reactions associated with atezolizumab have been updated to include guidelines for cytokine-release syndrome (CRS) to align with the definition, grading, and management of CRS reflected in a recent publication (Lee et al. 2019) (Appendix 13).
- To address a request by the French ANSM, the management guidelines for HLH and MAS have been modified to indicate that HLH should be considered when CRS presentation is atypical or prolonged, to add anticytokine therapy as an option for treating HLH or MAS, and to suggest that published guidelines should be followed for HLH or MAS events that do not respond to treatment within 24 hours (Appendix 13).

- Language has been added to clarify that hemophagocytic lymphohistiocytosis and macrophage activation syndrome are considered potential risks for atezolizumab (Appendix 13).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE Ib, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF IPATASERTIB IN COMBINATION WITH ATEZOLIZUMAB AND PACLITAXEL OR NAB-PACLITAXEL IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC TRIPLE-NEGATIVE BREAST CANCER**
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SPONSOR:	F. Hoffmann-La Roche Ltd

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

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form to the Sponsor or their designee.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE Ib, OPEN-LABEL, MULTICENTER STUDY EVALUATING THE SAFETY AND EFFICACY OF IPATASERTIB IN COMBINATION WITH ATEZOLIZUMAB AND PACLITAXEL OR NAB-PACLITAXEL IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC TRIPLE-NEGATIVE BREAST CANCER**
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TEST PRODUCTS:	Atezolizumab (RO5541267), Ipatasertib (RO5532961)
PHASE:	Phase Ib
INDICATION:	Metastatic triple-negative breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

Specific objectives and corresponding endpoints are outlined below (see Tables 1a–1c) for the following cohorts:

- Cohort 1: patients with locally advanced or metastatic triple-negative breast cancer (TNBC) that is not amenable to resection who have not previously received chemotherapy in the advanced setting
- Cohort 2: patients with locally advanced or metastatic TNBC that is not amenable to resection who have received no more than two lines of prior systemic chemotherapy and are willing to undergo serial biopsies (biopsy cohort)
- Cohort 3: patients with locally advanced cT2–4 cN0–3 cM0 TNBC (hereafter referred to as T2–4 TNBC)
- Cohort 4: patients with PD-L1–positive locally advanced or metastatic TNBC that is not amenable to resection who have not previously received chemotherapy in the advanced setting

Patients from Cohort 4 will be pooled with patients from Cohort 1 with PD-L1–positive tumors to investigate treatment effect in patients with PD-L1–positive TNBC.

Table 1a Objectives and Corresponding Endpoints for Cohorts 1 and 4

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of Ipat + Atezo combined with either paclitaxel (Cohorts 1 and 4) or nab-paclitaxel (Cohort 1 only) in all patients regardless of PD-L1 status (Cohort 1 only) or in patients with PD-L1–positive tumors only (Cohorts 1 and 4)	• ORR, defined as the proportion of patients with a confirmed complete response or partial response on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1 (primary endpoint) • DOR, defined as the time from the first occurrence of a documented confirmed complete response or partial response to the first date of recorded disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause (whichever occurs first) (secondary endpoint)
Primary Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of Ipat + Atezo combined with either paclitaxel (Cohorts 1 and 4) or nab-paclitaxel (Cohort 1 only)) in all patients regardless of PD-L1 status (Cohort 1 only) or in patients with PD-L1–positive tumors only (Cohorts 1 and 4)	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in targeted clinical laboratory test results
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of Ipat + Atezo combined with either paclitaxel (Cohorts 1 and 4) or nab-paclitaxel (Cohort 1 only)) in all patients regardless of PD-L1 status (Cohort 1 only) or in patients with PD-L1–positive tumors only (Cohorts 1 and 4)	• PFS, defined as the time from enrollment to the date of the first recorded occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause (whichever occurs first) • CBR, defined as proportion of patients with stable disease for at least 24 weeks or with confirmed complete or partial response, as determined by the investigator according to RECIST v1.1 • OS, defined as the time from enrollment to death from any cause

Note: Patients from Cohort 4 will be pooled with patients from Cohort 1 with PD-L1–positive tumors to investigate treatment effect in patients with PD-L1–positive TNBC.

ADA = anti-drug antibody; CBR = clinical benefit rate; DOR = duration of response; nab-paclitaxel = nanoparticle albumin-bound paclitaxel; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Table 1a Objectives and Corresponding Endpoints for Cohorts 1 and 4 (cont.)

Pharmacokinetic Objective	Corresponding Endpoint
• To characterize the pharmacokinetics of ipatasertib and its metabolite (G-037720) and atezolizumab when administered in combination with paclitaxel (Cohorts 1 and 4) or nab-paclitaxel (Cohort 1 only)) in all patients regardless of PD-L1 status (Cohort 1 only) or in patients with PD-L1–positive tumors only (Cohorts 1 and 4)	• Plasma concentration of ipatasertib, G-037720, and atezolizumab at specified timepoints for analysis using non-compartment methodology or population PK methodology
Exploratory Pharmacokinetic Objectives	Corresponding Endpoints
• To evaluate potential relationships between ipatasertib exposure and safety and efficacy endpoints	• Relationship between ipatasertib plasma concentration and safety and efficacy endpoints
Immunogenicity Objective	Corresponding Endpoint
• To evaluate the immune response to Ipat + Atezo combined with either paclitaxel (Cohorts 1 and 4) or nab-paclitaxel (Cohort 1 only)) in all patients regardless of PD-L1 status (Cohort 1 only) or in patients with PD-L1–positive tumors only (Cohorts 1 and 4)	• Presence of ADAs during the study relative to the presence of ADAs at baseline
Exploratory Immunogenicity Objective	Corresponding Endpoint
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	Corresponding Endpoints
• To identify biomarkers that are predictive of response to study treatment (i.e., predictive biomarkers) or are associated with progression to a more severe disease state (i.e., prognostic biomarkers) • To assess the mechanisms of intrinsic and acquired resistances	• Relationship between biomarkers in blood and tumor tissue and efficacy • Changes in molecular biomarkers in pretreatment and post-progression tumor tissues, plasma, and blood

Note: Patients from Cohort 4 will be pooled with patients from Cohort 1 with PD-L1–positive tumors to investigate treatment effect in patients with PD-L1–positive TNBC.

ADA = anti-drug antibody; CBR = clinical benefit rate; DOR = duration of response; nab-paclitaxel = nanoparticle albumin-bound paclitaxel; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Table 1b Objectives and Corresponding Endpoints for Cohort 2 (Biopsy)

Exploratory Biomarker Objectives	Corresponding Endpoints
• To evaluate the pharmacodynamic effects of ipatasertib and Ipat + Atezo in tumor cells and on the tumor microenvironment • To identify biomarkers that are predictive of response to study treatment (i.e., predictive biomarkers) or are associated with progression to a more severe disease state (i.e., prognostic biomarkers) • To assess the mechanisms of intrinsic and acquired resistances	• Changes in markers of immune cell infiltration and activity as well as in pretreatment and on-treatment tumor tissues • Change in circulating immune cell repertoires • Changes in molecular biomarkers in pretreatment and on-treatment tumor tissues • Relationship between biomarkers in blood and tumor tissue and efficacy • Changes in molecular biomarkers in pretreatment and post-progression tumor tissues, plasma, and blood
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To evaluate the anti-tumor activity of Ipat + Atezo as 2L/3L treatment in patients with TNBC and in patients with TNBC who have *PIK3CA/AKT1/PTEN*-altered tumors	The following endpoints will be evaluated using RECIST v1.1: • ORR • DOR • CBR • PFS • OS
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of Ipat + Atezo in patients in Cohort 2 (i.e., biopsy cohort)	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in targeted clinical laboratory test results

2L = second line; 3L = third line; Atezo = atezolizumab; CBR = clinical benefit rate; DOR = duration of response; Ipat = ipatasertib; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; TNBC = triple-negative breast cancer.

Table 1c Objectives and Corresponding Endpoints for Cohort 3

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of neoadjuvant Ipat + Atezo + AC followed by Ipat + Atezo + Pac	• pCR rate, defined as the proportion of patients who have no residual invasive disease in the breast and no residual disease in the lymph nodes (ypT0/Tis ypN0 in the current AJCC staging system)
Primary Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of neoadjuvant Ipat + Atezo + AC followed by Ipat + Atezo + Pac	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in targeted clinical laboratory test results

Table 1c Objectives and Corresponding Endpoints for Cohort 3 (cont.)

Exploratory Pharmacokinetic Objective	Corresponding Endpoint
• To characterize the pharmacokinetics of ipatasertib and its metabolite (G-037720) and atezolizumab when administered in combination with paclitaxel or AC	• Plasma concentration of ipatasertib and G-037720 at specified timepoints • Serum concentration of atezolizumab at specified timepoints
Exploratory Immunogenicity Objectives	Corresponding Endpoints
• To evaluate the immune response to atezolizumab	• Incidence of ADAs to atezolizumab during the study and prevalence of ADAs to atezolizumab at baseline
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	Corresponding Endpoint
• To identify and/or evaluate biomarkers that are predictive of response to study treatment (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to study treatment, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety	• Relationship between biomarkers in blood, plasma, and tumor tissue and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

AC = doxorubicin plus cyclophosphamide; ADA = anti-drug antibody; AJCC = American Joint Committee on Cancer; Atezo = atezolizumab; EFS = event-free survival; Ipat = ipatasertib; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; Pac = paclitaxel; pCR = pathologic complete response; PK = pharmacokinetic.

Study Design

Description of Study

This is a Phase Ib, open-label, multicenter study consisting of four cohorts. In Cohort 1, the safety and efficacy of ipatasertib + atezolizumab + paclitaxel (Ipat + Atezo + Pac) and ipatasertib + atezolizumab + nab-paclitaxel (Ipat + Atezo + Nab-Pac) will be evaluated in patients with locally advanced or metastatic TNBC who have not previously received chemotherapy in the advanced setting. In Cohort 2 (biopsy cohort), Ipat + Atezo (with no chemotherapy) will be administered in the second-line and third-line setting to patients with locally advanced or metastatic TNBC for the main purpose of conducting exploratory biomarker assessments. In Cohort 3, the safety and efficacy of neoadjuvant ipatasertib + atezolizumab + doxorubicin + cyclophosphamide (Ipat + Atezo + AC) followed by Ipat + Atezo + Pac will be evaluated in patients with locally advanced T2–4 TNBC. In Cohort 4, the safety and efficacy of Ipat + Atezo + Pac will be evaluated in patients with PD-L1–positive locally advanced or metastatic TNBC who have not previously received chemotherapy in the advanced setting.

There is a known and acceptable safety profile of ipatasertib with paclitaxel and atezolizumab with paclitaxel or nab-paclitaxel. If an unexpected safety signal is detected at any time, doublet

safety of ipatasertib with atezolizumab may be further evaluated. The safety and efficacy of the combination of ipatasertib with atezolizumab is being assessed both in Cohort 2 of this trial and separately (i.e., in Study CO39611 for HR-positive/HER2-negative metastatic breast cancer and Study CO40115 for TNBC).

Up to 25 sites in North America, Europe, and the Asia Pacific will enroll approximately 202 patients (114 patients in Cohort 1, 14 patients in Cohort 2, 24 patients in Cohort 3, and 50 patients in Cohort 4).

Number of Patients

Approximately 178 patients with locally advanced or metastatic TNBC that is not amenable to resection and approximately 24 patients with locally advanced T2–4 TNBC are expected to be enrolled in this study.

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 (absolute neutrophil count [ANC] ≥ 1500/μL) (Cohort 3 patients should meet this criterion without granulocyte colony–stimulating factor support within the preceding 2 weeks)
  - For Cohort 3: lymphocyte count ≥ 500/μL
  - Hemoglobin ≥ 9 g/dL (Cohort 3 patients should meet this criterion in the absence of any transfusion within the preceding 2 weeks)
  - Platelet count ≥ 100,000/μL (Cohort 3 patients should meet this criterion in the absence of any transfusion within the preceding 2 weeks)
  - Serum albumin ≥ 3 g/dL
  - Total bilirubin ≤ 1.5 × the upper limit of normal (ULN) (Cohorts 1, 2, and 4) or total bilirubin ≤1.0 ×ULN (Cohort 3), 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:

    Cohort 1, 2, and 4 patients with documented liver or bone metastases may have AST and ALT ≤ 5 × ULN.
  - ALP ≤ 2 × ULN, with the following exceptions:

    Cohort 1, 2, and 4 patients with known liver involvement may have ALP ≤5 × ULN

    Cohort 1, 2, and 4 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.

- 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 serum glucose ≤ 150 mg/dL and glycosylated hemoglobin $\leq 7.5\%$

- For Cohorts 1, 2, and 4: life expectancy of at least 6 months
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 1 month after the last dose of ipatasertib, 5 months after the last dose of atezolizumab, 6 months after the last dose of paclitaxel, nab-paclitaxel, or doxorubicin, and 12 months after the last dose of cyclophosphamide, whichever occurs later. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  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; 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: consider conserving sperm before treatment because of possible irreversible infertility due to therapy with paclitaxel, 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 1 month after the last dose of ipatasertib or 6 months after the last dose of paclitaxel, nab-paclitaxel, cyclophosphamide, or doxorubicin, 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 1 month after the last dose of ipatasertib or 6 months after the last dose of paclitaxel, nab-paclitaxel, cyclophosphamide, or doxorubicin, 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, 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.

Disease-Specific Inclusion Criteria

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

- For Cohorts 1, 2, and 4: histologically documented TNBC (negative HER2, ER, and PgR status) 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 (non–fine-needle aspiration [FNA] sample) as assessed locally (or centrally, if not available locally) according to the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines
- For Cohort 2: disease progression following one or two lines of systemic therapy for inoperable locally advanced or metastatic TNBC
  - Patients may have received prior neoadjuvant or adjuvant chemotherapy and/or radiation treatment for early stage breast cancer, provided all chemotherapy was completed $\geq$12 months prior to Day 1 of Cycle 1.
- For Cohorts 1, 2, and 4: measurable disease according to RECIST v1.1
- For Cohort 2: Treated brain or spinal cord metastases are allowed if patients have stable disease and are not on steroid treatment.
- For Cohort 3: histologically documented TNBC (negative HER2, ER, and PgR status) that meets both of the following criteria:
  - Primary breast tumor size of $>$2 cm by at least one radiographic or clinical measurement
  - Disease stage at presentation of cT2–4 cN0–3 cM0

    Note: Receptor status at study entry should correspond to the evaluation of the most recent biopsy (non-FNA sample) as assessed locally (or centrally, if not available locally) according to the ASCO/CAP guidelines. Patients with multifocal tumors (more than one tumor confined to the same quadrant as the primary tumor) are eligible provided all discrete lesions have been biopsied and centrally confirmed as TNBC.
- For Cohort 3: patient agreement to undergo appropriate surgical management, including axillary lymph node surgery and partial or total mastectomy, after completion of neoadjuvant treatment
- Submission of a formalin-fixed, paraffin-embedded tumor (FFPE) tissue block or a minimum of 20 (for Cohorts 1 and 2) or 15 (for Cohorts 3 and 4) freshly cut unstained, serial tumor slides from the most recently collected tumor tissue for central analysis of PD-L1 status to determine eligibility for Cohort 4 and for central molecular analysis (retrospective next generation sequencing [NGS] testing for *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.

- For Cohorts 1, 2, and 4: If a more recent 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 if the patient is willing to consent to and undergo an additional pretreatment core or excisional biopsy of a non-target lesion (a non-target lesion is preferred if it is assessable and the biopsy can be safely obtained). In general, a minimum of three core biopsies for NGS testing are required.
- For Cohort 3: If the specimen is either insufficient or unavailable, the patient may still be eligible if the patient is willing to undergo an additional pretreatment core biopsy. In general, a minimum of three core biopsies for NGS testing are required.
- For Cohort 4: Patients must have a PD-L1–positive tumor (defined as $\geq$ 1% expressing tumor-infiltrating immune cells [%ICs] evaluated as proportion of tumor area) as determined by central testing prior to enrollment.

  If multiple tumor specimens are submitted (e.g., an archival specimen and tissue from relapsed disease), patients may be eligible if at least one specimen is evaluable for PD-L1. The PD-L1 score for each patient will be the maximum PD-L1 score among the samples.

  If a patient already has results based on the commercial FoundationOne® CDx assay by Foundation Medicine, 10 freshly cut unstained, serial tumor slides from the most recently collected tumor tissue are acceptable for central molecular analysis (as described above), upon confirmation by the Medical Monitor.

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 antibiotics
- History of or current evidence of 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 total hepatitis B core antibody test, accompanied by a negative HBV DNA test) are eligible.
  - Patients positive for HCV antibody are eligible only if polymerase chain reaction 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 (other than anticipated breast surgery for Cohort 3) 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 1 month after the last dose of ipatasertib, 5 months after the last dose of atezolizumab, 6 months after the last dose of paclitaxel, nab-paclitaxel, or doxorubicin, or 12 months after the last dose of cyclophosphamide, 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 within 48 hours prior to initiation of study treatment.
- New York Heart Association (NYHA) 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 $>$ 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
- Treatment with approved or investigational cancer therapy within 14 days prior to Day 1 of Cycle 1
- Prior treatment with an Akt inhibitor
  - Note that prior PI3K or mechanistic target of rapamycin inhibitors are allowed
- 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 for Cohorts 1, 2, and 4

For Cohorts 1, 2, and 4, patients who meet any of the following disease-specific criteria will be excluded from study entry:

- Patients with leptomeningeal carcinomatosis
- For Cohorts 1 and 4 only: history of or known presence of brain or spinal cord metastases
- For Cohorts 1 and 4: previous systemic therapy for inoperable locally advanced or metastatic TNBC, including chemotherapy, immune checkpoint inhibitors, or targeted agents
  - Patients in Cohorts 1 and 4 may have received prior neoadjuvant or adjuvant chemotherapy and/or radiation treatment for early stage breast cancer, provided all chemotherapy was completed $\geq$ 12 months prior to Day 1 of Cycle 1.
- 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
- 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 (i.e., stable in the 14 days before Day 1 of Cycle 1).
  - Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation (Grade 1 or better) 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., bone metastasis) should be considered for loco-regional therapy if appropriate prior to enrollment.

- 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

Exclusion Criteria for Cohort 3

For Cohort 3, patients who meet any of the following criteria will be excluded from study entry:

- Prior history of invasive breast cancer
- Prior systemic therapy for treatment and/or prevention of invasive breast cancer
- Previous therapy with anthracyclines or taxanes for any malignancy
- Bilateral breast cancer
- Undergone incisional and/or excisional biopsy of primary tumor and/or axillary lymph nodes with one exception:
  - Patients who have undergone sentinel lymph node biopsy (SLNB) prior to initiation of neoadjuvant therapy (as per local practice) may be eligible if the SLNB is free of invasive carcinoma. However, any patient with a positive SLNB result (involved with invasive carcinoma) is ineligible to participate in this study.
- Undergone axillary lymph node dissection prior to initiation of neoadjuvant therapy
- History of other malignancy within 5 years prior to screening, with the exception of those with a negligible risk of metastasis or death (e.g., 5-year overall survival > 90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, or Stage I uterine cancer
- History of cerebrovascular accident within 12 months prior to initiation of study treatment
- Cardiopulmonary dysfunction as defined by any of the following prior to initiation of study treatment:
  - History of Common Terminology Criteria for Adverse Events, Version 4.0, Grade ≥ 3 symptomatic congestive heart failure, NYHA Class II, III, or IV heart failure, or left ventricular ejection fraction < 53%
  - Angina pectoris requiring anti-anginal medication, serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality, or clinically significant valvular disease
  - High-risk uncontrolled arrhythmias (e.g., atrial tachycardia with a heart rate > 100 beats per minute at rest, significant ventricular arrhythmia [ventricular tachycardia], or second- or third-degree atrioventricular block)
  - Significant symptoms (Grade ≥ 2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia
  - Myocardial infarction within 12 months prior to initiation of study treatment
  - Uncontrolled hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 100 mmHg)
  - Evidence of transmural infarction on ECG
  - Requirement for oxygen therapy
- Known allergy or hypersensitivity to the components of cyclophosphamide or doxorubicin formulations
- Known allergy or hypersensitivity to filgrastim or pegfilgrastim formulations

- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment
  - Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
- Prior treatment with CD137 agonists or immune checkpoint–blockade therapies, including anti-CD40, anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications

Ipatasertib-Specific Exclusion Criteria

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

- History of Type I or Type II diabetes mellitus requiring insulin
  - Patients who are on a stable dose of oral diabetes medication ≥ 2 weeks prior to initiation of study treatment are eligible for enrollment.
- Grade ≥ 2 uncontrolled or untreated hypercholesterolemia or hypertriglyceridemia
- History of or active inflammatory bowel disease (e.g., Crohn'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 treatment

Atezolizumab-Specific Exclusion Criteria

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

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

  Patients with a history of autoimmune-related hypothyroidism who are on 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 computed tomography 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.

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

End of Study

The study will end when the last data point required for statistical analysis is collected and safety follow-up is completed, or the Sponsor decides to end the trial, whichever occurs first.

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3–5 years.

Investigational Medicinal Products

Test Product (Investigational Drugs)

The investigational medicinal products for this study are ipatasertib, atezolizumab, paclitaxel, nab-paclitaxel, doxorubicin, and cyclophosphamide. Ipatasertib is to be administered before atezolizumab and chemotherapy. Atezolizumab is to be administered before chemotherapy.

Ipatasertib

In Cohort 1, ipatasertib will be administered at the starting dose of 400 mg orally once a day (QD), beginning on Cycle 1, on Days 1–21 of each 28-day cycle (in Arms A, B, and C), until the patient experiences disease progression, intolerable toxicity, or withdraws consent. In Arm D, ipatasertib will be administered at the starting dose of 400 mg orally QD on Days 15–21 of the first cycle. In all subsequent treatment cycles (Cycles $\geq$2), ipatasertib 400 mg will be

administered orally QD on Days 1–21 until the patient experiences disease progression, intolerable toxicity, or withdraws consent.

In Cohort 2, ipatasertib 400 mg will be administered orally QD on Days 1–28 of Cycle 1 (35-day cycle) and on Days 1–21 of subsequent cycles (28-day cycles).

In Arm F of Cohort 3, ipatasertib will be administered orally QD at a dose of 300 mg on Days 1–21 of Cycles 1 and 2 and at a dose of 400 mg on Days 1–21 of Cycles 3–5. In Arm G of Cohort 3, ipatasertib will be administered orally QD at a dose of 400 mg on Days 1–21 of Cycles 1–5.

In Cohort 4, ipatasertib 400 mg will be administered orally QD on Days 1–21 of each 28-day cycle.

Atezolizumab

In Cohort 1, patients will receive atezolizumab 840 mg administered by IV infusion every 2 weeks (on Days 1 and 15) of each 28-day cycle (in Arms A, B, and D). In Arm C, atezolizumab 840 mg will be administered by IV infusion on Day 15 of the first cycle. In all subsequent treatment cycles (Cycles ≥ 2) atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle.

In Cohort 2, atezolizumab 840 mg will be administered by IV infusion on Days 8 and 22 of Cycle 1 (35-day cycle) and on Days 1 and 15 of subsequent cycles (28-day cycles).

In Cohort 3, atezolizumab 840 mg will be administered by IV infusion on Days 1 and 15 of Cycles 1–5 (28-day cycles).

In Cohort 4, atezolizumab 840 mg will be administered by IV infusion on Days 1 and 15 of each 28-day cycle.

Chemotherapy

In Cohorts 1 and 4, the dose of paclitaxel is 80 mg/m^2 administered by IV infusion on Days 1, 8, and 15 of each 28-day cycle. Nab-paclitaxel will be administered by IV infusion at a starting dose of 100 mg/m^2 on Days 1, 8, and 15 of every 28-day cycle.

In Cohort 3, doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 will be administered by IV infusion on Days 1 and 15 of Cycles 1 and 2. Paclitaxel 80 mg/m^2 will be administered by IV infusion on Days 1, 8, 15, and 22 of Cycles 3–5.

Non-Investigational Medicinal Products

Because of the known potential for allergic reactions to paclitaxel and/or the Cremophor® vehicle, precautions must be taken to decrease the risk of anaphylaxis. Patients must be premedicated prior to paclitaxel with dexamethasone, diphenhydramine, and an 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.

In general, chemotherapy supportive care should be administered per ASCO, European Organisation for Research and Treatment of Cancer, or European Society for Medical Oncology guidelines or institutional practice. In Cohort 3, filgrastim or pegfilgrastim must be used in conjunction with each AC administration. Chemotherapy-induced nausea and vomiting prophylaxis and treatment should be administered as clinically indicated. It is highly recommended that aprepitant be included as premedication for AC to prevent nausea and/or vomiting. Because systemic corticosteroids may attenuate the potential beneficial immunologic effects of treatment with atezolizumab, alternative agents should be considered when clinically feasible.

To improve diarrhea management and patient experiences, loperamide (2 mg twice a day) will be administered daily as prophylaxis for diarrhea in the first cycle. If side effects are not tolerated, doses may be reduced. Investigators are encouraged to continue this dosing for the remainder of the study using their discretion based on clinical judgments.

Because of the risk of rash, patients should receive the following prophylactic treatment, unless contraindicated, during the first cycle in which all three study treatments (ipatasertib, atezolizumab, and taxane) are to be given in Cohorts 1 and 4 or during the first 28 days (i.e., Weeks 1–4) in which all four study treatments (ipatasertib, atezolizumab, and AC) are to be given in Cohort 3: On days when patients will receive atezolizumab, patients should receive at least 10 mg/day prednisone (or equivalent) as premedication, followed by a fixed dose of

10 mg/day prednisone (or equivalent) for 2–4 consecutive days thereafter. The timing of corticosteroid administration on days when patients will receive atezolizumab and paclitaxel will be determined by the investigator according to best medical judgment. In addition, patients should receive daily oral antihistamine for at least the first cycle in which all three treatments (four treatments for Cohort 3) are to be given. It is suggested that a non-sedating oral antihistamine (such as loratadine, cetirizine, or fexofenadine) and a longer-acting formulation be used. Protocol-required premedication should be omitted on the day of paclitaxel infusion if already administered as taxane premedication per institutional practice.

Statistical Methods

Primary Analysis

Objective Response Rate

Objective response rate (ORR) is defined as the proportion of patients with a confirmed complete response or partial response on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1. Patients without a postbaseline tumor assessment will be considered as non-responders. ORR is defined as the proportion of patients who have an objective response; an estimate of ORR will be calculated for each treatment arm, and its 95% CI will be calculated using the Clopper–Pearson method.

Duration of Response

Duration of response (DOR) will be analyzed to support ORR. DOR is defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first. Patients who have not progressed or died at the time of analysis will be censored at the last disease assessment date.

Determination of Sample Size

There is no formal hypothesis testing planned. The determination of sample size for each cohort is described below.

Cohorts 1 and 3: Safety Run-In Stage

In Cohorts 1 and 3, the number of patients enrolled during the safety run-in stage ($n = 6$) in each arm (i.e., A1, B1, C1, D1, F1, and G1) allows for a reasonable likelihood of observing a given adverse event in at least 1 patient even when the incidence of the specific adverse event is low

Cohort 1: Expansion Stage

No formal statistical hypothesis testing is planned in this study. Instead, the analysis here is for hypothesis generation, and the emphasis is on estimations. To evaluate the primary endpoint of overall response rate for Cohort 1, for each arm, the analyses will be based on combining patients enrolled in the safety run-in and expansion stages, which is approximately 20 patients (Cohort 1, Arms A and B) or 12 patients (Cohort 1, Arms C and D). Twenty patients provide reasonably reliable estimates for hypothesis generation in the expansion stage in Arms A and B. Twelve patients will provide reasonably reliable estimates for hypothesis generation in the expansion stage in Arms C and D.

Cohort 2: Biopsy

If there is sufficient evidence of meaningful benefit from the combination of ipatasertib and atezolizumab with taxane in Cohort 1, (e.g., ORR $\geq$ 50%), the Sponsor may decide to open enrollment of a separate mandatory on-treatment biopsy cohort to evaluate biomarker endpoints of patients treated with ipatasertib combined with atezolizumab to further understand the molecular basis of treatment benefit. To provide a reliable estimate of the effects of ipatasertib and ipatasertib + atezolizumab on immune cell infiltration and activation, as well as molecular tumor biomarkers and circulating immune cell repertoires, a total of up to 14 patients will be enrolled in this cohort for exploratory analyses.

Cohort 3: Expansion Stage

No formal statistical hypothesis testing is planned in this study. Instead, the analysis here is for hypothesis generation, and the emphasis is on estimations. To evaluate the primary efficacy endpoint of pCR for Cohort 3, for each arm, the analyses will be based on combining patients enrolled in the safety run-in stage ($n = 6$) and expansion stage ($n = 6$ or 12, as determined by the Sponsor) for a total of either 12 patients or 18 patients. The minimum sample size, 12 patients, will provide reasonably reliable estimates for hypothesis generation in the expansion stage in Arms F and G. Any additional patients will strengthen the evidence by reducing estimate uncertainty.

Cohort 4

No formal statistical hypothesis testing is planned in this study. Patients from Cohort 4 (approximately 50 patients with PD-L1–positive tumors) will be pooled with approximately 40 patients with PD-L1–positive tumors in Cohort 1. The total sample size for this pooled analysis is expected to be approximately 90 patients, which will provide a reasonably reliable estimate for the ORR in the PD-L1–positive population compared with historical data in this population.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADA	anti-drug antibody
Akt	protein kinase B
ALND	axillary lymph node dissection
ASCO	American Society of Clinical Oncology
CAP	College of American Pathologists
CBR	clinical benefit rate
CIT	cancer immunotherapy
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DOR	duration of response
EBC	early breast cancer
EC	Ethics Committee
ECHO	echocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
EORTC	European Organisation for Research and Treatment of Cancer
ER	estrogen receptor
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded tumor
FMI	Foundation Medicine, Inc.
FNA	fine-needle aspiration
G-CSF	granulocyte colony–stimulating factor
HbA_{1c}	glycosylated hemoglobin
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HLH	*hemophagocytic lymphohistiocytosis*
HR	hormone receptor
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation

Abbreviation	Definition
IMP	investigational medicinal product
IND	Investigational New Drug (application)
IRR	infusion-related reaction
IRB	Institutional Review Board
ITT	intent-to-treat (population)
LVEF	left ventricular ejection fraction
MAS	*macrophage activation syndrome*
MBC	metastatic breast cancer
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition (scan)
nab-paclitaxel	nanoparticle albumin-bound–paclitaxel
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGS	next-generation sequencing
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
pCR	pathologic complete response
PFS	progression-free survival
PI3K	phosphoinositide 3-kinase
PI3K/Akt	phosphoinositide 3-kinase/protein kinase B
PIK3CA	phosphatidylinositol-4, 5–bisphosphate 3-kinase, catalytic subunit, alpha
PgR	progesterone receptor
PK	pharmacokinetic
popPK	population PK
PRO	patient-reported outcome
PTEN	phosphatase and tensin homolog
Q2W	every 2 weeks
Q3W	every 3 weeks
QD	once a day
QTcF	QT interval corrected using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RBR	Research Biosample Repository
sb-paclitaxel	solvent based
SLNB	sentinel lymph node biopsy
T3	triiodothyronine

Abbreviation	Definition
TNBC	triple-negative breast cancer
TNF-α	tumor necrosis factor–α
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON TRIPLE-NEGATIVE BREAST CANCER

Globally, breast cancer is the second most common invasive malignancy and the most common cause of cancer-related mortality in women, with a 5-year survival rate following metastatic diagnosis of approximately 15% (Jemal et al. 2011; Ferlay et al. 2015).

Triple-negative breast cancer (TNBC) accounts for approximately 20% of all breast cancers and is defined by the absence of immunostaining for estrogen receptor (ER), progesterone receptor (PgR), and non-amplified HER2 expression (per American Society of Clinical Oncology [ASCO] /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). There is a pressing need for clinically active agents for the triple-negative subtype of metastatic breast cancer (MBC).

Both National Comprehensive Cancer Network (NCCN; 2017) and the European Society for Medical Oncology (ESMO; 2016) (clinical practice guidelines cite paclitaxel as 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). The response rates for paclitaxel administered as a single agent to patients with MBC are approximately 25% in first-line treatment (Wilson et al. 1994; Seidman et al. 1995; Nabholtz et al. 1996; Gradishar et al. 2005).

Nanoparticle albumin-bound (nab)-paclitaxel is an albumin-bound formulation of paclitaxel that was developed to avoid the toxicities associated with the vehicles that are necessary for parenteral administration of solvent-based (sb)-paclitaxel (polyethylated castor oil and polysorbate 80). Nab-paclitaxel can be administered without steroid or antihistamine premedication. Based on the results of the randomized Phase III study in which patients received either nab-paclitaxel or sb-paclitaxel (control) administered every 3 weeks (Q3W) ($n = 460$; Gradishar et al. 2005), nab-paclitaxel was approved for the treatment of MBC after failure of front-line combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Although it is not labeled for use in the front-line metastatic setting, NCCN and ESMO clinical practice guidelines include nab-paclitaxel as a standard of care that may be administered as a single agent to patients with recurrent or metastatic breast cancer (Cardoso et al. 2017; NCCN 2017).

Early-stage TNBC accounts for 10%–20% of all new diagnoses of early breast cancer (EBC), defined as Stages I–III (Lehmann et al. 2011; Howlader et al. 2016). Three-year event-free survival (EFS) rates of 74%–76% have been reported for patients with TNBC who have received neoadjuvant anthracycline- and taxane-containing therapy (Sikov et al. 2016). Upon relapse, patients with metastatic TNBC have poor outcomes, with rapid progression and decreased OS (Kassam et al. 2009).

Multi-agent chemotherapy regimens have proven benefit as neoadjuvant or adjuvant therapy for early-stage TNBC, improving both disease-specific and OS outcomes (Berry et al. 2006; Senkus et al. 2015; NCCN 2016). It is currently recommended that chemotherapy be given preoperatively (neoadjuvant) or postoperatively (adjuvant) to reduce the risk of relapse in patients with early-stage TNBC.

The most effective chemotherapy combinations used for early-stage TNBC include anthracyclines, topoisomerase II inhibitors, platinum agents, cyclophosphamide, and/or taxanes (Early Breast Cancer Trialists' Collaborative Group 2005; Peto et al. 2012). Studies looking at optimizing the dose and schedule of EBC chemotherapy regimens (Citron et al. 2003; Sparano et al. 2008; Budd et al. 2015) have established one of the optimal regimens with respect to maximizing efficacy as doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 administered every 2 weeks (Q2W) for four cycles, followed by paclitaxel 80 mg/m^2 administered once a week for 12 weeks. This regimen is included as a preferred option in international guidelines (Senkus et al. 2015; NCCN 2016).

However, despite having received standard anthracycline- or taxane-based therapy, approximately 30%–40% of patients with clinically localized TNBC at diagnosis develop metastatic disease and die of the cancer (Haffty et al. 2006; Tan et al. 2008; Budd et al. 2015). Thus, there is a substantial need to improve long-term treatment outcomes for patients with early-stage TNBC.

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 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 (Cancer Genome Atlas Network 2012).

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 adenosine triphosphate competitive. Ipatasertib binding inhibits the kinase activity of Akt and suppresses the phosphorylation of its direct substrates, including PRAS40, and additional downstream targets, such as S6 ribosomal protein, resulting in G_1 arrest and/or apoptosis in human cancer cells (Lin et al. 2012). In clinical tumor samples, robust Akt pathway inhibition by ipatasertib can be achieved at clinically relevant doses (Yan et al. 2013).

Up-regulation 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 (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-negative breast cancer (Study PAM4983g, Arm C), a randomized Phase II study (Study GO29227, LOTUS) comparing ipatasertib + paclitaxel versus placebo + paclitaxel as first-line treatment for patients with inoperable locally advanced or metastatic TNBC, and a randomized Phase II study (FAIRLANE) comparing neoadjuvant ipatasertib + paclitaxel versus placebo + paclitaxel in patients with early TNBC (defined as T $\geq$ 1.5 cm, N0–2).

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

In the Phase II FAIRLANE study, pathologic complete response (pCR) rate, defined as ypT0/Tis ypN0, following administration of ipatasertib+paclitaxel versus placebo+paclitaxel was 17% versus 13%, respectively, in the ITT population (n=151) and 18% versus 12%, respectively, in the *PIK3CA/AKT1/PTEN*-altered population (n=62). Complete response rate following administration of ipatasertib+paclitaxel versus placebo+paclitaxel was 28% versus 13%, respectively, in the ITT population and 39% versus 9%, respectively, in the *PIK3CA/AKT1/PTEN*-altered population.

Common adverse events associated with ipatasertib include nausea, vomiting, diarrhea, stomatitis/mucosal inflammation, asthenia, hyperglycemia, and rash. No new safety findings were identified with the combination with paclitaxel. For benefit–risk assessments of study treatments, refer to Section 1.4.

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 IgG1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). Atezolizumab has minimal binding to 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 patients with cancer 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 for the treatment of urothelial carcinoma, non–small cell lung cancer, small-cell lung cancer, TNBC*, hepatocellular carcinoma, and melanoma*.

In metastatic TNBC, combination treatment with nab-paclitaxel showed promising activity in the Phase 1b study GP28328. Arm F (atezolizumab 800 mg IV Q2W + nab-paclitaxel 125 mg/m^2 21-day on/7-day off dosing schedule) of the six treatment arms in this Phase Ib study evaluated preliminary anti-tumor activity of patients with metastatic TNBC. As of the clinical cut-off date of 14 January 2016, 32 patients with metastatic TNBC across various lines of therapy were evaluable for efficacy: first line = 13 patients; second line = 9 patients, third line + = 10 patients. Overall, the investigator-assessed objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) was 37.5% (confirmed responses). Clinical benefit was observed across all lines of therapy, with first-line and third-line + patients having ORRs that were comparable (46.2% and 40.0%, respectively). The one complete response of the 12 responders was in first-line therapy.

Atezolizumab in combination with chemotherapeutic regimens, including anthracyclines and cyclophosphamide, is currently being investigated in various indications in Studies GP28328, BO29563, and GO29831. Thus far, reported adverse events for combination regimens have been similar to those experienced with each individual agent and have generally been manageable. According to data available from the metastatic TNBC cohort in Study GP28328 (atezolizumab in combination with nab-paclitaxel), the most commonly occurring adverse events (≥ 30% incidence) have been fatigue, diarrhea, nausea, constipation, alopecia, peripheral sensory neuropathy, pyrexia, cough, decreased neutrophil count, peripheral neuropathy, and neutropenia.

Safety findings of single-agent atezolizumab across multiple tumor types in the clinical development program are consistent with the known mechanism of action of atezolizumab and the underlying disease. Overall, treatment with atezolizumab is well tolerated, with a manageable adverse event profile. Currently, no maximum tolerated dose, no dose-limiting toxicities, and no clear dose-related trends in the incidence of adverse events have been determined. Across all studies and tumor types, the most commonly reported adverse events with single-agent atezolizumab include fatigue, nausea, decreased appetite, diarrhea, constipation, and cough.

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

1.4 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

TNBC remains a challenging disease. Outcomes for patients with high-risk primary TNBC remain relatively poor compared with those of other breast cancer subtypes.

Chemotherapy remains the mainstay of treatment, but benefits are frequently short-lived with rapid development of resistance. Approximately 40% of patients receiving neoadjuvant anthracycline- and taxane-based chemotherapy achieve a pCR (ypT0 ypN0 or ypT0/is ypN0). The literature supports the existence of a correlation between pCR and long-term clinical benefit with regard to EFS hazard ratio for patients achieving pCR vs. patients not achieving pCR: 0.24 [95% CI: 0.18 to 0.33]) and OS (hazard ratio for patients achieving pCR vs. patients not achieving pCR: 0.16 [95% CI: 0.11 to 0.25]) (Cortazar et al. 2014). While several randomized trials and a meta-analysis of neoadjuvant chemotherapy have demonstrated that TNBC is more chemo-sensitive than other breast cancer subtypes, as demonstrated by substantially increased pCR rates and clinical response rates, patients with TNBC still have a poorer prognosis overall, as demonstrated by significantly higher disease recurrence and lower survival rates. The poor long-term outcome in TNBC has been found to be driven by patients who did not achieve a pCR after neoadjuvant chemotherapy, making it a clinical priority to develop new treatment strategies that can improve pCR rates in TNBC.

For patients with 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). Although chemotherapy is a mainstay treatment, resistance inevitably develops and benefit is often short-lived.

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).

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

This Phase Ib study is designed to evaluate safety, tolerability, and efficacy of ipatasertib in combination with atezolizumab and chemotherapy.

The clinical safety profile of ipatasertib as a single agent in the Phase Ia study (PAM4743g), in combination with paclitaxel in the Phase Ib (PAM4983g) and Phase II (GO29227) studies, supports continued development of ipatasertib in MBC. As a single agent, ipatasertib has reasonable pharmacokinetic (PK) profile with a half-life of approximately 48 hours and significantly down-regulates 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. No new safety signals were identified. 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 with a $\geq$3% higher incidence in the ipatasertib arm than in the placebo arm included diarrhea, neutropenia, 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. Please refer to the Ipatasertib Investigator's Brochure 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 and frequency of patients with new onset of diarrhea decreased with increased treatment duration; and, no cases of colitis were reported. Diarrhea generally responded to loperamide treatment, 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 and implemented subsequently as clinically indicated. Patients will be provided with educational materials and monitored for early signs of diarrhea symptoms, and investigators are provided with comprehensive management guidelines (Section 5.1.9.4 and Table 6) for study treatment–related symptoms or potential risks.

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, and meningoencephalitis. Guidance regarding the management of immune-mediated adverse events is provided in Section 5.1.9.4 and Appendix 13 of the protocol.

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

2. OBJECTIVES AND ENDPOINTS

Specific objectives and corresponding endpoints are outlined below (see Tables 1a–1c) for the following cohorts:

- Cohort 1: patients with locally advanced or metastatic TNBC that is not amenable to resection who have not previously received chemotherapy in the advanced setting
- Cohort 2: patients with locally advanced or metastatic TNBC that is not amenable to resection who have received no more than two lines of prior systemic chemotherapy and are willing to undergo serial biopsies (biopsy cohort)
- Cohort 3: patients with locally advanced cT2–4 cN0–3 cM0 TNBC (hereafter referred to as T2–4 TNBC)
- Cohort 4: patients with PD-L1–positive locally advanced or metastatic TNBC that is not amenable to resection who have not previously received chemotherapy in the advanced setting

Patients from Cohort 4 will be pooled with patients from Cohort 1 with PD-L1–positive tumors to investigate treatment effect in patients with PD-L1–positive TNBC.

In this protocol, "study treatment" refers to the combination of treatments assigned to patients as part of this study (i.e., ipatasertib, atezolizumab, paclitaxel, nab-paclitaxel, doxorubicin, and/or cyclophosphamide).

Table 1a Objectives and Corresponding Endpoints for Cohorts 1 and 4

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of Ipat + Atezo combined with either paclitaxel (Cohorts 1 and 4) or nab-paclitaxel (Cohort 1 only) in all patients regardless of PD-L1 status (Cohort 1 only) or in patients with PD-L1–positive tumors only (Cohorts 1 and 4)	• ORR, defined as the proportion of patients with a confirmed complete response or partial response on two consecutive occasions ≥ 4 weeks apart, as determined by the investigator according to RECIST v1.1 (primary endpoint) • DOR, defined as the time from the first occurrence of a documented confirmed complete response or partial response to the first date of recorded disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause (whichever occurs first) (secondary endpoint)
Primary Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of Ipat + Atezo combined with either paclitaxel (Cohorts 1 and 4) or nab-paclitaxel (Cohort 1 only)) in all patients regardless of PD-L1 status (Cohort 1 only) or in patients with PD-L1–positive tumors only (Cohorts 1 and 4)	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in targeted clinical laboratory test results
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of Ipat + Atezo combined with either paclitaxel (Cohorts 1 and 4) or nab-paclitaxel (Cohort 1 only)) in all patients regardless of PD-L1 status (Cohort 1 only) or in patients with PD-L1–positive tumors only (Cohorts 1 and 4)	• PFS, defined as the time from enrollment to the date of the first recorded occurrence of disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause (whichever occurs first) • CBR, defined as proportion of patients with stable disease for at least 24 weeks or with confirmed complete or partial response, as determined by the investigator according to RECIST v1.1 • OS, defined as the time from enrollment to death from any cause

Note: Patients from Cohort 4 will be pooled with patients from Cohort 1 with PD-L1–positive tumors to investigate treatment effect in patients with PD-L1–positive TNBC.

ADA = anti-drug antibody; CBR = clinical benefit rate; DOR = duration of response; nab-paclitaxel = nanoparticle albumin-bound paclitaxel; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Table 1a Objectives and Corresponding Endpoints for Cohorts 1 and 4 (cont.)

Pharmacokinetic Objective	Corresponding Endpoint
• To characterize the pharmacokinetics of ipatasertib and its metabolite (G-037720) and atezolizumab when administered in combination with paclitaxel (Cohorts 1 and 4) or nab-paclitaxel (Cohort 1 only)) in all patients regardless of PD-L1 status (Cohort 1 only) or in patients with PD-L1–positive tumors only (Cohorts 1 and 4)	• Plasma concentration of ipatasertib, G-037720, and atezolizumab at specified timepoints for analysis using non-compartment methodology or population PK methodology
Exploratory Pharmacokinetic Objectives	Corresponding Endpoints
• To evaluate potential relationships between ipatasertib exposure and safety and efficacy endpoints	• Relationship between ipatasertib plasma concentration and safety and efficacy endpoints
Immunogenicity Objective	Corresponding Endpoint
• To evaluate the immune response to Ipat + Atezo combined with either paclitaxel (Cohorts 1 and 4) or nab-paclitaxel (Cohort 1 only)) in all patients regardless of PD-L1 status (Cohort 1 only) or in patients with PD-L1–positive tumors only (Cohorts 1 and 4)	• Presence of ADAs during the study relative to the presence of ADAs at baseline
Exploratory Immunogenicity Objective	Corresponding Endpoint
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	Corresponding Endpoints
• To identify biomarkers that are predictive of response to study treatment (i.e., predictive biomarkers) or are associated with progression to a more severe disease state (i.e., prognostic biomarkers) • To assess the mechanisms of intrinsic and acquired resistances	• Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.7) and efficacy • Changes in molecular biomarkers in pretreatment and post-progression tumor tissues, plasma, and blood

Note: Patients from Cohort 4 will be pooled with patients from Cohort 1 with PD-L1–positive tumors to investigate treatment effect in patients with PD-L1–positive TNBC.

ADA = anti-drug antibody; CBR = clinical benefit rate; DOR = duration of response; nab-paclitaxel = nanoparticle albumin-bound paclitaxel; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

Table 1b Objectives and Corresponding Endpoints for Cohort 2 (Biopsy)

Exploratory Biomarker Objectives	Corresponding Endpoints
• To evaluate the pharmacodynamic effects of ipatasertib and Ipat + Atezo in tumor cells and on the tumor microenvironment • To identify biomarkers that are predictive of response to study treatment (i.e., predictive biomarkers) or are associated with progression to a more severe disease state (i.e., prognostic biomarkers) • To assess the mechanisms of intrinsic and acquired resistances	• Changes in markers of immune cell infiltration and activity as well as in pretreatment and on-treatment tumor tissues • Change in circulating immune cell repertoires • Changes in molecular biomarkers in pretreatment and on-treatment tumor tissues • Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.7) and efficacy • Changes in molecular biomarkers in pretreatment and post-progression tumor tissues, plasma, and blood
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To evaluate the anti-tumor activity of Ipat + Atezo as 2L/3L treatment in patients with TNBC and in patients with TNBC who have *PIK3CA/AKT1/PTEN*-altered tumors	The following endpoints will be evaluated using RECIST 1.1: • ORR • DOR • CBR • PFS • OS
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of Ipat + Atezo in patients in Cohort 2 (i.e., biopsy cohort)	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in targeted clinical laboratory test results

2L = second line; 3L = third line; Atezo = atezolizumab; CBR = clinical benefit rate; DOR = duration of response; Ipat = ipatasertib; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; TNBC = triple-negative breast cancer.

Table 1c Objectives and Corresponding Endpoints for Cohort 3

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of neoadjuvant Ipat + Atezo + AC followed by Ipat + Atezo + Pac	• pCR rate, defined as the proportion of patients who have no residual invasive disease in the breast and no residual disease in the lymph nodes (ypT0/Tis ypN0 in the current AJCC staging system)
Primary Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of neoadjuvant Ipat + Atezo + AC followed by Ipat + Atezo + Pac	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in targeted clinical laboratory test results
Exploratory Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the pharmacokinetics of ipatasertib and its metabolite (G-037720) and atezolizumab when administered in combination with paclitaxel or AC	• Plasma concentration of ipatasertib and G-037720 at specified timepoints • Serum concentration of atezolizumab at specified timepoints
Exploratory Immunogenicity Objectives	**Corresponding Endpoints**
• To evaluate the immune response to atezolizumab	• Incidence of ADAs to atezolizumab during the study and prevalence of ADAs to atezolizumab at baseline
• To evaluate potential effects of ADAs	• Relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To identify and/or evaluate biomarkers that are predictive of response to study treatment (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with acquired resistance to study treatment, are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide evidence of study treatment activity (i.e., pharmacodynamic biomarkers), or can increase the knowledge and understanding of disease biology and drug safety	• Relationship between biomarkers in blood, plasma, and tumor tissue (listed in Section 4.5.7) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

AC = doxorubicin plus cyclophosphamide; ADA = anti-drug antibody; AJCC = American Joint Committee on Cancer; Atezo = atezolizumab; EFS = event-free survival; Ipat = ipatasertib; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; Pac = paclitaxel; pCR = pathologic complete response; PK = pharmacokinetic.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase Ib, open-label, multicenter study consisting of four cohorts. In Cohort 1, the safety and efficacy of ipatasertib + atezolizumab + paclitaxel (Ipat + Atezo + Pac) and ipatasertib + atezolizumab + nab-paclitaxel (Ipat + Atezo + Nab-Pac) will be evaluated in patients with locally advanced or metastatic TNBC who have not previously received chemotherapy in the advanced setting. In Cohort 2 (biopsy cohort), Ipat + Atezo (with no chemotherapy) will be administered in the second-line and third-line setting to patients with locally advanced or metastatic TNBC for the main purpose of conducting exploratory biomarker assessments. In Cohort 3, the safety and efficacy of neoadjuvant ipatasertib + atezolizumab + doxorubicin + cyclophosphamide (Ipat + Atezo + AC) followed by Ipat + Atezo + Pac will be evaluated in patients with locally advanced T2–4 TNBC. In Cohort 4, the safety and efficacy of Ipat + Atezo + Pac will be evaluated in patients with PD-L1–positive locally advanced or metastatic TNBC who have not previously received chemotherapy in the advanced setting.

There is a known and acceptable safety profile of ipatasertib with paclitaxel and atezolizumab with paclitaxel or nab-paclitaxel (Sections 1.2 and 1.3). If an unexpected safety signal is detected at any time, doublet safety of ipatasertib with atezolizumab may be further evaluated. The safety and efficacy of the combination of ipatasertib with atezolizumab is being assessed both in Cohort 2 of this trial and separately (i.e., in Study CO39611 for HR-positive/HER2-negative MBC and Study CO40115 for TNBC).

Up to 25 sites in North America, Europe, and the Asia Pacific will enroll approximately 202 patients (114 patients in Cohort 1, 14 patients in Cohort 2, 24 patients in Cohort 3, and 50 patients in Cohort 4).

3.1.1 Overview of Study Design

Two triplets (Arm A and Arm B) are being evaluated as first-line treatment for patients with locally advanced or metastatic TNBC in Cohort 1 (see Figure 1). Both arms have a safety run-in cohort of 6 patients (Stage 1 within each arm [A1 and B1]) who will be evaluated for safety and tolerability before the expansion stage of 14 patients (Stage 2 within each arm [A2 and B2]). Two additional arms (Arms C and D) will explore staggered dosing schedules of the triplet combination to obtain additional safety and tolerability data (see Figure 1). Both of these additional arms have a safety run-in cohort of 6 patients (Stage 1 within each arm [C1 and D1]) who will be evaluated for safety and tolerability of the staggered dosing schedule before the expansion stage of 6 patients (Stage 2 within each arm [C2 and D2]).

Based on a confirmed ORR of >70% being reached in the first 26 patients enrolled, Arm A in Cohort 1 will be extended to include up to approximately 50 additional patients (Arm A3) in the expansion phase (Stage 3 for Arm A [A3]) to further investigate the tolerability and efficacy of the triplet combination in first-line locally advanced or

metastatic TNBC. Arm A3 will open after Arms C2 and D2 have been filled. If a differential efficacy signal is detected, the Sponsor may elect to restrict enrollment to patients with a particular tumor biomarker status.

A biopsy cohort (Cohort 2) evaluating biomarker assessments of the doublet of ipatasertib plus atezolizumab (Arm E) in 14 patients in the second-line and third-line setting was opened for enrollment after preliminary encouraging efficacy and acceptable tolerability from Cohort 1 (see Figure 1).

A locally advanced T2–4 TNBC cohort (Cohort 3) of approximately 24 patients was added to enable evaluation of neoadjuvant Ipat + Atezo + AC for two cycles followed by Ipat + Atezo + Pac for three cycles (duration of each cycle, 28 days). In Arm F, the ipatasertib dose will be 300 mg for the first two cycles and 400 mg for the remaining three cycles. In Arm G, the ipatasertib dose will be 400 mg for all five cycles. Both arms have a safety run-in cohort of 6 patients (Stage 1 within each arm [F1 and G1]) who will be evaluated for safety and tolerability before the expansion stage (Stage 2), in which a total of 12 patients may be enrolled, with the Sponsor determining allocation to Arm F2, Arm G2, or both (see Figure 1). Patients should undergo breast surgery between 2 and 6 weeks after the final dose of neoadjuvant treatment. Efficacy will be evaluated in relation to tumor biomarker status (e.g., PD-L1 expression or alteration in PIK3CA, AKT1, or PTEN).

Because of lower prevalence of PD-L1–positive tumors relative to PD-L1–negative tumors and the availability of data in patients with PD-L1–positive tumors (Study WO29522 [IMpassion130]), Cohort 4 will further evaluate the triplet combination of Ipat + Atezo + Pac as first-line treatment in approximately 50 additional patients with PD-L1–positive tumors (see Figure 1).

Patients in Cohorts 1, 2, and 4 will continue to be treated until unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status (e.g., symptomatic deterioration such as pain secondary to disease). Because of the possibility of an initial increase in tumor burden caused by immune-cell infiltration in the setting of a T-cell response (termed pseudoprogression) with atezolizumab treatment, radiographic progression per RECIST v1.1 may not be indicative of true disease progression. In the absence of unacceptable toxicity, patients who meet criteria for disease progression per RECIST v1.1 while receiving atezolizumab will be permitted to continue atezolizumab if they meet all of the following criteria:

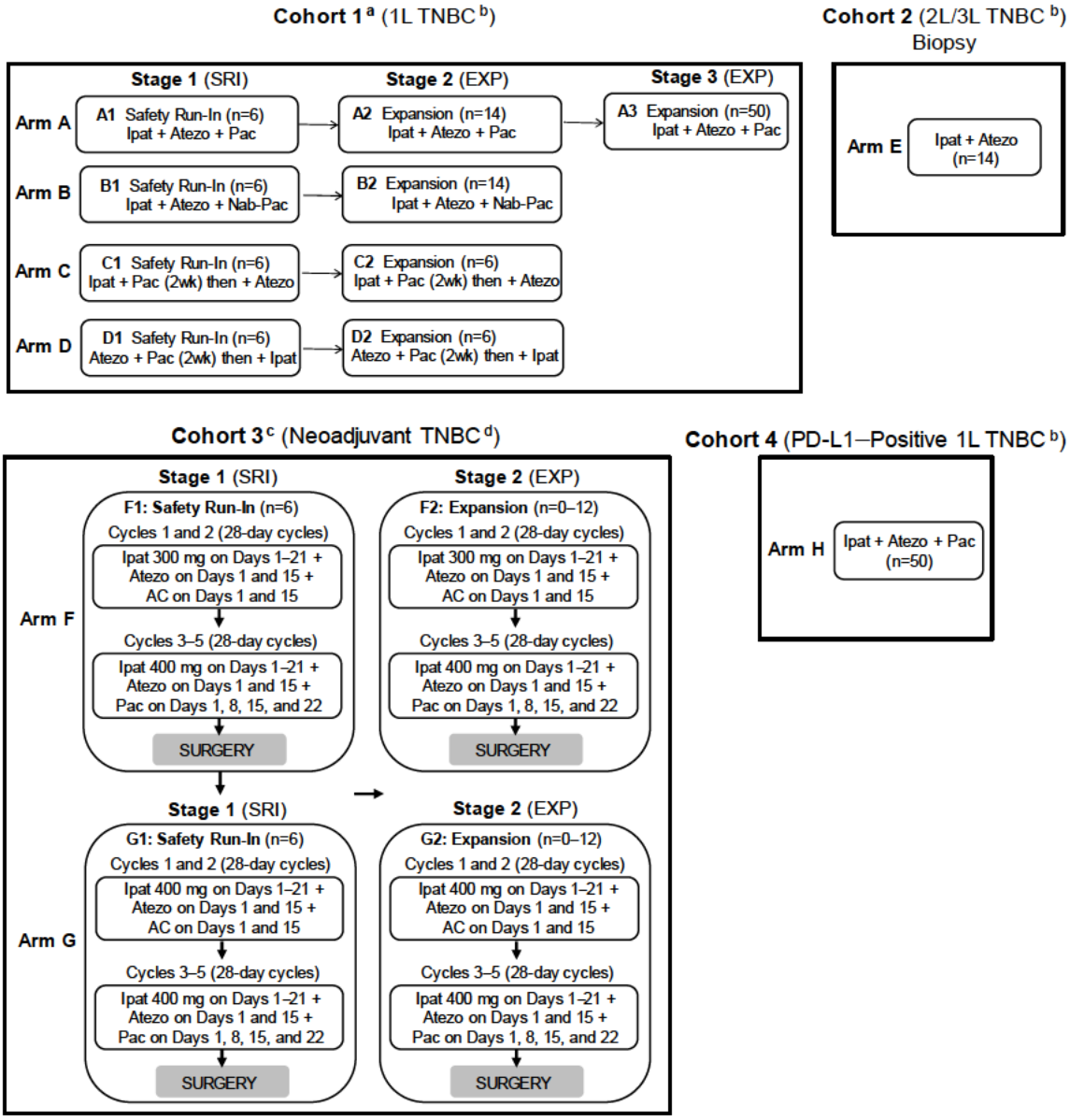
- Evidence of clinical benefit, as determined by the investigator following a review of all available data
- Absence of symptoms and signs (including laboratory values, such as new or worsening hypercalcemia) indicating unequivocal progression of disease

- Absence of decline in ECOG Performance Status (see Appendix 7) that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Patients in Cohort 3 will continue to be treated for five cycles (28-day cycles; 20 weeks) or until disease progression or unacceptable toxicity, whichever occurs first.

A schedule of activities is provided for Cohorts 1, 2, 3, and 4 in Appendix 1, Appendix 2, Appendix 3, and Appendix 1, respectively, and the dosing schedule for each arm is provided in Figure 2.

Figure 1 Study Schema



1L = first line; 2L/3L = second line/third line; AC = doxorubicin + cyclophosphamide; Atezo = atezolizumab; EXP = expansion; Ipat = ipatasertib; Nab-Pac = nab-paclitaxel; Pac = paclitaxel; SRI = safety run-in; TNBC = triple-negative breast cancer.

[a] Enrollment order for Cohort 1 is as follows: A1 → B1 → A2 → B2/C1 → D1 → C2 → D2 → A3. Both Arms B2 and Arms C or D can be open simultaneously, but priority for filling of arms will go to Arms C and D.

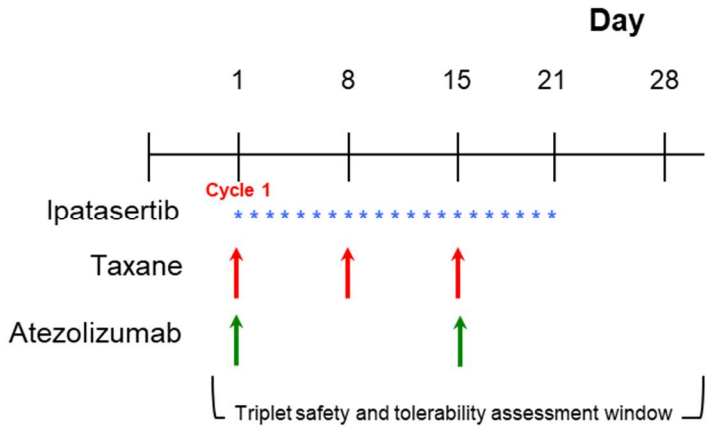
[b] Locally advanced or metastatic TNBC.

[c] Enrollment order for Cohort 3 is as follows: F1 → G1 → F2 and/or G2.

[d] Locally advanced cT2–4 cN0–3 cM0 TNBC.

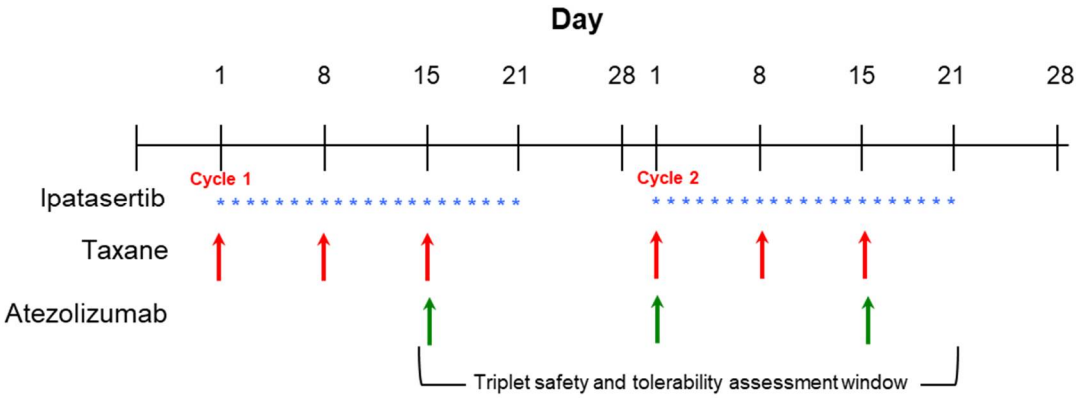
Figure 2 Dosing Schedule

Arms A, B, and H: ipatasertib + taxane [a] + atezolizumab



[a] Paclitaxel or nab-paclitaxel for Arms A and B; paclitaxel for Arm H.

Arm C: ipatasertib + paclitaxel alone for 2 weeks, then + atezolizumab



Arm D: atezolizumab + paclitaxel alone for 2 weeks, then + ipatasertib

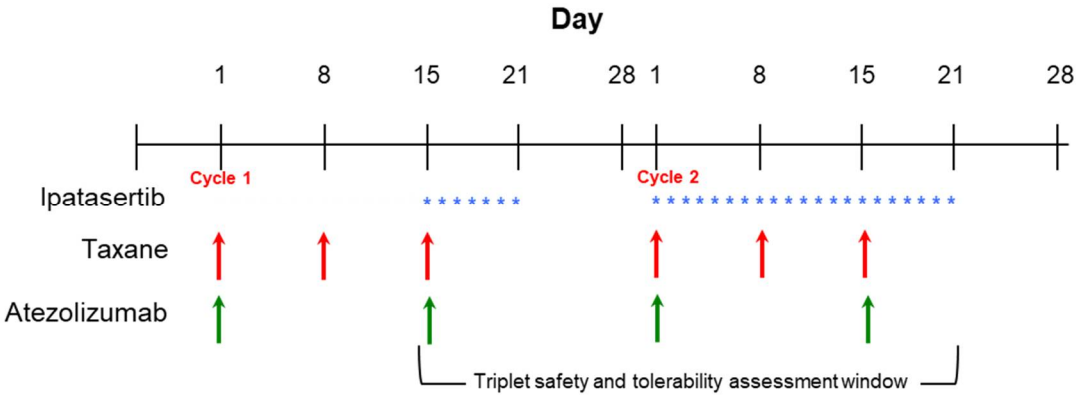
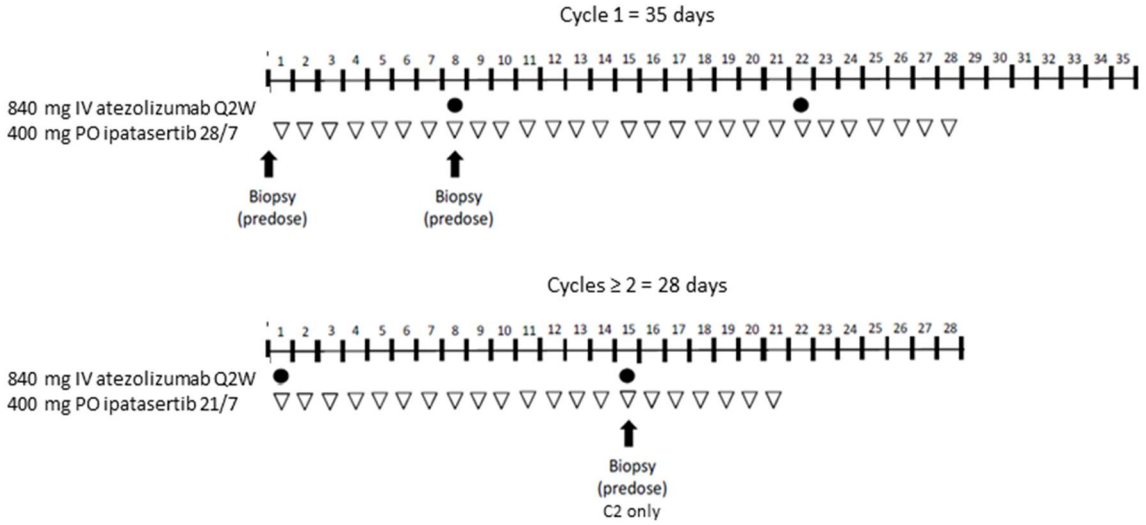


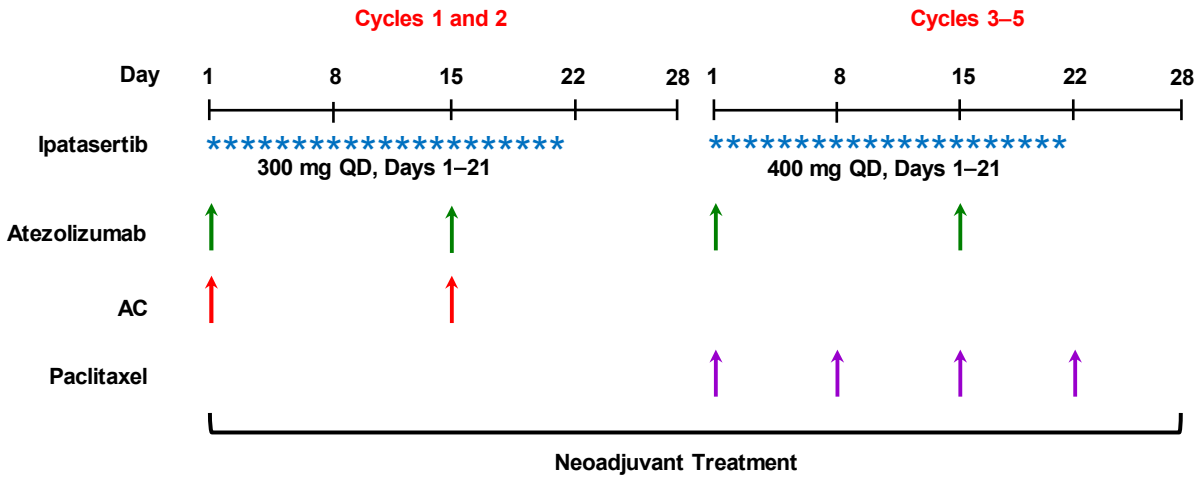
Figure 2 Dosing Schedule (cont.)

Arm E (biopsy cohort): ipatasertib + atezolizumab



21/7 = 21-days on/7-days off dosing schedule; C2 = Cycle 2; PO = by mouth; Q2W = every 2 weeks.

Arm F: ipatasertib + atezolizumab + AC (ipatasertib dose of 300 mg) followed by ipatasertib + atezolizumab + paclitaxel (ipatasertib dose of 400 mg)

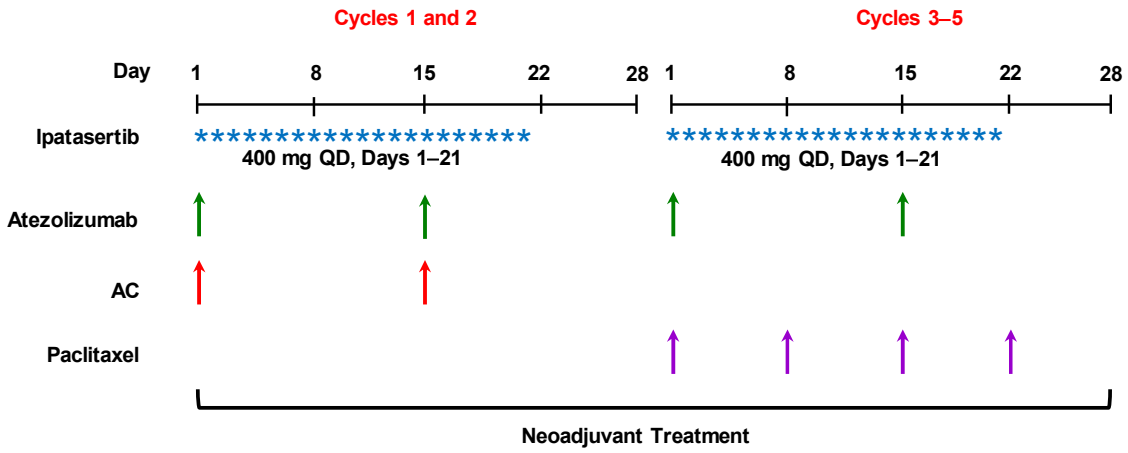


AC = doxorubicin + cyclophosphamide; QD = once a day.

Note: Each cycle is 28 days.

Figure 2 Dosing Schedule (cont.)

Arm G: ipatasertib + atezolizumab + AC (ipatasertib dose of 400 mg) followed by ipatasertib + atezolizumab + paclitaxel (ipatasertib dose of 400 mg)



AC = doxorubicin + cyclophosphamide; QD = once a day.
Note: Each cycle is 28 days.

3.1.2 Safety Run-In Stage with Safety Assessment Window (Cohort 1: Arms A1 and B1)

Up to 6 patients were enrolled in Arm A to evaluate the safety and tolerability of ipatasertib in combination with atezolizumab and paclitaxel in an initial 28-day (1 cycle) period (Cohort 1, hereafter referred to as A1; see Figure 1 in Section 3.1.1). Ipatasertib 400 mg was administered orally once a day (QD) on Days 1–21, and atezolizumab was administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle. Paclitaxel 80 mg/m^2 was administered by IV infusion on Days 1, 8, and 15 of each 28-day cycle. Tolerability was assessed during the safety assessment window following the first dose of ipatasertib for 28 days. Patients who withdraw from the study prior to completing the safety assessment for any reason other than a treatment-related adverse event will be replaced. In addition, patients who miss more than 7 total days of dosing of ipatasertib during the safety assessment window for reasons other than a treatment-related toxicity will be replaced. Patients will not be allowed to make up missed doses of study drugs (refer to Section 4.3.2.1 on study treatment administration); patients will resume dosing at their next scheduled dose. All patients who do not receive three doses of chemotherapy or two doses of atezolizumab during the safety assessment window for any reason other than a treatment-related toxicity will be replaced. The totality of safety information from patients in A1 were assessed by all participating investigators together with the Sponsor.

After enrollment was completed for Arm A Cohort 1 (i.e., A1), up to 6 patients were enrolled into Arm B to evaluate safety of ipatasertib in combination with atezolizumab

and nab-paclitaxel (Cohort 1, hereafter referred to as B1). Ipatasertib 400 mg was administered orally QD on Days 1–21, with atezolizumab 840 mg administered by IV infusion on Days 1 and 15. Nab-paclitaxel 100 mg/m^2 was administered by IV infusion on Days 1, 8, and 15 of each 28-day cycle. Tolerability was assessed similarly to A1.

Beyond the safety assessment period, patients will continue to be treated until loss of clinical benefit, unacceptable toxicity, withdrawal of consent, or end of the study. The pharmacokinetics of ipatasertib and its metabolite G-037720, and atezolizumab will be assessed in all patients receiving the study drugs. Any patient who does not receive any study treatment will be replaced.

3.1.3 Expansion Stage (Cohort 1: Arms A2, B2, and A3)

The Sponsor opened enrollment into the expansion arms with input from all participating investigators, after an integrated assessment of safety data from Arms A1 and B1 had been reviewed. Up to 14 patients were enrolled into the expansion stage of each corresponding arm (hereafter referred to as A2 or B2, correspondingly).

Based on a confirmed overall response rate of $>$ 70% being reached in the first 26 patients enrolled, Arm A will be further extended (after completion of Arms A1, B1, A2, B2, C1, D1, C2, and D2 enrollment) to include up to approximately 50 additional patients (Arm A3) into the expansion phase (Stage 3 of Arm A) to further investigate the tolerability and efficacy of the triplet combination in first-line metastatic TNBC.

Up to approximately 114 patients would be enrolled in Cohort 1 (i.e., ipatasertib-atezolizumab-taxane arms) of the study. Patients' *PIK3CA/AKT1/PTEN*-altered tumor status would be evaluated on an ongoing basis. Based on the observed prevalence, enrollment may be restricted to patients with *PIK3CA/AKT1/PTEN*-altered tumors.

3.1.4 Safety Run-In Stage with Safety Assessment Window (Cohort 1: Arms C1 and D1)

To further explore tolerability of the triplet combination, an additional two arms (Arms C and D) evaluating staggered dosing have been added to the study to obtain additional safety and tolerability data. Enrolment into these arms will supersede enrollment into Arm B2.

Up to 6 patients will be enrolled in a safety run-in cohort of Arm C to evaluate the safety and tolerability of a 2-week lead-in with ipatasertib in combination with paclitaxel, followed by the addition of atezolizumab, in an initial 28-day (1 cycle) period (hereafter referred to as Arm C1; see Figure 1 in Section 3.1.1). Ipatasertib 400 mg will be administered orally QD on Days 1–21, with paclitaxel 80 mg/m^2 administered by IV infusion on Days 1, 8, and 15. Atezolizumab 840 mg will be administered by IV infusion on Day 15 of the first cycle (see Figure 2). In all subsequent treatment cycles (Cycles $\geq$2), ipatasertib 400 mg will be administered orally QD on Days 1–21, paclitaxel 80 mg/m^2 will be administered by IV infusion on Days 1, 8, and 15, and atezolizumab will

be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle (see Figure 2). Tolerability will be assessed within the initial 28 days of the triplet regimen (safety assessment window). Patients who withdraw from the study prior to completing the safety assessment for any reason other than a treatment-related adverse event will be replaced. In addition, patients who miss more than 7 total days of dosing of ipatasertib during the safety assessment window for reasons other than a treatment-related toxicity will be replaced. Patients will not be allowed to make up missed doses of study drugs (refer to Section 4.3.2.1 on study treatment administration); patients will resume dosing at their next scheduled dose. All patients who do not receive three doses of chemotherapy or one dose of atezolizumab during the safety assessment window for any reason other than a treatment-related toxicity will be replaced. The totality of safety information from patients in Arm C1 will be shared with all participating investigator.

After enrollment is completed for Arm C1, up to 6 patients will be enrolled into a safety run-in cohort of Arm D to evaluate the safety and tolerability of a 2-week lead-in with atezolizumab in combination with paclitaxel, followed by the addition of ipatasertib in an initial 28-day (1 cycle) period (hereafter referred to as Arm D1). Atezolizumab 840 mg will be administered by IV infusion on Days 1 and 15, with paclitaxel 80 mg/m^2 administered by IV infusion on Days 1, 8, and 15. Ipatasertib 400 mg will be administered orally QD on Days 15–21 of the first cycle (see Figure 2). In all subsequent treatment cycles (Cycles $\geq$2), ipatasertib 400 mg will be administered orally QD on Days 1–21, paclitaxel 80 mg/m^2 will be administered by IV infusion on Days 1, 8, and 15, and atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle (see Figure 2). Tolerability will be assessed within the initial 28 days of the triple regimen (safety assessment window), similar to Arm C1.

Beyond the safety assessment period, patients will continue to be treated until loss of clinical benefit, unacceptable toxicity, withdrawal of consent, or end of the study. The pharmacokinetics of ipatasertib and its metabolite G-037720, and atezolizumab will be assessed in all patients receiving the study drugs. Any patient who does not receive any study treatment will be replaced.

3.1.5 Expansion Stage (Cohort 1: Arms C2 and D2)

After either Arms C1 or D1 is assessed and the safety is found to be acceptable, up to 6 patients may be enrolled into the expansion stage of each corresponding arm (hereafter referred to as C2 or D2, correspondingly). Initiation of Arm D2 enrollment will follow completion of Arm C2 enrollment when applicable. Patients' *PIK3CA/AKT1/PTEN*-altered tumor status will be evaluated on an ongoing basis. Based on the observed prevalence, enrollment may be restricted to patients with *PIK3CA/AKT1/PTEN*-altered tumors.

Arms C1, C2, D1, and D2 may not need to be opened or be fully accrued if safety management and toxicity profile is deemed jointly by Sponsor and investigators to be well understood any time during the study.

3.1.6 Biopsy Cohort (Cohort 2)

Since the combination of ipatasertib and atezolizumab with taxane in Cohort 1 demonstrated meaningful clinical activity (i.e., ORR at least 50%), the Sponsor opened enrollment of a separate mandatory on-treatment biopsy cohort (to be called Cohort 2) to evaluate biomarker endpoints in patients treated with ipatasertib combined with atezolizumab to further understand the molecular basis of treatment benefit. The opening of the biopsy cohort was enabled with input from all participating investigators, along with the Sponsor, after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), safety data, and clinical status (e.g., symptomatic deterioration such as pain secondary to disease) from Cohort 1 (safety run-in and expansion stages) had been reviewed.

Up to 14 patients with TNBC who have progressed after at least one line of chemotherapy in the advanced setting and who have a safely accessible tumor will undergo serial biopsies. Any patient who does not undergo at least two evaluable biopsies will be replaced.

Prior to Day 1 of Cycle 1, a tumor tissue sample will be collected from all patients, preferably by means of a biopsy performed at study entry if it is safely accessible, according to the treating physician. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted, provided that the tissue was obtained from a biopsy performed within 6 months prior to enrollment and that the patient has not received any anti-cancer therapy since the time of the biopsy. The archival biopsy must be from the same lesion from which subsequent biopsies will be collected. In other words, if serial biopsy is not possible at the site where the archival biopsy is from, a new biopsy from another site appropriate for serial biopsies should be performed. Tumor locations more appropriate for serial biopsies (such as cutaneous lesions or superficial lymph node metastases) should be prioritized over visceral sites (such as lung or liver metastasis). Furthermore, the Sponsor will clarify that all tumor biopsies (i.e., initial and subsequent serial biopsies) should come from the same site to help isolate tumor response to treatment from inter-tumoral heterogeneity.

Patients in the biopsy expansion cohort will start treatment with ipatasertib alone on Day 1 of Cycle 1 and will receive the first dose of atezolizumab on Day 8 of Cycle 1. The first on-treatment biopsy will be collected either Day 7 or 8 of Cycle 1, prior to the patient receiving atezolizumab. An additional biopsy will be collected on Day 15 of Cycle 2, prior to receiving the scheduled dose of atezolizumab. For patients in the biopsy expansion cohort, the first treatment cycle will be 35 days, and all following treatment cycles will be 28 days in duration (see Figure 2). Ipatasertib 400 mg will be administered orally QD on Days 1–28 of Cycle 1 (35-day cycle) and on Days 1–21 of

subsequent cycles (28-day cycles). Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 8 and 22 of Cycle 1 and on Days 1 and 15 of subsequent cycles. See Appendix 2 and Appendix 5 for a schedule of safety and PK assessments, respectively.

3.1.7 Safety Run-In Stage with Safety Assessment Window (Cohort 3: Arms F1 and G1)

Up to 6 patients will be enrolled in Arm F1 to evaluate the safety and tolerability of Ipat + Atezo + AC (ipatasertib dose of 300 mg) followed by Ipat + Atezo + Pac (ipatasertib dose of 400 mg) before surgery (see Figure 1 in Section 3.1.1). Patients will be treated for five cycles of 28 days each. Ipatasertib will be administered orally QD at a dose of 300 mg on Days 1–21 of Cycles 1 and 2 and at a dose of 400 mg on Days 1–21 of Cycles 3–5. Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of Cycles 1–5. Doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 will be administered by IV infusion (with filgrastim or pegfilgrastim support) on Days 1 and 15 of Cycles 1 and 2. Paclitaxel 80 mg/m^2 will be administered by IV infusion on Days 1, 8, 15, and 22 of Cycles 3–5 (see Figure 2). Tolerability will be assessed when at least 6 patients have completed at least 4 weeks of study treatment (safety assessment window). Patients who receive non-protocol therapy prior to surgery will be discontinued from study treatment. Patients who discontinue all study treatment prior to completing the safety assessment window for any reason other than treatment-related toxicity will be replaced. Patients who miss more than 7 total days of dosing of ipatasertib during the treatment period for any reason other than treatment-related toxicity will be replaced. In addition, patients who do not receive at least three doses of chemotherapy and at least two doses of atezolizumab during the treatment period for any reason other than treatment-related toxicity will be replaced. Patients will not be allowed to make up missed doses of *ipatsertib and atezolizumab* study drugs; patients will resume dosing at their next scheduled dose (refer to Section 4.3.2.1 for details on study treatment administration). *If clinically possible, patients should receive 4 doses of doxorubicin and cyclophosphamide and 12 doses of weekly paclitaxel prior to surgery, as per local standard of care.* The totality of safety information from patients in Arm F1 will be assessed by all participating investigators together with the Sponsor, with the Sponsor retaining the ultimate decision about whether to move forward to Arm G1.

If the treatment regimen for Arm F1 is found to be acceptable, up to 6 patients will be enrolled in Arm G1 to evaluate the safety and tolerability of Ipat + Atezo + AC (ipatasertib dose of 400 mg) followed by Ipat + Atezo + Pac (ipatasertib dose of 400 mg) before surgery (see Figure 1 in Section 3.1.1). Patients will be treated for five cycles of 28 days each. Ipatasertib 400 mg will be administered orally QD on Days 1–21 of Cycles 1–5. Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of Cycles 1–5. Doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 will be administered by IV infusion (with filgrastim or pegfilgrastim support) on Days 1 and 15 of

Cycles 1 and 2 (see Figure 2). Paclitaxel 80 mg/m^2 will be administered by IV infusion on Days 1, 8, 15, and 22 of Cycles 3–5. Tolerability for Arm G1 will be assessed in the same manner as for Arm F1.

3.1.8 Expansion Stage (Cohort 3: Arms F2 and G2)

If the treatment regimens for Arms F1 and G1 are found to be acceptable, a total of up to 12 patients may be enrolled during the expansion stage, with the Sponsor determining allocation to Arm F2, Arm G2, or both.

3.1.9 PD-L1–Positive Cohort (Cohort 4: Arm H)

Approximately 50 patients with PD-L1–positive tumors will be enrolled in Cohort 4 to further investigate the tolerability and efficacy of the Ipat + Atezo + Pac as first-line treatment in patients with locally advanced or metastatic TNBC. Ipatasertib 400 mg will be administered orally QD on Days 1–21, atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15, and paclitaxel 80 mg/m^2 will be administered by IV infusion on Days 1, 8, and 15 of each 28-day cycle.

3.1.10 Assessments and Monitoring

All patients will be closely monitored for adverse events throughout the study, and adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). Laboratory safety assessments will include the regular monitoring of hematology and blood chemistry.

Blood samples will be taken at various timepoints before and during study treatment administration to enable PK and immunogenicity analyses. On the basis of a review of real-time safety data and available PK data, treatment regimens may be modified by the Sponsor as deemed appropriate. The schedule of activities for PK samples is presented in Appendix 4, Appendix 5, and Appendix 6.

Patients in Cohorts 1, 2, and 4 will undergo tumor assessments every 8 weeks (from Day 1 of Cycle 1). Response will be assessed by the investigator using RECIST v1.1 (see Appendix 10).

Patients in Cohort 3 will undergo radiographic and other disease assessments as outlined in Section 4.5.6. Evaluation of the primary efficacy endpoint, pCR rate (ypT0/Tis ypN0), will be based on local review following completion of neoadjuvant therapy and surgery. Details on disease staging are provided in Section 4.5.6.

Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If a biopsy is not deemed feasible by the investigator, archival tumor tissue may be submitted, provided that the tissue was obtained from a biopsy performed within 6 months prior to enrollment and that the patient has not received any anti-cancer therapy since the time of the biopsy. If deemed clinically

feasible by the investigator, tumor tissue will also be collected for patients who discontinue because of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator. For patients enrolled in Cohort 2 (i.e., mandatory on-treatment biopsy cohort), two additional tumor tissue samples will be collected during treatment (if clinically feasible). These samples, as well as blood samples collected during the study, will be utilized for biomarker research (see rationale for biomarker assessments in Section 3.3.10 and details on tissue sample collection in Section 4.5.7).

3.1.11 Internal Safety Monitoring

The Study Team, including the Study Medical Monitor and Safety Scientist, will monitor 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 will review 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 (i.e., Arms A1, B1, C1, D1, F1, and G1) will be performed by the Study Team prior to opening enrollment for the expansion cohorts.

3.2 END OF STUDY AND LENGTH OF STUDY

The study will end when the last data point required for statistical analysis is collected and safety follow-up is completed, or the Sponsor decides to end the trial, whichever occurs first.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 3–5 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Patient Population

Despite multiple treatment options, TNBC remains a challenging disease. Although chemotherapy is a mainstay treatment for TNBC, resistance inevitably develops and benefit is often short lived. Ipatasertib with paclitaxel has shown encouraging clinical benefit for advanced TNBC in 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.

Taxanes, particularly paclitaxel or docetaxel, are increasingly used for adjuvant treatment of HER2-negative breast cancers worldwide. Many patients are expected to have received adjuvant chemotherapy, including taxanes, which causes concern about re-challenge with taxane treatment at recurrence when patients first relapse in the advanced setting. Although there has been no specific prospective trial to evaluate the efficacy of re-challenge with paclitaxel in the metastatic setting after prior adjuvant

taxane exposure, guidelines support the 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, for Cohorts 1, 2, and 4, patients must have a minimum 12-month window between completion of any neoadjuvant/adjuvant chemotherapy treatment (including taxane) and initiation of study treatment, thus selecting for patients who are likely to retain sensitivity to taxane chemotherapy in the metastatic setting.

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 MBC, a platinum regimen may be a preferred option, if not previously administered (Cardoso et al. 2017). The efficacy of ipatasertib or atezolizumab for patients with homologous recombination repair deficiency (e.g., patients with *BRCA1/2* germline mutation–positive disease) is unknown.

Cohort 1 evaluates the benefit/risk of ipatasertib with atezolizumab and a taxane in locally advanced or metastatic TNBC with no previous systemic treatment in the advanced setting.

Cohort 3 evaluates the combination of ipatasertib, atezolizumab, AC, and paclitaxel as neoadjuvant treatment in patients with locally advanced T2–4 TNBC. This cohort will enroll patients with T2–4 TNBC (see Section 4.1.1) because increased primary tumor size has been identified as a poor prognostic variable and has been associated with decreased disease-free survival and increased likelihood of early metastatic disease in patients with TNBC (Pistelli et al. 2013; Rosa Mendoza et al. 2013).

Cohort 4 evaluates the benefit versus risk of ipatasertib, atezolizumab, and paclitaxel in patients with PD-L1–positive locally advanced or metastatic TNBC who have not previously received chemotherapy in the advanced setting.

3.3.2 Rationale for Ipatasertib in Combination with Atezolizumab and Paclitaxel or Nab-Paclitaxel

3.3.2.1 Rationale for Targeting the PI3K/Akt Pathway

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).

Up-regulation 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 patients with breast cancer have been conducted.

In the randomized, placebo-controlled Phase II study (GO29227) in patients with locally advanced or metastatic TNBC, ipatasertib 400 mg was administered QD on Days 1–21 of each 28-day cycle, and paclitaxel 80 mg/m^2 was administered weekly on Days 1, 8, and 15 of each 28-day cycle. Patients 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 with ipatasertib + paclitaxel vs. 4.9 months with paclitaxel alone) compared with patients with *PIK3CA/AKT1/PTEN* non-altered tumors (hazard ratio = 0.76, 5.3 months with ipatasertib + paclitaxel vs. 3.7 months with paclitaxel alone) or unselected ITT patients (hazard ratio = 0.60, 6.2 months with ipatasertib + paclitaxel vs. 4.9 months with paclitaxel alone). The combination of ipatasertib and paclitaxel has been generally well tolerated. The most common adverse events in the ipatasertib + paclitaxel arm (incidence of $\geq$ 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 taxane treatment and that patients with PI3K/Akt-activated tumors are more sensitive to ipatasertib.

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

3.3.2.2 Rationale for Immunotherapy in Breast Cancer

CIT has demonstrated extraordinary success, with 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).

3.3.2.3 Rationale for Combining Ipatasertib with Atezolizumab

Recently, the loss of PTEN, a direct antagonist of Akt, 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 or nab-paclitaxel.

3.3.3 Rationale for Combination Treatment with Ipatasertib, Atezolizumab, Paclitaxel, Doxorubicin, and Cyclophosphamide

Multi-agent chemotherapy regimens have proven beneficial as neoadjuvant or adjuvant therapy for EBC, improving both disease-specific and OS outcomes (Berry et al. 2006; NCCN 2016). The most effective combination regimens include anthracyclines, topoisomerase II inhibitors, cyclophosphamide, and taxanes (Early Breast Cancer Trialists' Collaborative Group 2005; Peto et al. 2012). In the neoadjuvant setting, anthracycline- and taxane-based regimens have routinely been used in patients with TNBC, resulting in reported pCR rates of 41%–48% (Sparano et al. 2008; Sikov et al. 2015; Untch et al. 2016). Three-year EFS rates of 74%–76% have been reported for patients with TNBC who have received neoadjuvant anthracycline- and taxane-containing therapy (von Minckwitz et al. 2014; Sikov et al. 2015), leaving room for improvement in outcomes.

A commonly used regimen for TNBC is weekly paclitaxel for 12 weeks followed by AC every 2–3 weeks for four cycles (14-day cycles). A recent meta-analysis by the Early Breast Cancer Trialists Collaborative Group including individual patient data from seven randomized trials with 10,004 women demonstrated that patients who received chemotherapy every 2 weeks were 17% and 15% less likely to have disease recurrence and die from breast cancer within 10 years, respectively, compared with those who received treatment every 3 weeks. The 15% risk reduction was similar in ER-positive and ER-negative disease, and did not differ significantly with respect to any other patient or tumor characteristics, including age, HER2 status, nodal status, tumor size, and tumor grade (Gray et al. SABCS 2017). The chemotherapy regimen included in this study is built upon the aforementioned regimen.

Treatment with CIT has demonstrated significant survival benefits 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 PD-L1 or PD-1. Emerging clinical trial data have shown that the addition of immune checkpoint inhibitors to chemotherapy enhances efficacy as determined by pCR. In TNBC, early results from combination trials of anti–PD-1/PD-L1 checkpoint inhibitors and anthracycline- and taxane-based neoadjuvant chemotherapy have demonstrated high pCR rates of around 60% (Nanda et al. 2014; Schmid et al. 2017). Phase III studies are underway to confirm these results.

As stated in Section 1.3, the safety of atezolizumab in combination with chemotherapeutic regimens, including anthracyclines and cyclophosphamide, is

currently being investigated in various indications in Studies GP28328, BO29563, and GO29831. Thus far, reported adverse events for combination regimens have been similar to those experienced with each individual agent and have generally been manageable.

While PD-1/PD-L1–targeting agents have resulted in remarkable clinical therapeutic success for various cancer indications, ongoing research indicates that a series of stepwise events is 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 (which is common in TNBC) and impaired anti-tumor immune responses, including reduced CD8 T-cell infiltration and reduced efficacy of anti–PD-1 therapy in patients with melanoma. Furthermore, nonclinical studies reveal synergistic anti-tumor responses when combining PI3K-Akt pathway inhibition and PD-1/PD-L1 axis blockade (Peng et al. 2016). In addition, Akt inhibitors may restore and enhance physiologic 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).

Results of the randomized LOTUS study (GO29227) demonstrate that adding ipatasertib to paclitaxel as first-line therapy for metastatic TNBC improves PFS in the ITT population; the PFS improvement was more pronounced in patients with *PIK3CA/AKT1/PTEN*-altered tumors identified by NGS (representing approximately 40% of the randomized patients in this setting). On the basis of these results as well as the tolerable safety profiles of atezolizumab and ipatasertib, combination treatment with these two agents appears to have promising therapeutic potential in TNBC.

The value of ipatasertib and atezolizumab added to a standard neoadjuvant chemotherapy approach has not yet been determined, and the net impact on immune response is unknown. However, the current experience with ipatasertib in combination with atezolizumab and taxanes in this study (Cohort 1) suggests that the study treatments can be given with an acceptable toxicity profile along with promising confirmed response rates. All patients enrolled in the Cohort 3 will be closely monitored for safety and tolerability.

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 PK 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 3.3.12), 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 Section 1.2 and Section 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).

Doxorubicin is not a substrate of CYP3A and is not reported to be a CYP3A4 inhibitor or inducer in vivo. As such, no drug–drug interaction is expected between doxorubicin and ipatasertib. CYP3A4 does not play a major role in metabolism of cyclophosphamide, and cyclophosphamide is not reported to be a CYP3A4 inhibitor or inducer in vivo. As such, no drug–drug interaction is expected between cyclophosphamide and ipatasertib. Atezolizumab is a monoclonal antibody, is not metabolized by CYP450 enzymes, and does not inhibit or induce CYP450 enzymes in vivo. As such, no drug–drug interaction is expected between atezolizumab and ipatasertib.

In addition, the totality of pharmacodynamics data from Phase I (PAM4743g, PK/pharmacodynamic analysis) and safety and efficacy data 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) and exploratory exposure-response analyses for both safety and efficacy endpoints (data on file) 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/placebo due to any adverse event occurred in 4 patients (6.6%) in the ipatasertib arm compared with 1 patient (1.6%) in the control arm. The median cumulative dose intensity of both ipatasertib and paclitaxel in the ipatasertib arm was maintained at 99.0% (ipatasertib) and 100% (paclitaxel). Discontinuation of paclitaxel due to any adverse event was 6.6% in the ipatasertib arm and 8.1% in the control arm.

A relative bioavailability and food-effect study (GO29868) was conducted in healthy subjects. This study confirmed that the Phase III tablet formulation of ipatasertib to be used in this study will provide exposures similar to the exposures observed following

administration of powder-in-capsule formulation and Phase II tablet formulation of ipatasertib 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 without amplified HER2 expression and for whom endocrine therapy is not an option. 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 Q3W (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 = 1.02, 95% CI: 1.08–1.32), while OS was statistically higher among patients receiving weekly paclitaxel (5 studies, 1471 patients, hazard ratio = 0.78, 95% CI: 0.67–0.89). 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; Seidman et al. 2008; Miller et al. 2007).

In several recent randomized studies of paclitaxel in combination with targeted agents versus paclitaxel control, the median PFS seen in patients with HR-positive and HER2-negative disease 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 (LOTUS), 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 Q3W (175 mg/m^2, as recommended by the current prescribing information for paclitaxel IV injection [Taxol® US PI; Paclitaxel UK PC]). The control arm (paclitaxel + placebo) demonstrated a median PFS of 4.93 months (90% CI: 3.58–5.36 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). In LOTUS, the ipatasertib arm showed an ORR 40% compared to control arm of 32% in the ITT population.

Cohorts 1 and 4 of the current study will use the same paclitaxel dose and schedule as in Study GO29227. Paclitaxel (80 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle) is considered an appropriate regimen for studying the added effect of ipatasertib in the TNBC populations as specified.

3.3.6 Rationale for Treatment with Nab-Paclitaxel and Choice of Nab-Paclitaxel Regimen

Nab-paclitaxel is an albumin-bound formulation of paclitaxel that was developed to mitigate the significant toxicities associated with the vehicles that are necessary for parenteral administration of sb-paclitaxel (polyethylated castor oil and polysorbate 80). In addition, it has an advantageous PK profile compared with sb-paclitaxel and achieves a 33% higher tumor uptake in preclinical models (Yardley 2013). Steroids are routinely administered with sb-paclitaxel to lower the risk of hypersensitivity allergic reactions, but steroid premedication is not required with the use of nab-paclitaxel.

Nab-paclitaxel received a label from the U.S. Food and Drug Administration (FDA) for the treatment of MBC after failure of front-line combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, based on the pivotal Phase III study performed by Gradishar et al. (2005). However, in real-world practice, nab-paclitaxel is used throughout the continuum of care for patients with MBC. Both the NCCN and ESMO clinical practice guidelines include nab-paclitaxel as a standard of care that may be administered as a single agent to patients with newly diagnosed recurrent or metastatic breast cancer (Cardoso et al. 2017; NCCN 2017).

The Q3W dose of nab-paclitaxel (260 mg/m^2) in the FDA label established from the Phase III study comparing sb-paclitaxel with nab-paclitaxel (Gradishar et al. 2005) is not generally used in current clinical practice. Instead, weekly dosing of nab-paclitaxel is the most commonly utilized schedule given the better tolerability and suggestions of increased efficacy of weekly dosing compared to Q3W dosing.

The superiority of the weekly regimen of nab-paclitaxel was first demonstrated in a randomized Phase II study conducted in patients with previously untreated MBC (Gradishar et al. 2009). In the four arms of this study, the ORRs were 37% with Q3W nab-paclitaxel, 45% with weekly nab-paclitaxel 100 mg/m^2 (3-weeks-on/1-week-off schedule), 49% with weekly nab-paclitaxel 150 mg/m^2 (3-weeks-on/1-week-off schedule), and 35% with Q3W docetaxel 100 mg/m^2 (independent radiologist assessment), illustrating the anti-tumor advantages of the weekly dosing schedule. PFS was 11.0 months, 12.8 months, 12.9 months, and 7.5 months (independent radiologist assessment) for each of the four arms, respectively. The difference in PFS and ORR between the 100- and 150-mg/m^2 weekly dose levels of nab-paclitaxel was not statistically significant, but patients receiving the higher dose experienced a greater

incidence of Grade 3 or 4 neutropenia (44% vs. 25%) and Grade 3 sensory neuropathy (14% vs. 8%).

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

To date, 100 mg/m^2 of nab-paclitaxel weekly on a 3-weeks-on/1-week-off schedule is the best-studied and tolerated dose, with suggestions of improved efficacy and decreased toxicities in MBC compared with both higher weekly doses and the Q3W dosing schedule of the same drug. As a result, subjects on this study will receive nab-paclitaxel 100 mg/m^2 via IV infusion on Days 1, 8, and 15 of every 28-day cycle.

3.3.7 Rationale for Atezolizumab Dose and Schedule

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg Q2W, which is an approved dosage for atezolizumab (Tecentriq® U.S. Package Insert).

3.3.8 Rationale for Staggered Dose and Schedule

The development of combination treatments, while desirable, poses unique challenges. These include the selection of agents for combination therapy that may lead to improved efficacy while maintaining acceptable toxicity. To date, most combinations have added one or more investigational agents to a standard backbone already in clinical practice (Hurwitz et al. 2004; Pirker et al. 2009; Bang et al. 2010; Flaherty et al. 2012; Scagliotti et al. 2012). One challenge is the need to distinguish the incremental toxicity of the combination. Hamberg et al. (2010) proposes some solutions, including an intra-patient control (e.g., by introducing the novel agent after the standard backbone has been started).

To explore the effect of stepwise introduction of the treatment drugs in the first cycle on tolerability, a staggered dosing schedule has been proposed for Cohort 1, Arms C and D (see Section 3 for detailed description of the schedule). This approach will enable a better understanding of the contribution of individual agents with the goal of refining adverse event management guidance.

3.3.9 Rationale for Atezolizumab Treatment beyond Initial Radiographic Progression

In studies of immunotherapeutic agents, complete response, partial response, and stable disease have each been shown to occur after radiographic evidence of an

apparent increase in tumor burden. This initial increase in tumor burden caused by immune cell infiltration in the setting of a T-cell response has been termed "pseudoprogression" (Hales et al. 2010). In Study PCD4989g, evidence of tumor growth followed by a response was observed in several tumor types. In addition, in some responding patients with radiographic evidence of progression, biopsies of new lesions or areas of new growth in existing lesions revealed immune cells and no viable cancer cells. Because of the potential for a response after pseudoprogression, this study will allow patients in Cohorts 1, 2, and 4 to continue combination treatment after apparent radiographic progression per RECIST v1.1, provided the benefit–risk ratio is judged to be favorable by the investigator (see criteria in Section 4.6.1). Patients should be discontinued for unacceptable toxicity or loss of clinical benefit as determined by the investigator after an integrated assessment of radiographic and biochemical data, local biopsy results (if available), and clinical status.

3.3.10 Rationale for Pathologic Complete Response as Primary Endpoint in Cohort 3

The primary objective for Cohort 3 is to evaluate the efficacy of neoadjuvant treatment with Ipat + Atezo + Pac followed by Atezo + AC (Arm F) or Ipat + Atezo + Pac followed by Ipat + Atezo + AC (Arm G) in patients with locally advanced T2–4 TNBC. pCR was selected as the primary efficacy endpoint for Cohort 3. It is a validated, meaningful measure of response to therapy. Data from several analyses and clinical trials and meta-analyses indicate there is a correlation between pCR and long-term clinical benefit (Liedtke et al. 2008; von Minckwitz et al. 2012; Cortazar et al. 2014). This correlation was especially strong in patients with TNBC (EFS hazard ratio for patients achieving pCR vs. patients not achieving pCR: 0.24 [95% CI: 0.18 to 0.33]; OS hazard ratio for patients achieving pCR vs. patients not achieving pCR: 0.16 [95% CI: 0.11 to 0.25]) (Cortazar et al. 2014).

pCR will be defined as the absence of residual invasive cancer in the breast and absence of residual disease in the lymph nodes (ypT0/Tis ypN0 in the current American Joint Committee on Cancer staging system), based on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant therapy, which is in line with the U.S. FDA and European Medicines Agency guidance for industry on pCR endpoints.

3.3.11 Rationale for Biomarker Assessments

Breast cancer is a heterogeneous disease with 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 the study treatments.

Through the use of NGS, whole genome sequencing (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.

3.3.11.1 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 TNBCs (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 evaluate 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 will be determined using an NGS assay (e.g., Foundation Medicine, Inc. [FMI]), and the results will be used for secondary and exploratory analyses. Review of *PIK3CA/AKT1/PTEN*-altered status in archival tissue and response measures will be performed on an ongoing basis, and in the dose-expansion cohorts, enrollment may be restricted to patients with tumors demonstrating PI3K/Akt pathway activation.

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.

3.3.11.2 Rationale for Collection of Blood Samples for Non-Invasive 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 to enable evaluation of oncogenic genetic alterations at baseline and to assess for the possible emergence of new alteration after treatment with ipatasertib, atezolizumab, and taxane. Genetic alterations will be evaluated in relevant genes in the PI3K/Akt pathway (including, but not limited to, *PIK3CA* and *AKT1*) and other cancer-related genes. 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, atezolizumab, and paclitaxel or nab-paclitaxel.

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

Genomics is increasingly informing researcher's 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 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 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 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. 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 enrollment 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.

3.3.11.4 Rationale for Optional Collection of New Tumor Biopsies at Disease Progression for Exploratory Purposes, Mandatory Collection of Serial Tumor Biopsies for Biopsy Cohort, and Mandatory Collection of Tumor Tissue from Surgical Resection in Cohort 3

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). 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 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.

Understanding the mechanisms of resistance to the combination of ipatasertib, atezolizumab, and paclitaxel or nab-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.

Pharmacodynamic biomarkers will be assessed to demonstrate evidence of biologic activity of ipatasertib in combination with atezolizumab in patients and will be assessed in on-treatment biopsies, which will be collected from patients who consent to this procedure. Tumor immunobiology, stromal markers, and critical signaling targets of the PI3K/Akt signaling cascade may also be analyzed.

Progression biopsy tissue samples will aid in determining a resistance mechanism for the combination of ipatasertib, atezolizumab, and paclitaxel or nab-paclitaxel; 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).

Evaluation of tumor tissue samples from surgical resection will aid in determining a resistance mechanism for the combination of ipatasertib, atezolizumab, AC, and paclitaxel, and may potentially influence future therapies for patients who progress on a PI3K/Akt inhibitor. NGS may be performed by a clinical cancer genomic profiling laboratory (e.g., FMI).

3.3.12 Rationale for the Pharmacokinetic Evaluation Schedule

Serum and plasma samples for PK characterization of atezolizumab and ipatasertib (parent and its metabolite G-037720), respectively, will be collected as outlined in Appendix 4, Appendix 5, and Appendix 6. The sampling schedule is designed to enable characterization of ipatasertib using population PK (popPK) methodology. 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 are altered in combination with atezolizumab and paclitaxel/nab-paclitaxel.

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

In the biopsy cohort, samples will also be collected to measure coproporphyrin I and III, which are putatively transported into the liver by uptake transporters OATP1B1 and OATP1B3. The levels of these endogenous substrates of OATP transporters will be measured in an exploratory way to understand the impact of ipatasertib on OATP functionality.

Doxorubicin is not a substrate of CYP3A and is not reported to be a CYP3A4 inhibitor or inducer in vivo. As such, no drug–drug interaction is expected between doxorubicin and ipatasertib. Therefore, doxorubicin pharmacokinetics will not be evaluated in this study.

CYP3A4 does not play a major role in metabolism of cyclophosphamide, and cyclophosphamide is not reported to be a CYP3A4 inhibitor or inducer in vivo. As such, no drug–drug interaction is expected between cyclophosphamide and ipatasertib. Therefore, cyclophosphamide pharmacokinetics will not be evaluated in this study.

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

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 178 patients with locally advanced or metastatic TNBC that is not amenable to resection and approximately 24 patients with locally advanced T2–4 TNBC are expected to be enrolled in this study.

4.1.1 Inclusion Criteria

Women or men with locally advanced or metastatic TNBC who have not received prior systemic chemotherapy in this setting and who are candidates for taxane therapy may be eligible for Cohort 1 of this study. Women or men with locally advanced or metastatic

TNBC who have received no more than two lines of prior systemic chemotherapy may be eligible for Cohort 2 of this study. Women or men with locally advanced T2–4 TNBC may be eligible for Cohort 3 of this study. In patients with BRCA-associated tumors, PARP inhibitors in addition to platinum chemotherapy as potentially the preferred treatment option (Cardoso et al. 2017) should be taken into consideration when determining if this study may be appropriate for these patients. For Cohorts 1, 2, and 4, patients may have received prior chemotherapy in the neoadjuvant/adjuvant setting, and locally advanced disease must not be amenable to resection with curative intent. Patients must have sufficient tumor tissues for central molecular assessment of *PIK3CA/AKT1/PTEN*-altered status and must comply with all eligibility criteria to be enrolled. Inclusion criteria for Cohort 4 are identical to Cohort 1, with the addition of the requirement for PD-L1–positive tumors (as defined below) as determined by central testing prior to enrollment.

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 (absolute neutrophil count [ANC] ≥ 1500/μL) (Cohort 3 patients should meet this criterion without granulocyte colony–stimulating factor [G-CSF] support within the preceding 2 weeks)
  - For Cohort 3: lymphocyte count ≥ 500/μL
  - Hemoglobin ≥ 9 g/dL (Cohort 3 patients should meet this criterion in the absence of any transfusion within the preceding 2 weeks)

    Platelet count ≥ 100,000/μL (Cohort 3 patients should meet this criterion in the absence of any transfusion within the preceding 2 weeks)
  - Serum albumin ≥ 3 g/dL
  - Total bilirubin ≤ 1.5 × the upper limit of normal (ULN) (Cohorts 1, 2, and 4) or total bilirubin ≤ 1.0 × ULN (Cohort 3), 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:

    Cohort 1, 2, and 4 patients with documented liver or bone metastases may have AST and ALT ≤ 5 × ULN.

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

  Cohort 1, 2, and 4 patients with known liver involvement may have ALP $\leq 5 \times$ ULN.

  Cohort 1, 2, and 4 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.

- 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 serum glucose $\leq$ 150 mg/dL and glycosylated hemoglobin (HbA_{1c}) $\leq 7.5\%$

- For Cohorts 1, 2, and 4: life expectancy of at least 6 months
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception, and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $< 1\%$ per year during the treatment period and for 1 month after the last dose of ipatasertib, 5 months after the last dose of atezolizumab, 6 months after the last dose of paclitaxel, nab-paclitaxel, or doxorubicin, and 12 months after the last dose of cyclophosphamide, whichever occurs later. Women must refrain from donating eggs during this same period.3

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  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; 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: consider conserving sperm before treatment because of possible irreversible infertility due to therapy with paclitaxel, 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 1 month after the last dose of ipatasertib or 6 months after the last dose of paclitaxel, nab-paclitaxel, cyclophosphamide, or doxorubicin, 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 1 month after the last dose of ipatasertib or 6 months after the last dose of paclitaxel, nab-paclitaxel, cyclophosphamide, or doxorubicin, 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, 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.

Disease-Specific Inclusion Criteria

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

- For Cohorts 1, 2, and 4: histologically documented TNBC (negative HER2, ER, and PgR status) 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 (non–fine-needle aspiration [FNA] sample) as assessed locally (or centrally, if not available locally) according to the ASCO/CAP guidelines (see Appendix 8 and Appendix 9)
- For Cohort 2: disease progression following one or two lines of systemic therapy for inoperable locally advanced or metastatic TNBC
  - Patients may have received prior neoadjuvant or adjuvant chemotherapy and/or radiation treatment for early stage breast cancer, provided all chemotherapy was completed ≥ 12 months prior to Day 1 of Cycle 1.

- For Cohorts 1, 2, and 4: measurable disease according to RECIST v1.1 (see Appendix 10)
- For Cohort 2: Treated brain or spinal cord metastases are allowed if patients have stable disease and are not on steroid treatment.
- For Cohort 3: histologically documented TNBC (negative HER2, ER, and PgR status) that meets both of the following criteria:
  - Primary breast tumor size of >2 cm by at least one radiographic or clinical measurement
  - Disease stage at presentation of cT2–4 cN0–3 cM0

    Note: Receptor status at study entry should correspond to the evaluation of the most recent biopsy (non-FNA sample) as assessed locally (or centrally, if not available locally) according to the ASCO/CAP guidelines (see Appendix 8 and Appendix 9). Patients with multifocal tumors (more than one tumor confined to the same quadrant as the primary tumor) are eligible provided all discrete lesions have been biopsied and centrally confirmed as TNBC.
- For Cohort 3: patient agreement to undergo appropriate surgical management, including axillary lymph node surgery and partial or total mastectomy, after completion of neoadjuvant treatment
- Submission of a formalin-fixed, paraffin-embedded tumor (FFPE) tissue block or a minimum of 20 (for Cohorts 1 and 2) or 15 (for Cohorts 3 and 4) freshly cut unstained, serial tumor slides from the most recently collected tumor tissue for central analysis of PD-L1 status to determine eligibility for Cohort 4 and for central molecular analysis (retrospective NGS testing for *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.
  - For Cohorts 1, 2, and 4: If a more recent 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 if the patient is willing to consent to and undergo an additional pretreatment core or excisional biopsy of a non-target lesion (a non-target lesion is preferred if it is assessable and the biopsy can be safely obtained). In general, a minimum of three core biopsies for NGS testing are required.
  - For Cohort 3: If the specimen is either insufficient or unavailable, the patient may still be eligible if the patient is willing to undergo an additional pretreatment core biopsy. In general, a minimum of three core biopsies for NGS testing are required.

- For Cohort 4: Patients must have a PD-L1–positive tumor (defined as ≥1% expressing tumor-infiltrating immune cells [%ICs] evaluated as proportion of tumor area) as determined by central testing prior to enrollment.

  If multiple tumor specimens are submitted (e.g., an archival specimen and tissue from relapsed disease), patients may be eligible if at least one specimen is evaluable for PD-L1. The PD-L1 score for each patient will be the maximum PD-L1 score among the samples.

  If a patient already has results based on the commercial FoundationOne® CDx assay by Foundation Medicine, 10 freshly cut unstained, serial tumor slides from the most recently collected tumor tissue are acceptable for central molecular analysis (as described above), upon confirmation by the Medical Monitor.

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 antibiotics
- History of or current evidence of 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 total 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 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 (other than anticipated breast surgery for Cohort 3) 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 1 month after the last dose of ipatasertib, 5 months after the last dose of atezolizumab, 6 months after the last dose of paclitaxel, nab-paclitaxel, or doxorubicin, or 12 months after the last dose of cyclophosphamide, whichever occurs later

  - Women of childbearing potential (who are not postmenopausal with ≥ 12 months of non-therapy induced amenorrhea, nor surgically sterile) must have a negative serum pregnancy test result within 48 hours prior to initiation of study treatment.
- New York Heart Association (NYHA) 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
- Treatment with approved or investigational cancer therapy within 14 days prior to Day 1 of Cycle 1
- Prior treatment with an Akt inhibitor
  - Note that prior PI3K or mechanistic target of rapamycin inhibitors are allowed
- 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 for Cohorts 1, 2, and 4

For Cohorts 1, 2, and 4, patients who meet any of the following disease-specific criteria will be excluded from study entry:

- Patients with leptomeningeal carcinomatosis
- For Cohorts 1 and 4 only: history of or known presence of brain or spinal cord metastases
- For Cohorts 1 and 4: previous systemic therapy for inoperable locally advanced or metastatic TNBC, including chemotherapy, immune checkpoint inhibitors, or targeted agents
  - Patients in Cohorts 1 and 4 may have received prior neoadjuvant or adjuvant chemotherapy and/or radiation treatment for early stage breast cancer, provided all chemotherapy was completed ≥ 12 months prior to Day 1 of Cycle 1.
- 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
- 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 (i.e., stable in the 14 days before Day 1 of Cycle 1).
  - Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Patients should be recovered from the effects of radiation (Grade 1 or better) 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., bone metastasis) should be considered for loco-regional therapy if appropriate prior to enrollment.
- 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

Exclusion Criteria for Cohort 3

For Cohort 3, patients who meet any of the following criteria will be excluded from study entry:

- Prior history of invasive breast cancer
- Prior systemic therapy for treatment and/or prevention of invasive breast cancer
- Previous therapy with anthracyclines or taxanes for any malignancy
- Bilateral breast cancer
- Undergone incisional and/or excisional biopsy of primary tumor and/or axillary lymph nodes with one exception:
  - Patients who have undergone sentinel lymph node biopsy (SLNB) prior to initiation of neoadjuvant therapy (as per local practice) may be eligible if the SLNB is free of invasive carcinoma. However, any patient with a positive SLNB result (involved with invasive carcinoma) is ineligible to participate in this study.

- Undergone axillary lymph node dissection (ALND) prior to initiation of neoadjuvant therapy
- History of other malignancy within 5 years prior to screening, with the exception of those with a negligible risk of metastasis or death (e.g., 5-year OS of $>90\%$), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, or Stage I uterine cancer
- History of cerebrovascular accident within 12 months prior to initiation of study treatment
- Cardiopulmonary dysfunction as defined by any of the following prior to initiation of study treatment:
  - History of NCI CTCAE v4.0 Grade ≥ 3 symptomatic congestive heart failure, NYHA Class II, III, or IV heart failure, or left ventricular ejection fraction (LVEF) $<53\%$
  - Angina pectoris requiring anti-anginal medication, serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality, or clinically significant valvular disease
  - High-risk uncontrolled arrhythmias (e.g., atrial tachycardia with a heart rate >100 beats per minute at rest, significant ventricular arrhythmia [ventricular tachycardia], or second- or third-degree atrioventricular block)
  - Significant symptoms (Grade ≥ 2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia
  - Myocardial infarction within 12 months prior to initiation of study treatment
  - Uncontrolled hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 mmHg)
  - Evidence of transmural infarction on ECG
  - Requirement for oxygen therapy
- Known allergy or hypersensitivity to the components of cyclophosphamide or doxorubicin formulations
- Known allergy or hypersensitivity to filgrastim or pegfilgrastim formulations
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment
  - Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
- Prior treatment with CD137 agonists or immune checkpoint–blockade therapies, including anti-CD40, anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies

- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications

Ipatasertib-Specific Exclusion Criteria

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

- History of Type I or Type II diabetes mellitus requiring insulin
- Patients who are on a stable dose of oral diabetes medication ≥ 2 weeks prior to initiation of study treatment are eligible for enrollment.
- Grade ≥2 uncontrolled or untreated hypercholesterolemia or hypertriglyceridemia
- History of or active inflammatory bowel disease (e.g., Crohn'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 treatment

Atezolizumab-Specific Exclusion Criteria

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

- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren'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 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 computed tomography (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.

Paclitaxel-Specific Exclusion Criteria

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

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

4.2 METHOD OF TREATMENT ASSIGNMENT

This Phase Ib study is open label. In Cohort 1, enrollment will be opened sequentially in the following order: A1 → B1 → A2 → B2 (see Figure 1). The Sponsor may open enrollment for more than one arm at a time. However, Arm A2 may be opened only after determination of safety from Arm A1, and Arm B2 may be opened only after determination of safety from Arm B1. To further explore tolerability of the combination treatment, additional arms with stepwise introduction of the treatment drugs will be opened. Enrollment order in Cohort 1 will then be as follows: A1 → B1 → A2 → B2/C1 → D1 → C2 → D2. Both Arm B2 and Arms C or D can be open simultaneously, but priority for filling of arms will go to Arms C and D. Arm A will be extended to include an expansion phase (Stage 3 Arm A3) to further investigate the tolerability and efficacy of the triplet combination in first-line metastatic TNBC. Arm A3 will open after Arms C2 and D2 have been filled. In Cohort 3, enrollment will be opened sequentially in the following order: F1 → G1 → F2 and/or G2 (see Figure 1). Arm F2 may be opened only after determination of safety from Arm F1, and Arm G2 may be opened only after determination of safety from Arm G1. During the expansion stage for Cohort 3, the Sponsor will determine the allocation of 12 total patients to Arm F2, Arm G2, or both.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are ipatasertib, atezolizumab, paclitaxel, nab-paclitaxel, doxorubicin, and cyclophosphamide. Loperamide (or racecadotril, which may more commonly be used in Europe) and other prophylactic medications (see Section 4.3.3) are non-IMPs in this study.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Ipatasertib

Ipatasertib drug product is intended for oral administration and will be supplied as 100- and 200-mg tablets. For information on the formulation and handling of ipatasertib, see the pharmacy manual and 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. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

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.

Paclitaxel may be locally supplied or may be supplied by the Sponsor.

4.3.1.4 Nab-Paclitaxel

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

Nab-paclitaxel may be locally supplied or may be supplied by the Sponsor.

4.3.1.5 Doxorubicin

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

Doxorubicin may be locally supplied or may be supplied by the Sponsor.

4.3.1.6 Cyclophosphamide

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

Cyclophosphamide may be locally supplied or may be supplied by the Sponsor.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1. Patients in Cohorts 1, 2, and 4 will continue to be treated until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurs first. Patients in Cohort 3 will continue to be treated for five cycles (28-day cycles; 20 weeks) or until loss of clinical benefit, unacceptable toxicity, or withdrawal of consent, whichever occurs first.

Ipatasertib is to be administered before atezolizumab and chemotherapy. Atezolizumab is to be administered before chemotherapy.

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 5.1.9 and Appendix 13.

4.3.2.1 Ipatasertib

In Cohort 1, ipatasertib 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 (in Arms A, B, and C) until the

patient experiences disease progression, intolerable toxicity, or withdraws consent. In Arm D, ipatasertib will be administered at the starting dose of 400 mg orally QD on Days 15–21 of the first cycle. In all subsequent treatment cycles (Cycles ≥2), ipatasertib 400 mg will be administered orally QD on Days 1–21 until the patient experiences disease progression, intolerable toxicity, or withdraws consent.

In Cohort 2, ipatasertib 400 mg will be administered orally QD on Days 1–28 of Cycle 1 (35-day cycle) and on Days 1–21 of subsequent cycles (28-day cycles).

In Arm F of Cohort 3, ipatasertib will be administered orally QD at a dose of 300 mg on Days 1–21 of Cycles 1 and 2 and at a dose of 400 mg on Days 1–21 of Cycles 3–5. In Arm G of Cohort 3, ipatasertib will be administered orally QD at a dose of 400 mg on Days 1–21 of Cycles 1–5.

In Cohort 4, ipatasertib 400 mg will be administered orally QD on Days 1–21 of each 28-day cycle.

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.

On study days requiring a predose blood draw for PK sampling, patients will be instructed to take their daily oral dose of ipatasertib in the clinic after completion of the pretreatment assessments (see Appendix 1, Appendix 2, and Appendix 3). Ipatasertib should be taken at approximately the same time each day. 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. 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 should be provided to the patient to last one treatment cycle. Patients will be instructed to bring their bottles of ipatasertib and their medication diaries to each study visit.

4.3.2.2 Atezolizumab

In Cohort 1, patients will receive atezolizumab 840 mg administered by IV infusion Q2W (on Days 1 and 15 [±3] days) of each 28-day cycle (in Arms A, B, and D). In Arm C, atezolizumab 840 mg will be administered by IV infusion on Day 15 of the first cycle. In all subsequent treatment cycles (Cycles ≥2), atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of each 28-day cycle.

In Cohort 2, atezolizumab 840 mg will be administered by IV infusion on Days 8 and 22 of Cycle 1 (35-day cycle) and on Days 1 and 15 of subsequent cycles (28-day cycles).

In Cohort 3, atezolizumab 840 mg will be administered by IV infusion on Days 1 and 15 of Cycles 1–5 (28-day cycles).

In Cohort 4, atezolizumab 840 mg will be administered by IV infusion on Days 1 and 15 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 2.

Table 2 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 recorded during the infusion and at 30 (±5) 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 13.

No dose modification for atezolizumab is allowed.

4.3.2.3 Paclitaxel

In Cohorts 1 and 4, the dose of paclitaxel 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. In Cohort 3, paclitaxel 80 mg/m^2 will be administered by IV infusion on Days 1, 8, 15, and 22 of Cycles 3–5. 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.

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

4.3.2.4 Nab-Paclitaxel

Nab-paclitaxel will be administered according to the local prescribing information. The starting dose level of nab-paclitaxel in this study will be 100 mg/m^2 administered intravenously over 30 minutes on Days 1, 8, and 15 of each 28-day cycle (21-days on/7-days off schedule). Dose modifications should be performed according to Section 5.1.9.

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

4.3.2.5 Doxorubicin

In Cohort 3, doxorubicin 60 mg/m^2 will be administered by IV infusion on Days 1 and 15 of Cycles 1 and 2. Doxorubicin should be given as an IV bolus over 3–5 minutes or as an IV infusion over 15–30 minutes, in accordance with institutional practice. Dose delays and dose reductions for toxicity are permitted in accordance with the local prescribing information. Doxorubicin and cyclophosphamide should be administered after atezolizumab.

Refer to the local prescribing information for details regarding the preparation and administration of doxorubicin.

4.3.2.6 Cyclophosphamide

In Cohort 3, cyclophosphamide 600 mg/m^2 will be administered by IV infusion on Days 1 and 15 of Cycles 1 and 2. The dose should be capped at 1200 mg. Note that oral cyclophosphamide is not permitted. Cyclophosphamide should be given as an IV bolus over 3–5 minutes or as an IV infusion over 1–2 hours, in accordance with institutional

practice. Dose delays and dose reductions for toxicity are permitted in accordance with the local prescribing information. Doxorubicin and cyclophosphamide should be administered after atezolizumab.

Refer to the local prescribing information for details regarding the preparation and administration of cyclophosphamide.

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, are excluded.

In general, chemotherapy supportive care should be administered per ASCO, European Organisation for Research and Treatment of Cancer (EORTC), or European Society for Medical Oncology (ESMO) guidelines or institutional practice. In Cohort 3, filgrastim or pegfilgrastim must be used in conjunction with each AC administration. Chemotherapy-induced nausea and vomiting prophylaxis and treatment should be administered as clinically indicated. It is highly recommended that aprepitant be included as premedication for AC to prevent nausea and vomiting. Because systemic corticosteroids may attenuate the potential beneficial immunologic effects of treatment with atezolizumab, alternative agents should be considered when clinically feasible (see Section 4.4.2 for further guidance).

Diarrhea is a common adverse event associated with ipatasertib and atezolizumab, and sometimes with chemotherapy treatment. In this current study, to improve diarrhea management and patient experiences, loperamide (2 mg twice a day) will be administered daily as prophylaxis for diarrhea in the first cycle. If side effects are not tolerated, doses may be reduced. Investigators are encouraged to continue this dosing for the remainder of the study using their discretion based on clinical judgments.

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 indicate 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. If diarrhea control is inadequate despite use of maximum dose of loperamide or due to intolerance of loperamide, additional anti-diarrheal agents may be used per institutional standards of care such as Lomotil® (diphenoxylate and atropine), codeine, or octreotide. Duration of diarrhea may be minimized by taking ipatasertib 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, 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.

If diarrhea occurs, it should be managed per guidelines in Section 5.1.9.4; upon resolution or when study treatment is restarted, loperamide prophylaxis should be considered to resume and continue based on clinical judgments.

Additionally, patients who experience diarrhea may have fecal samples collected to test fecal calprotectin, at the investigator's discretion, to provide additional information for aiding the Sponsor in understanding how to better guide future diarrhea management.

Because of the risk of rash, patients should receive the following prophylactic treatment, unless contraindicated, during the first cycle in which all three study treatments (ipatasertib, atezolizumab, and taxane) are to be given in Cohorts 1 and 4 or during the first 28 days (i.e., Weeks 1–4) in which all four study treatments (ipatasertib, atezolizumab, and AC) are to be given in Cohort 3: On days when patients will receive atezolizumab, patients should receive at least 10 mg/day prednisone (or equivalent) as premedication, followed by a fixed dose of 10 mg/day prednisone (or equivalent) for 2–4 consecutive days thereafter. The timing of corticosteroid administration on days when patients will receive atezolizumab and paclitaxel will be determined by the investigator according to best medical judgment. In addition, patients should receive daily oral antihistamine for at least the first cycle in which all three treatments (four treatments for Cohort 3) are to be given. It is suggested that a non-sedating oral antihistamine (such as loratadine, cetirizine, or fexofenadine) and a longer-acting formulation be used. Protocol-required premedication should be omitted on the day of paclitaxel infusion if already administered as taxane premedication per institutional practice.

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 practices. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the interactive voice or Web-based response system 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 evaluate the appropriateness of continuing to provide ipatasertib and/or atezolizumab to patients assigned to this treatment after evaluating the primary and secondary efficacy outcome measures and safety data gathered in the study. These analyses may be conducted prior to completion of the study.

The Sponsor will offer continued access to Sponsor study drug (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 drugs (ipatasertib 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 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

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

4.4.1 Permitted Therapy

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

- Oral contraceptives, as allowed per local guidelines
- For Cohorts 1, 2, and 4: palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be the only site of measurable disease).

  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). The patient may continue ipatasertib treatment after treatment holding has been completed and the patient has sufficiently recovered.
- For Cohort 2 only: radiotherapy to the brain as outlined below:

  History of radiotherapy (either stereotactic radiosurgery or whole-brain radiation therapy) to the brain is allowed provided that all of the following criteria are met:

  – The patient has no evidence of progression or hemorrhage after completion of CNS-directed therapy.

  – The most recent radiotherapy to the brain is completed more than 14 days prior to study treatment initiation.

  – The patient has no ongoing requirement for corticosteroids as therapy for CNS disease

    Patients who require corticosteroid therapy for more than 7 days after completion of radiotherapy may receive study treatment following Medical Monitor approval.

  – Anti-convulsant therapy, if required, is administered at a stable dose
- Premedication with antihistamines, antipyretics, and/or analgesics prior to atezolizumab or paclitaxel administration
- Prophylaxis use of loperamide (or racecadotril, which may more commonly be used in Europe)

  Treatment with loperamide is mandated in the first cycle 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 Section 5.1.9.4; please refer to that section for additional details. Patients are asked to be cognizant of the onset, duration, severity, and frequency of symptoms and the medications administered.

- For patients receiving paclitaxel, treatment with granulocyte colony-stimulating factor

  The primary prophylaxis should be administered per the ASCO, European Organisation for Research and Treatment of Cancer, and ESMO guidelines; namely, in patients who are ≥60 years of age and/or with comorbidities (Smith et al. 2006; Aapro et al. 2011).

- For patients receiving bisphosphonates or denosumab prior to enrollment, maintenance on bisphosphonate or denosumab therapy during screening and while actively treated with study drug

  Both types of agents have potential immunomodulatory properties, but may be used as clinically indicated.

- Luteinizing hormone-releasing hormone agonists for ovarian function preservation
- 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
- 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)
- For Cohort 3: G-CSF (i.e., filgrastim or pegfilgrastim)

  G-CSF is permitted for patients receiving chemotherapy and is required when patients are receiving AC. G-CSF should be administered as primary prophylaxis per the ASCO, EORTC, or ESMO guidelines (Smith et al. 2006; Crawford et al. 2009; Aapro et al. 2011) or institutional practice.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated and per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2-receptor antagonists (e.g., famotidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced

oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β2-adrenergic agonists).

4.4.2 Cautionary Therapy

For Cohorts 1, 2, and 4, 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). After the temporary treatment hold is complete, study treatment may be re-initiated with Medical Monitor approval when the patient has sufficiently recovered.

Systemic corticosteroids and tumor necrosis factor–α (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific immune-mediated adverse events when associated with atezolizumab (refer to Appendix 13 for details).

4.4.2.1 Medications Given with Precaution due to Effects Related to CYP450 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 approximately 50% when co-administered with enzalutamide, a strong CYP3A inducer. Itraconazole, a strong CYP3A4 inhibitor, increased ipatasertib AUC and C_{max} by approximately 5-fold and 2-fold, respectively (Study GP30057). As such, other strong CYP3A inhibitors are expected to increase ipatasertib exposures. 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

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.

Caution should be exercised when nab-paclitaxel is concomitantly administered with known inhibitors of CYP3A4 (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) and inducers of CYP3A4 (e.g., rifampin, phenobarbital, phenytoin, St. John's Wort, and carbamazepine). Caution should also be exercised when nab-paclitaxel is concomitantly administered with known inhibitors of CYP2C8 (e.g., gemfibrozil) and inducers of CYP2C8 (e.g., rifampin).

Patients who require short-term use of a strong CYP3A4/5 inhibitor 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 CYP3A4/5 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. FDA): http://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 (see Section 4.4.3) may be used during the study at the discretion of the investigator.

4.4.3 Prohibited Therapy

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

- Investigational therapy (other than protocol-mandated study treatment) 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), whether health authority–approved or experimental, 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).

- Quinidine or other anti-arrhythmic agents with narrow therapeutic index

  Stable doses of calcium-channel blockers are permitted.

  Stable doses of β-blockers, if an alternative treatment cannot be used, are permitted with caution.

- 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)
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab *or cyclophosphamide*, and for 5 months after the last dose of atezolizumab *or 3 months after the last dose of cyclophosphamide, whichever occurs later*.
- 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 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.

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, Appendix 2, and Appendix 3).

4.5 STUDY ASSESSMENTS

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

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

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). 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 by the Medical Monitor to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, 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 compliance with specific medications and incidence of certain adverse events, patients will complete a diary each day. Patients will receive the diary on the first day of each cycle and complete their portion at home, with site staff completing other information during clinic visits.

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 postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 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 body temperature (oral, axillary, temporal, or tympanic).

On chemotherapy dosing days, vital signs should be recorded prior to dosing and at the end of the infusion.

4.5.5 Tumor and Response Evaluations for Cohorts 1, 2, and 4

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, magnetic resonance imaging [MRI], and bone scans) through use of RECIST v1.1 (see Appendix 10). Images for tumor assessments will be collected to enable retrospective blinded independent central review when needed. 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). To be suitable for RECIST assessments, CT and MRI scans should have a maximum thickness of 5 mm and no gaps. 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. Contrast-enhanced (IV and oral) CT or (IV) MRI 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.

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 every 8 weeks 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, follow-up bone scans should be performed during Days 16–28 of every fourth cycle (every 16 weeks). 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 and undergo bone scans (if indicated) approximately every 16 weeks until documented progressive disease per RECIST v1.1.

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 Sponsor. 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 Disease Assessments and Management for Cohort 3

4.5.6.1 Disease Status Assessment

Assessments of primary tumor and regional lymph nodes must be done by physical examination during screening, within 3 days prior to each treatment cycle, within 14 days prior to surgery, and at the study completion or early termination visit. Clinical assessments of the breast and lymph nodes should be conducted in a consistent manner at each evaluation. Assessments should include measurement of tumors in the breast, preferably through use of calipers or a ruler or tape measure. The main purpose of performing physical examinations prior to each cycle is for patient safety and to rule out progressive disease that would lead to study treatment discontinuation.

Additional disease assessments (e.g., liver function tests, radiographs) may be performed when clinically indicated to exclude metastatic disease, as per current institutional practice. Whenever possible, disease recurrence should be confirmed pathologically.

4.5.6.2 Ultrasound of Breast and Axilla

Ultrasound of the breast and axilla is mandated during screening and within 14 days prior to surgery. It is strongly recommended that abnormal lymph nodes be marked by metallic indicator or other standard approach prior to neoadjuvant therapy.

4.5.6.3 Mammograms

A baseline bilateral mammogram is required. The unaffected breast should be imaged within 60 days prior to initiation of study treatment. The affected breast should be imaged within 28 days prior to initiation of study treatment. Mammograms are optional during neoadjuvant treatment (i.e., may be performed at the investigator's discretion). Results from optional mammograms are not required to be entered into the eCRF.
A bilateral mammogram is required within 14 days prior to surgery.

4.5.6.4 Other Radiographic Assessments

Additional Breast Imaging

Additional breast imaging such as MRI is not mandated by the protocol but may be performed at the investigator's discretion per local practice. If MRI is conducted, suggested timelines for MRI are within 28 days prior to treatment initiation, after completion of Cycle 2, and 14 days prior to surgery. Results from optional MRIs or other breast imaging (other than mammograms) should be entered into the eCRF.

Baseline Distant-Site Tumor Assessments

Baseline distant-site tumor staging procedures should be performed in alignment with National Comprehensive Cancer Network (NCCN) or national guidelines, within 28 days prior to initiation of treatment.

Per NCCN guidelines, baseline staging procedures are based on clinical stage as outlined below:

- Stage II and Stage IIIA: A bone scan should be performed in the presence of bone pain and/or elevated alkaline phosphatase. A CT scan of the abdomen and pelvis should be performed in case of elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, or abnormal physical examination. A chest CT scan should be performed for all patients.
- Stage IIIB and Stage IIIC: A bone scan and a CT scan of the chest, abdomen, and pelvis should be performed for all patients.

Additional radiographic modalities may be considered when clinically indicated to exclude metastatic disease.

4.5.6.5 Tumor Measurements

The tumor site must be marked with a radiopaque marker via radiographic guidance (e.g., ultrasound) prior to initiation of neoadjuvant therapy. Tumors should be measured at screening and within 14 days prior to surgery. Tumors should be accurately measured in at least one dimension (longest diameter to be recorded) through use of conventional techniques (most commonly mammogram, but may be supplemented as clinically indicated with positron emission tomography [PET] scan, CT scan, magnetic resonance imaging (MRI), ultrasound, or X-ray). If possible, these measurements should be conducted by the same assessor at screening and throughout the study.

4.5.6.6 Lymph Node Assessments and Staging

Patients who have clinically negative axillary nodes by physical examination or by any radiographic imaging (e.g., ultrasound) at screening should be staged as node negative. Patients with clinically negative axillary nodes may undergo sentinel lymph node biopsy (SLNB) prior to neoadjuvant therapy if consistent with institutional guidelines. If SLNB is conducted, it is strongly recommended that more than one lymph node (two to three minimum) be removed. Patients with a positive SLNB result (involved with invasive carcinoma) are ineligible to participate in the study.

Patients who have enlarged or suspicious axillary nodes by physical examination or by any radiographic imaging (e.g., cortical thickness >2 mm) at screening should undergo fine-needle aspiration (FNA) or core-needle biopsy prior to enrollment. Patients with a positive biopsy result (pN1–N3c) should be staged as node positive, and patients with a negative (pN0) or equivocal (pNX) biopsy result should be staged as node negative regardless of any other clinical measurements (see Appendix 14).

Patients who have clinically negative axillary nodes but have clinically positive internal mammary, subpectoral infraclavicular, or supraclavicular lymph nodes are not required to undergo FNA or core-needle biopsy.

4.5.6.7 Surgical Plan and Procedures

Patients should be evaluated at screening by a surgeon with experience in breast cancer surgery. The surgeon will propose a surgical treatment plan, which should be documented in the eCRF. Patients should be reassessed after completion of neoadjuvant therapy (prior to surgery), and the surgeon will determine whether to proceed with the proposed plan or a modified plan. The final surgical treatment plan should be documented in the eCRF.

Patients should undergo breast surgery between 2 and 6 weeks after the final dose of neoadjuvant therapy. Pre-operative laboratory tests should be performed as per institutional practice.

All patients with T4 tumors should undergo axillary lymph node dissection (ALND) at the time of surgery, unless not aligned with institutional guidelines. Patients without

T4 tumors who are node positive (pN1–N3c) as determined by FNA or core-needle biopsy should undergo ALND at the time of surgery. Patients without T4 tumors who are node negative as determined by physical examination or radiographic imaging, or by FNA or core-needle biopsy (pN0 or pNX), should undergo ALND or SLNB at the time of surgery (see Appendix 14).

For patients who undergo SLNB, it is strongly recommended that more than one lymph node (two to three minimum) be removed and that all patients with positive macrometastases in sentinel nodes undergo ALND regardless of the number of positive nodes.

4.5.6.8 Surgical Specimen Pathology

The primary efficacy endpoint (pCR) will be established via local review following completion of neoadjuvant therapy and surgery. Guidelines regarding pathology specimen preparation, labeling, and review are outlined in the Pathology Manual. The Sponsor will prospectively collect local pathology reports.

4.5.6.9 Confirmation of Disease Progression or Second Primary Cancer

During neoadjuvant treatment, diagnosis of disease progression or second primary cancer should be supported by clinical, laboratory, radiologic, and/or (preferably) histologic findings. The designation of disease progression, whether local, regional, or distant, or a diagnosis of a second primary cancer can be made only when clinical, laboratory, radiologic, and/or histologic findings support the diagnosis.

Disease follow-up will end at the study completion or early termination visit, scheduled to occur not more than 60 days after the final dose of study treatment (refer to schedule of activities in Appendix 3 for details)

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Laboratory samples should be drawn according to the schedule of activities (see Appendix 1, Appendix 2, and Appendix 3) and within 48 hours prior to study drug administration at the clinic; results of hematology, chemistry, and pregnancy tests should be available to assess dosing decision. Screening local laboratory assessments obtained ≤48 hours before Cycle 1, Day 1 do not have to be repeated for Cycle 1, Day 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 ANCs, lymphocytes), and platelet count

- Fasting serum chemistry: glucose, 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 following ≥8-hour fast

  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
- HbA_{1c}
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- 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 (must be performed within 48 hours prior to Cycle 1, Day 1). 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.

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

The following samples will be sent to the Sponsor or a designee for analysis:

- Fecal sample for calprotectin test (optional)
- Plasma or serum samples for PK analysis through use of a validated assay
- Serum samples for assessment of ADAs to atezolizumab through use of a validated assay
- Blood samples for WGS (if approved locally)
- Most recently collected tumor tissue for determination of PD-L1 expression to determine eligibility for Cohort 4 (prior to enrollment) and for determination of

PIK3CA/AKT1/PTEN-altered tumor status (using the FMI NGS assay) and for exploratory research on biomarkers

A representative FFPE tumor specimen in a paraffin block (preferred) or at least 20 (for Cohorts 1 and 2) or 15 (for Cohorts 3 and 4) slides containing unstained, freshly cut, serial sections should be submitted prior to planned study enrollment date.

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.

For Cohorts 1, 2, and 4: If a more recent submitted tissue specimen is determined to be unsuitable for required testing, a pretreatment tumor biopsy from a non-target lesion can be performed (minimum of three core biopsies is required for NGS evaluation), or older archival tissue may be submitted to obtain a valid result.

For Cohort 3: If the submitted tissue is determined to be unsuitable for required testing, a pretreatment tumor biopsy can be performed (minimum of three core biopsies is required for NGS evaluation).

- For Cohort 3: FFPE tumor tissue block with at least three core biopsies obtained during scheduled surgical resection for exploratory biomarker research
- For patients in Cohorts 1, 2, and 4 who experience diarrhea: stool sample for fecal calprotectin assay

  Optional stool sample should be collected at each clinic visit where patient reports diarrhea.
- Biomarker samples (blood, plasma, and tissue) for <u>mandatory</u> exploratory biomarker research may include, but are not limited to, the following assays and assay platforms:

  Mutations and copy-number variations by NGS 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

  T, B, NK cells enumeration

  Circulating cytokines

NGS of tissue samples collected *at baseline and* at the time of disease progression (optional biopsy for Cohorts 1, 2, and 4; see Section 4.5.11.3) or surgery (Cohort 3) may be performed by Foundation Medicine. If performed by Foundation Medicine, the investigator can obtain results from these analyses in the form of an NGS report, which is available upon request directly from Foundation Medicine *at the time of study treatment discontinuation*. If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by health authorities. The NGS report is generated for research purposes and is not provided 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 4.5.11), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Plasma samples collected for PK or immunogenicity analysis may be needed for additional or immunogenicity characterization, PK and immunogenicity assay development and validation, and evaluation of ipatasertib metabolites or its disposition related markers; 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 (if approved locally) 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 enrolled, 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.

4.5.8 Electrocardiograms and Cardiac Function Assessment

A cardiac function assessment by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan (ECHO preferred for Cohort 3) should be performed within 12 weeks of Day 1 of Cycle 1, with additional assessments performed for Cohort 3 on Day 1 of Cycle 3 and at the study completion or early termination visit. If the LVEF result as assessed by either of these imaging modalities is felt to be inconsistent with the clinical picture, the investigator may choose an alternative modality (i.e., cardiac MRI), if this is consistent with local standard practice. The same technique used for baseline cardiac evaluation should be used throughout the study.

Single 12-lead ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1, Appendix 2, and Appendix 3) and may be obtained at unscheduled timepoints as indicated. *In Cohort 3, a 12-lead ECG will be obtained during screening, at each doxorubicin administration (Days 1 and 15 of Cycles 1–2), at study completion/early termination visit, and as clinically indicated. Screening ECG assessments obtained ≤48 hours before Day 1 of Cycle 1 do not have to be repeated on Day 1 of Cycle 1.* 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) and should not be obtained within 3 hours after any meal. 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).

4.5.9 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 4.5.9) 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.

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.

4.5.10 Post-Treatment Follow-Up for Cohorts 1, 2, and 4

At post-treatment follow-up visit, survival follow-up information, subsequent treatment and outcome, and patient-reported outcomes (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 survival information unless the patient requests to be withdrawn from study survival 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 survival follow-up, patients will be followed every 8–12 weeks for tumor assessments (disease follow-up clinic visits; see Appendix 1 and Appendix 2) 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.

4.5.11 Optional Samples for Research Biosample Repository

4.5.11.1 Overview of the Research Biosample Repository

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

4.5.11.2 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 4.5.11) will not be applicable at that site.

4.5.11.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to 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)
- For Cohorts 1, 2, and 4: **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.

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).

4.5.11.4 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.

4.5.11.5 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.

4.5.11.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in

writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study CO40151 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study CO40151.

If a patient wishes to withdraw consent to the testing of his or her specimens 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

4.5.11.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the 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:

- Intolerable toxicity related to study treatment, including development of an immune-mediated adverse event determined by the investigator to be unacceptable given the individual patient’s potential response to therapy and severity of the event
- Any medical condition that 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
- Loss of clinical benefit per Investigator’s assessment according to RECIST v1.1, unless a patient has consented to treatment beyond progression
- Confirmation of disease progression or disease recurrence

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

Patients will return to the clinic for a treatment discontinuation visit 28 (±3) days after the last dose of study treatment or prior to initiation of new anti-cancer therapy, whichever is sooner (see Appendix 1, Appendix 2, and Appendix 3 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 will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until approximately 2 years after enrollment (unless the patient withdraws consent from the study or the Sponsor terminates the study).

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.

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.

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. Administration of atezolizumab will be performed in a monitored setting in which there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

Guidelines for managing patients who experience anticipated adverse events, including prophylaxis (for diarrhea), and criteria for dose modification (interruption, dose reduction or discontinuation) for the management of specific adverse events attributable to ipatasertib, atezolizumab, and paclitaxel or nab-paclitaxel, are summarized in Section 5.1.9.4). 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 and for paclitaxel or nab-paclitaxel are listed in Table 3, Table 4, and Table 5. There is no dose reduction for atezolizumab allowed. Dose reductions for doxorubicin and/or cyclophosphamide are permitted at the investigator's discretion. Management guidelines for treatment interruption or discontinuation because of toxicities are provided in Section 5.1.9.4 and Appendix 13.

The Study Team (see Internal Safety Monitoring, Section 3.1.11) will be responsible for the ongoing monitoring of patient safety in the study.

5.1.1 Risks Associated with Ipatasertib

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

Refer to Section 6 of the Ipatasertib Investigator's Brochure for a detailed description of anticipated safety risks for Ipatasertib.

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, myositis, nephritis, *and severe cutaneous adverse reactions*. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis *(HLH)* and macrophage activation syndrome *(MAS)* (considered to be potential risks for atezolizumab). Refer to Appendix 13 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 Ipatasertib in Combination with Paclitaxel

Ipatasertib in combination with paclitaxel has been administered to 61 patients with cancer in Study GO29227 (LOTUS). Adverse events related to ipatasertib/placebo whose incidences were higher by $\geq$10% in patients receiving ipatasertib + paclitaxel versus placebo + paclitaxel were diarrhea (93.4% vs. 19.4%) and nausea (41.0% vs. 19.4%). The most frequent Grade $\geq$ 3 adverse events (reported in $\geq$5% of patients in either treatment arm) in patients in the ipatasertib + paclitaxel arm versus 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 5.1.9.4.

Refer to the Ipatasertib Investigator's Brochure for further information regarding the nonclinical and clinical safety evaluation of ipatasertib as a single agent and in combination with chemotherapy.

5.1.5 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 ≥ 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 5.1.9.4 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.

5.1.6 Risks Associated with Nab-Paclitaxel

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

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

For more details regarding the safety profile of nab-paclitaxel, refer to the local prescribing information.

5.1.7 Risks Associated with Doxorubicin

Doxorubicin is known to cause serious cardiomyopathy; arrhythmias, including life-threatening arrhythmias; increased incidence of secondary acute myelogenous leukemia and myelodysplastic syndrome; extravasation and tissue necrosis; severe myelosuppression resulting in serious infection, septic shock, need for transfusions, hospitalization, and death; tumor lysis syndrome; radiation sensitization and radiation recall; embryofetal toxicity; alopecia; and vomiting, nausea, and other gastrointestinal effects.

Patients treated with doxorubicin are at risk of developing cumulative dose-related myocardial damage. Significant cardiac events, including acute heart failure and LVEF of $<$40%, have been observed in clinical trials of doxorubicin. Cardiomyopathy may develop during treatment or up to several years after completion of treatment. There is an additive or potentially synergistic increase in the risk of cardiomyopathy in patients who have received radiotherapy to the mediastinum or concomitant therapy with other known cardiotoxic agents such as cyclophosphamide. Patients must meet specified LVEF requirements to be included in this study (see Section 4.1.2). Left ventricular function will be monitored by measurement of ejection fraction through use of ECHO or MUGA scans as described in Section 4.5.8 and the schedule of activities (see Appendix 3).

Refer to the doxorubicin local prescribing information for more details regarding the full safety profile of doxorubicin, including boxed warnings and contraindications.

5.1.8 Risks Associated with Cyclophosphamide

Cyclophosphamide has been associated with myelosuppression sometimes leading to severe immunosuppression and infections that can be serious and sometimes fatal; hemorrhagic cystitis, pyelitis, ureteritis, and hematuria; myocarditis, myopericarditis, pericardial effusion, arrhythmias, and congestive heart failure; pulmonary toxicity including pneumonitis, pulmonary fibrosis, and pulmonary veno-occlusive disease leading to respiratory failure; secondary malignancies; veno-occlusive liver disease; embryo–fetal toxicity; alopecia; and nausea, vomiting, and diarrhea.

Refer to the cyclophosphamide local prescribing information for more details regarding the full safety profile of cyclophosphamide, including boxed warnings and contraindications.

5.1.9 Management of Patients Who Experience Specific Adverse Events

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

Patients may hold ipatasertib for up to 4 consecutive weeks (approximately 28 consecutive days) in order to recover from toxicity or an adverse event related to the study drug. 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).

If the patient does not tolerate the QD dosing of ipatasertib, dosing with food may be used to alleviate gastrointestinal symptoms, including nausea, vomiting, and/or diarrhea.

For Cohorts 1, 2, and 4 and for Arms G1 and G2 of Cohort 3, the dose of ipatasertib can be reduced by 100 mg once a day (one dose level) decrements up to two times for management of drug-related toxicities (i.e., from 400 to 300 mg and then from 300 to 200 mg) as outlined in Table 3. If further dose reduction is indicated after two dose reductions for a specified drug-related adverse event, the patient must discontinue ipatasertib but may continue treatment with atezolizumab and chemotherapy or atezolizumab alone or chemotherapy alone at the investigator's discretion.

Table 3 Suggested Dose Reductions for Ipatasertib: Cohorts 1, 2, and 4 and Arms G1 and G2 of Cohort 3

Dose Level	Ipatasertib
Starting dose	400 mg
First dose reduction	300 mg
Second dose reduction	200 mg
Third dose reduction	Discontinue [a]

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

For Arms F1 and F2 of Cohort 3, the dose of ipatasertib can be reduced by 100 mg once a day (one dose level) decrements up to one time (i.e., from 300 to 200 mg) during Cycles 1 and 2 and up to two times (i.e., from 400 to 300 mg and then from 300 to 200 mg) during Cycles 3–5 for management of drug-related toxicities as outlined in Table 4. If further dose reduction is indicated after one dose reduction during Cycles 1 and 2 or after two dose reductions during Cycles 3–5 for a specified drug-related adverse event, the patient must discontinue ipatasertib but may continue treatment with

atezolizumab and chemotherapy or atezolizumab alone or chemotherapy alone at the investigator's discretion. If a patient in Arm F1 or F2 is experiencing a drug-related toxicity at the start of Cycle 3, the ipatasertib dose can be maintained at 300 mg rather than escalating to 400 mg.

Table 4 Suggested Dose Reductions for Ipatasertib: Arms F1 and F2 of Cohort 3

Cycles	Dose Level	Ipatasertib
Cycles 1 and 2	Starting dose	300 mg
	First dose reduction	200 mg
	Second dose reduction	Discontinue [a]
Cycles 3–5	Starting dose	400 mg
	First dose reduction	300 mg
	Second dose reduction	200 mg
	Third dose reduction	Discontinue [b]

[a] If the patient continues to experience specified drug-related adverse events after the first reduction in Cycles 1 and 2, the treatment should be discontinued.

[b] If the patient continues to experience specified drug-related adverse events after the second reduction in Cycles 3–5, the treatment should be discontinued.

Dose modifications for paclitaxel or nab-paclitaxel 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 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. Suggested dose reductions for paclitaxel and nab-paclitaxel are provided in Table 5.

Table 5 Suggested Dose Reductions for Paclitaxel and Nab-Paclitaxel

Dose Level	Paclitaxel [a]	Nab-paclitaxel
Starting dose	80 mg/m^2	100 mg/m^2
First dose reduction	65 mg/m^2	75 mg/m^2
Second dose reduction	Discontinue	50 mg/m^2
Third dose reduction	Not Applicable	Discontinue

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

For guidelines regarding dose modifications for doxorubicin- or cyclophosphamide-associated toxicities, refer to the local prescribing information for each agent.

5.1.9.1 Treatment Interruption for Toxicities

Atezolizumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If atezolizumab is withheld for > 12 weeks, the patient will be discontinued from atezolizumab. However, atezolizumab may be withheld for > 12 weeks to allow for patients to taper off corticosteroids prior to resuming treatment. Atezolizumab can be resumed after being withheld for > 12 weeks if the 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. The investigator and the Medical Monitor will determine the acceptable length of treatment interruption. Following discussion with the Medical Monitor, the investigator may determine the acceptable length of treatment interruption based on sound medical and clinical judgment, and taking into consideration the overall benefit–risk for the patient.

Ipatasertib treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered to ≤ 10 mg/day oral prednisone or equivalent before ipatasertib can be resumed, if clinically appropriate. If ipatasertib is withheld for > 28 days, the patient will be discontinued from ipatasertib. If the investigator believes the patient is likely to derive clinical benefit and the Medical Monitor is in agreement, ipatasertib treatment can be resumed after being withheld for > 28 days. Steroids used as prophylaxis (i.e., prior to scans, as protocol-directed rash prophylaxis, or prior to taxane or atezolizumab) do not require holding of ipatasertib. Steroids used on a single day to manage IRRs or allergic reactions similarly do not require holding of ipatasertib.

If either atezolizumab or ipatasertib is discontinued, the other drug along with chemotherapy can be continued if the patient is likely to derive clinical benefit, as determined by the investigator and following discussion with the Medical Monitor.

For guidelines regarding treatment interruption rules for doxorubicin- or cyclophosphamide-associated toxicities, refer to the local prescribing information for each agent.

5.1.9.2 General Guidelines

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).

- If ipatasertib treatment is interrupted, atezolizumab and chemotherapy treatment should continue as applicable.
- If chemotherapy treatment is interrupted, consider delaying the ipatasertib and atezolizumab 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 chemotherapy may be administered later in the same cycle, ideally on Day 22, taking into consideration the chemotherapy dosing starting on Day 1 of the next cycle.
- 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 taxane chemotherapy administration only be on Day 1, Day 8, Day 15, (or Day 22 as a day to compensate for missed chemotherapy on any of the 3 prior days), and that atezolizumab be given on Day 1 or Day 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 chemotherapy treatment to be omitted, clinic visits (and study procedures) associated with the administration of chemotherapy in that cycle may also be omitted. However, laboratory assessments and clinical visits should be scheduled as needed for follow-up of adverse events. In addition, tumor assessments, as outlined in the schedule of activities, 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 (other than Cycle 1 in Cohort 2, which contains 35 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 at the start of a treatment cycle.
- Patients who require chemotherapy dose reductions and tolerate the reduced dose for more than 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).

- Chemotherapy may be interrupted to manage toxicity. A dosing gap of up to 4 consecutive weeks (approximately 28 days) is permitted.

Any 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 5.1.9.4. As applicable, patients should continue treatment with remaining study drugs (after discussion with the Medical Monitor).

5.1.9.3 Infusion-Related Reactions to Paclitaxel

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 per institutional guidelines.

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.

5.1.9.4 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Appendix 13, Table 6, and prescribing information, as outlined below:

- Appendix 13 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 13 and that ipatasertib be withheld or discontinued per the guidelines in Table 6.
- Table 6 provides guidelines for the management of patients who experience the following potential overlapping toxicities for atezolizumab and ipatasertib: gastrointestinal, dermatologic, hepatic, pulmonary, and hyperglycemia events. It is recommended that study treatments be withheld or discontinued per the guidelines in Table 6. For these potential overlapping toxicities, guidelines in Table 6 should be followed instead of guidelines in Appendix 13.
- Table 6 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 6.
- Guidelines for the management of patients who experience chemotherapy-related adverse events are found in the local prescribing information for each agent.

For cases in which management guidelines are not covered in Table 6 or Appendix 13, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

On the planned day of treatment, chemotherapy may be administered only if all of the following criteria are met:

- ANC $\geq$ 1500/μL
- Platelet count $\geq$ 100,000/μL
- Grade $\leq$ 2 clinically significant chemotherapy-related gastrointestinal toxicity

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Ipatasertib and Atezolizumab

Event	Action to Be Taken
IRRs and anaphylaxis	• Follow guidelines for atezolizumab in Appendix 13. • Withhold ipatasertib. • For anaphylaxis precautions, see Appendix 12. • For severe hypersensitivity reactions, permanently discontinue atezolizumab and ipatasertib.
Gastrointestinal toxicity	
General guidance	• For all patients, dispense loperamide 2 mg BID 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, 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 CRP, 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: Medication 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 Lomotil® (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.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Ipatasertib and Atezolizumab (cont.)

Event	Action to Be Taken
General guidance (cont.)	Medication (cont.) – To minimize duration of diarrhea, encourage taking ipatasertib 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 by one level at a time (i.e., 400 to 300 mg; 300 to 200 mg) as outlined in Table 3 and Table 4. If Grade ≥2 diarrhea persists following dose reductions of ipatasertib to 200 mg daily and with maximum treatment for diarrhea, discontinue ipatasertib. 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. • Initiate supportive care and monitor patient closely. • Investigate etiology, referring patient to GI 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.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Ipatasertib and Atezolizumab (cont.)

Event	Action to Be Taken
Diarrhea, Grade 2	• Withhold atezolizumab and ipatasertib. • 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 fixed dose. If not, permanently discontinue atezolizumab and contact Medical Monitor. [a, b, c] • Interrupt ipatasertib until diarrhea improves to Grade 1 or better. Ipatasertib can be resumed at the same dose or one dose lower per investigator's evaluation upon improvement to Grade 1 or better. • Reduce ipatasertib by one (or one additional) dose level (see Table 3 and 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.
Diarrhea, Grade 3	• Withhold ipatasertib, atezolizumab, and taxanes. • 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 and taxanes until diarrhea improves to Grade 1 or better. Ipatasertib should be reduced by one dose level (see Table 3 and Table 4) when treatment is restarted. Consider resuming taxanes at the same dose. • For recurrent Grade 3 diarrhea, reduce ipatasertib dose by one additional dose level (see Table 3 and Table 4). Consider reducing taxanes 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.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Ipatasertib and Atezolizumab (cont.)

Event	Action to Be Taken
Diarrhea, Grade 4	• Permanently discontinue atezolizumab and ipatasertib 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 taxanes until diarrhea improves to Grade 1 or better. Consider resuming taxanes by one dose level lower (see Table 5) or discontinuing taxanes per investigator's discretion.
Colitis, Grade 1	• Continue atezolizumab and ipatasertib. • 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. • 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 fixed dose. If not, permanently discontinue atezolizumab and ipatasertib and contact Medical Monitor. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume ipatasertib with dose reduced by one level. If not, permanently discontinue ipatasertib.
Colitis, Grade 3	• Withhold atezolizumab and ipatasertib. • 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.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Ipatasertib and Atezolizumab (cont.)

Event	Action to Be Taken
Colitis, Grade 3 (cont.)	• If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and ipatasertib and contact Medical Monitor. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume ipatasertib with dose reduced by one level. If not, permanently discontinue ipatasertib.
Colitis, Grade 4	• Permanently discontinue atezolizumab and ipatasertib 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.
Endocrine disorders	
Asymptomatic hypothyroidism	• Follow guidelines for atezolizumab in Appendix 13. • Continue ipatasertib.
Symptomatic hypothyroidism	• Follow guidelines for atezolizumab in Appendix 13. • Continue ipatasertib.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Follow guidelines for atezolizumab in Appendix 13. • Continue ipatasertib. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Follow guidelines for atezolizumab in Appendix 13. • Continue ipatasertib. • For life-threatening immune-mediated hyperthyroidism, withhold ipatasertib. If event becomes clinically manageable within 28 days, resume ipatasertib with dose reduced by one level (see Table 3 and Table 4). If not, permanently discontinue ipatasertib.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Ipatasertib and Atezolizumab (cont.)

Event	Action to Be Taken
Symptomatic adrenal insufficiency, Grade 2, 3, or 4	• Follow guidelines for atezolizumab in Appendix 13. • Continue ipatasertib.
Hyperglycemia, Any Grade 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 an event of fasting glucose value 250–500 mg/dL. • In workup, include confirmation of fasting blood glucose, urinary glucose and ketones, arterial blood gas, serum bicarbonate, HbA_{1c}, C-peptide levels, anti-islet antibodies, and anti-GADD45 antibody. • Treat hyperglycemia per institutional guidelines with fluid replacement, insulin, and correction of electrolyte abnormalities.
Hyperglycemia, fasting glucose value > ULN to 160 mg/dL (8.9 mmol/L)	• Continue atezolizumab and ipatasertib. • 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, fasting glucose value >160–250 mg/dL (> 8.9–13.9 mmol/L)	• Withhold atezolizumab and ipatasertib dosing until fasting glucose value resolves to ≤160 mg/dL. (Investigate for diabetes. If patient has Type 1 diabetes, treat as a fasting glucose value 250–500 mg/dL event. If patient does not have Type 1 diabetes, treat as per institutional guidelines.) • 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 should be reduced by one dose level (refer to Table 3 and Table 4). • If the patient previously has not been receiving any oral anti-diabetic medication, ipatasertib may be resumed at the previous dose level with initiation of oral anti-diabetic medication.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Ipatasertib and Atezolizumab (cont.)

Event	Action to Be Taken
Hyperglycemia, glucose value >250–500 mg/dL (>13.9–27.8 mmol/L)	• Withhold atezolizumab and ipatasertib dosing until fasting glucose value resolves to ≤160 mg/dL 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 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 may be resumed at the previous dose level with initiation of oral anti-diabetic medication. • If hyperglycemia 250–500 mg/dL recurs, the dose of ipatasertib should be reduced by one dose level (see Table 3 and Table 4) when treatment is restarted. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hyperglycemia, glucose value >500 mg/dL (> 27.8 mmol/L); life-threatening consequences	• Withhold atezolizumab and ipatasertib dosing until fasting glucose value resolves to ≤ 160 mg/dL. • 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 ≤160 mg/dL, reduce ipatasertib by one dose level (see Table 3 and Table 4) when treatment is restarted. • Resume atezolizumab when symptoms resolve and glucose levels are stable. • If glucose value >500 mg/dL recurs, permanently discontinue ipatasertib and atezolizumab and contact Medical Monitor.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Ipatasertib and Atezolizumab (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.
Pulmonary event, Grade 1	• Continue atezolizumab and ipatasertib. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	• Withhold atezolizumab and ipatasertib. • 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 fixed dose. If not, permanently discontinue atezolizumab and ipatasertib and contact Medical Monitor. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume ipatasertib at current dose. • For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and ipatasertib 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 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. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Ipatasertib and Atezolizumab (cont.)

Event	Action to Be Taken
Hepatic events	
General guidance	• When the cause of the hepatic event is unclear, suggested workup may include a reviewing of symptoms, concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets; ruling out autoimmune or alcoholic hepatitis, non-alcoholic steatohepatitis, hypoxic/ischemic hepatopathy, biliary tract disease, and acute viral hepatitis types A, B, C, D, and E; reviewing exposure to environmental chemical agents; and conducting additional tests to evaluate liver function (e.g., INR, direct bilirubin).
AST/ALT $>$ ULN to $\leq 3 \times$ ULN with total bilirubin $\leq 2 \times$ ULN	• Continue atezolizumab and ipatasertib. • Monitor LFTs [d] until values resolve to within normal limits or to baseline values.
AST/ALT $> 3 \times$ ULN to $5 \times$ ULN with total bilirubin $\leq 2 \times$ ULN	• Continue atezolizumab and ipatasertib. • Monitor LFTs [d] every 48–72 hours until decreasing and then weekly until return to baseline. In instances when patients have baseline elevation of LFTs, clinical judgment should be used when determining appropriate frequency for monitoring LFTs (e.g., patients with documented liver or bone metastases may have baseline AST/ALT elevations of up to 5×ULN); monitoring of LFTs for such patients may be as per clinical judgment until a threshold of ALT/AST $>5\times$ ULN. • Consider patient referral to a hepatologist and liver biopsy. **Suspected immune-**mediated **events of $>$ 5 days' duration:** • Consider withholding atezolizumab. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If atezolizumab is withheld and event resolves to AST/ALT $\leq 3 \times$ ULN with total bilirubin $\leq 2 \times$ ULN within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and ipatasertib and contact Medical Monitor. [a, b, c]
AST/ALT $> 5 \times$ ULN to $< 10 \times$ ULN with total bilirubin $>$ ULN to $\leq 2 \times$ ULN	• Continue atezolizumab and ipatasertib. • Monitor LFTs [d] every 48–72 hours until decreasing and then weekly until return to baseline. • Consider patient referral to hepatologist and liver biopsy.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Ipatasertib and Atezolizumab (cont.)

Event	Action to Be Taken
AST/ALT > 5 × ULN to < 10 × ULN with total bilirubin > ULN to ≤ 2 × ULN (cont.)	**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 fixed dose. If not, permanently discontinue atezolizumab and ipatasertib 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.
AST/ALT > 3 × ULN to < 10 × ULN with total bilirubin > 2 × ULN	• Withhold atezolizumab and ipatasertib. • Monitor LFTs [d] every 48–72 hours until decreasing and then monitor weekly. • Refer patient to hepatologist 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 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 with dose reduced by one level (see Table 3 and Table 4). If not, permanently discontinue ipatasertib. • Permanently discontinue atezolizumab and ipatasertib for life-threatening hepatic events and contact the Medical Monitor.
AST/ALT > 10 × ULN	• Permanently discontinue atezolizumab and ipatasertib and contact Medical Monitor. [c] • Monitor LFTs [d] every 48–72 hours until decreasing and then monitor weekly. • Refer patient to hepatologist 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. • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN, taper corticosteroids over ≥ 1 month.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Ipatasertib and Atezolizumab (cont.)

Event	Action to Be Taken
Dermatologic toxicity	
General guidance	• Ipatasertib 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 are shown below • Consider having a dermatologist evaluate persistent and/or severe rash or pruritus. • Antihistamine prophylaxis is strongly recommended for 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 taxane infusion if the taxane premedication already includes an antihistamine. • First 28-day cycle of triplet study drug combination: On days when patients will receive atezolizumab (typically Day 1 and Day 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 taxane is to give at least 10 mg/day prednisone on the day of taxane, then the additional 10 mg prophylactic prednisone should not be given on that day to prevent rash. • *Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. Atezolizumab should be permanently discontinued for confirmed cases (see Appendix 13).*
Dermatologic event, Grade 1	• Consider referring patient to a dermatologist. • Continue atezolizumab and ipatasertib. • Initiate supportive care (e.g., topical corticosteroids and continue antihistamine administration). • Consider treatment with 10 mg/day oral prednisone or equivalent.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Ipatasertib and Atezolizumab (cont.)

Event	• Action to Be Taken
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 higher steroid dose may be necessary as clinically indicated. • Ipatasertib: interrupt ipatasertib treatment until resolution to Grade ≤ 1 or the toxicity is no longer clinically significant. If steroid dose is ≤ 10 mg/day, ipatasertib may be resumed if clinically appropriate. • Atezolizumab: If steroid dose is ≤ 10 mg/day, atezolizumab should be continued.
Dermatologic event, Grade 3	• Withhold atezolizumab and ipatasertib. • 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 within 12 weeks, resume atezolizumab at 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: if event resolves to Grade ≤ 1 or the toxicity is no longer clinically significant, resume ipatasertib at the same dose or dose reduced by one level after discussion with Medical Monitor. Only restart ipatasertib if steroid dose is ≤ 10 mg/day. If not, permanently discontinue ipatasertib.
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and ipatasertib and contact Medical Monitor. [c]

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Ipatasertib and Atezolizumab (cont.)

Event	Action to Be Taken
Neutropenia	
Grade 2	• Ipatasertib 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 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 and taxane 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 maximum dose reduction to 65 mg/m^2 for paclitaxel and 50 mg/m^2 for nab-paclitaxel, the taxane should be permanently discontinued, but the patient may continue to receive ipatasertib 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 following discussion with the Medical Monitor.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Ipatasertib and Atezolizumab (cont.)

Event	Action to Be Taken
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 and taxane should be reduced by one dose level when treatment is restarted. – Recurrent episode: Ipatasertib 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–related toxicities not described above	
Grade ≥3	• Withhold ipatasertib. Continue atezolizumab. • If the toxicity resolves to Grade 1 or better within 2 weeks, treatment may resume with ipatasertib at the prior dose level. • If the toxicity resolves to Grade 1 or better within 2–4 weeks, the dose of the ipatasertib should be reduced by one level per the suggested guidelines in Table 3 and 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 with dose reduction, or the ipatasertib may be permanently discontinued, at the discretion of the investigator.

Table 6 Guidelines for Management of Patients Who Experience Specific Adverse Events with Ipatasertib and Atezolizumab (cont.)

Event	Action to Be Taken
Atezolizumab- related toxicities not described above	
Grade ≥ 3	• Follow guidelines for atezolizumab in Appendix 13. • Withhold ipatasertib until resolution to Grade 1. • If the toxicity resolves to Grade 1 or better within 2 weeks, treatment with ipatasertib may resume at the prior dose level. • If the toxicity resolves to Grade 1 or better within 2–4 weeks, the dose of ipatasertib should be reduced by one level per the suggested guidelines in Table 3 and 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 with dose reduction, or ipatasertib may be permanently discontinued, at the discretion of the investigator.

ANC= absolute neutrophil count; BAL = bronchoscopic alveolar lavage ; BID = twice a day; CRP = C-reactive protein; G-CSF = granulocyte-colony stimulating factor; GI = gastrointestinal; HbA_{1c} = glycosylated hemoglobin; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

[a] 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.

[b] Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

[d] The LFT panel should include AST, ALT, alkaline phosphatase, and total bilirubin.

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 5.3.5.13.

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.8 and 5.3.5.9 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study treatment
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

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

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

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

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions) even if they are not serious. Adverse events of special interest for the study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.6) and based on the following observations:

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

  Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

- Suspected transmission of an infectious agent by the study treatment, 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)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Grade ≥ 3 rash
- Grade ≥ 3 diarrhea or Grade 2 diarrhea that persists for longer than 5 days despite optimal medical management.
- Grade $\geq$ 3 hyperglycemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis, erythema multiforme)

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 (maculopapular, erythema, urticarial, dermatitis, rash papular, 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 5.3.5.13–5.6.

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 treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study treatment, all adverse events will be reported until 30 days after the last 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 last 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?"

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 7 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 7 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 8):

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

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

Table 8 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 treatment, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study treatment; and/or the adverse event abates or resolves upon discontinuation of the study treatment or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment).

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

5.3.5 Procedures for Recording Adverse Events

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

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.

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

5.3.5.1 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.

5.3.5.2 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.

5.3.5.3 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.

5.3.5.4 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 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 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 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$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 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

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).

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 survival 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).

5.3.5.8 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").

5.3.5.9 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 due to breast cancer, it should be reported as an adverse event.

5.3.5.10 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study 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 an adverse event instead:

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

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

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF, as described in Section 5.3.5.12. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No safety data related to overdosing of ipatasertib or atezolizumab are available.

Paclitaxel overdosage does not have a known antidote. Bone marrow suppression, peripheral neurotoxicity, and mucositis are the primary anticipated complications of overdosage of paclitaxel.

All doses must be documented in the patient diary and on the dosing administration eCRF for each study drug. Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF and reported as a protocol deviation.

5.3.5.12 Reporting Requirements for 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, atezolizumab, paclitaxel/nab-paclitaxel, doxorubicin, and cyclophosphamide, 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, atezolizumab, paclitaxel/nab-paclitaxel, doxorubicin, or cyclophosphamide, 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 Left Ventricular Systolic Dysfunction

Symptomatic left ventricular systolic dysfunction should be reported as a serious adverse event. If the diagnosis is heart failure, it should be reported as such and not in terms of the individual signs and symptoms thereof. Heart failure should be graded according to the NCI CTCAE v4.0 and also according to the NYHA classification. Heart failure occurring during the study and after the study (see Section 5.6) must be reported, irrespective of causal relationship, and followed 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.

Asymptomatic declines in LVEF should generally not be reported as adverse events because LVEF data are collected separately in the eCRF. Exceptions to this rule are as follows:

- An asymptomatic decline in LVEF of ≥ 10 percentage points from baseline to an LVEF of $< 50\%$ must be reported as an adverse event with the term "ejection fraction decreased" as per NCI CTCAE v4.0.
- An asymptomatic decline in LVEF requiring treatment delay or leading to discontinuation of ipatasertib, atezolizumab, nab-paclitaxel, doxorubicin, or cyclophosphamide must be reported as an adverse event with the term "ejection fraction decreased," and, in addition, a comment in the adverse event comments field should confirm that this event was asymptomatic.

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., Ph.D. (Primary)

Mobile Telephone No.: [redacted]

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

Mobile Telephone No.: [redacted]

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

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

5.4.2.1 Events That Occur prior to Study Treatment Initiation

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

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study drug, serious adverse events will be reported until 30 days after the last 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 last 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 Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur > 28 days 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 1 month after the last dose of ipatasertib or nab-paclitaxel, 5 months after the last dose of atezolizumab, 6 months after the last dose of paclitaxel or doxorubicin, or 12 months after the last dose of cyclophosphamide, whichever occurs later. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until 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 1 month after the last dose of ipatasertib or 6 months after the last dose of paclitaxel, nab-paclitaxel, cyclophosphamide, or doxorubicin, whichever occurs later. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. 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 when updated information on the course and outcome of the pregnancy 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 treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

5.6.1 Reporting for Cohorts 1, 2, and 4

After the end of the adverse event reporting period for serious adverse events and adverse events of special interest (defined as 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF 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 treatment, the event should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.6.2 Reporting for Cohort 3

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first), if the event is believed to be related to prior study drug treatment. These events 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 Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

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

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities 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
- E.U. Summary of Product Characteristics for paclitaxel
- E.U. Summary of Product Characteristics for nab-paclitaxel
- E.U. Summary of Product Characteristics for doxorubicin
- E.U. Summary of Product Characteristics for cyclophosphamide

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This study is designed to obtain preliminary safety, tolerability, efficacy, PK, or biomarker information for the following:

- Cohort 1
  - Arm A: Ipat + Atezo + Pac
  - Arm B: Ipat + Atezo + Nab-Pac
  - Arm C: Ipat + Pac alone for 2 weeks, then + Atezo
  - Arm D: Atezo + Pac alone for 2 weeks, then + Ipat
- Cohort 2 (biopsy cohort)
  - Arm E: Ipat + Atezo

- Cohort 3
  - Arm F: Ipat + Atezo + AC (ipatasertib dose of 300 mg) followed by Ipat + Atezo + Pac (ipatasertib dose of 400 mg)
  - Arm G: Ipat + Atezo + AC (ipatasertib dose of 400 mg) followed by Ipat + Atezo + Pac (ipatasertib dose of 400 mg)
- Cohort 4
  - Arm H: Ipat + Atezo + Pac

There is no formal hypothesis testing planned. Cohort 1, Cohort 2, Cohort 3, and Cohort 4 may be analyzed separately. Patients with PD-L1–positive tumors receiving Ipat + Atezo + Pac in Cohort 1 will be pooled with patients in Cohort 4 for analyses.

6.1 DETERMINATION OF SAMPLE SIZE

There is no formal hypothesis testing planned. The determination of sample size for each cohort is described below.

6.1.1 Cohorts 1 and 3: Safety Run-In Stage

In Cohorts 1 and 3, the number of patients enrolled during the safety run-in stage (n = 6) in each arm (i.e., A1, B1, C1, D1, F1, and G1) allows for a reasonable likelihood of observing a given adverse event in at least 1 patient even when the incidence of the specific adverse event is low (see Table 9).

Table 9 Probabilities of Observing Adverse Events with Different Underlying Incidences: Safety Run-In Stage for Cohorts 1 and 3

Underlying AE Incidence	Probability of Observing the AE in ≥ 1 of 6 Patients
0.02	0.11
0.04	0.22
0.06	0.31
0.08	0.39
0.10	0.47

AE = adverse event.

6.1.2 Cohort 1: Expansion Stage

No formal statistical hypothesis testing is planned in this study. Instead, the analysis here is for hypothesis generation, and the emphasis is on estimations. To evaluate the primary endpoint of overall response rate for Cohort 1, for each arm, the analyses will be based on combining patients enrolled in the safety run-in and expansion stages, which is approximately 20 patients (Cohort 1, Arms A and B) or 12 patients (Cohort 1, Arms C and D). Table 10 shows estimated ORR and its 95% CI based on the Clopper–Pearson method given various observed numbers of responders among the 20 patients in Arms A and B, respectively. Twenty patients provide reasonably reliable estimates for

hypothesis generation in the expansion stage in Arms A and B. Table 11 shows estimated ORR and its 95% CI based on the Clopper–Pearson method given various observed numbers of responders among the 12 patients in Arms C and D. Twelve patients will provide reasonably reliable estimates for hypothesis generation in the expansion stage in Arms C and D. With enrolling additional up to 50 patients into Arm A3, Table 12 shows the estimated ORR and its 95% CI under different response rate scenarios when pooling all patients in Arm A (A1, A2, A3) and Arm B (B1, B2).

Table 10 Estimated Objective Response Rate and Its 95% CI for 20 Patients in Arms A and B, Respectively

Number of Responders	ORR (%)	95% CI (%)
4	20	5.73, 43.66
6	30	11.89, 54.28
8	40	19.12, 63.95
10	50	27.20, 72.80
12	60	36.05, 80.88
14	70	45.72, 88.11
16	80	56.34, 94.27

ORR = objective response rate.

Table 11 Estimated Objective Response Rate and Its 95% CI for 12 Patients in Arms C and D, Respectively

Number of Responders	ORR (%)	95% CI (%)
2	16.67	2.09, 48.41
4	33.33	9.92, 65.11
6	50	21.09, 78.91
8	66.67	34.89, 90.08
10	83.33	51.59, 97.91

ORR = objective response rate.

Table 12 Estimated Objective Response Rate and Its 95% CI for 90 Patients in Arm A and B Combined

Number of Responders	ORR (%)	95% CI (%)
60	66.67	55.95 76.26
63	70	59.43 79.21
66	73.33	62.97 82.11
69	76.67	66.57 84.94

ORR = objective response rate.

6.1.3 Cohort 2: Biopsy

If there is sufficient evidence of meaningful benefit from the combination of ipatasertib and atezolizumab with taxane in Cohort 1, (e.g., ORR ≥ 50%), the Sponsor may decide to open enrollment of a separate mandatory on-treatment biopsy cohort to evaluate biomarker endpoints of patients treated with ipatasertib combined with atezolizumab to further understand the molecular basis of treatment benefit. To provide a reliable estimate of the effects of ipatasertib and ipatasertib + atezolizumab on immune cell infiltration and activation, as well as molecular tumor biomarkers and circulating immune cell repertoires, a total of up to 14 patients will be enrolled in this cohort for exploratory analyses.

6.1.4 Cohort 3: Expansion Stage

No formal statistical hypothesis testing is planned in this study. Instead, the analysis here is for hypothesis generation, and the emphasis is on estimations. To evaluate the primary efficacy endpoint of pCR for Cohort 3, for each arm, the analyses will be based on combining patients enrolled in the safety run-in stage (n =6) and expansion stage (n =6 or 12, as determined by the Sponsor) for a total of either 12 patients or 18 patients. Table 13 and Table 14 show estimated pCR rate and its 95% CI based on the Clopper−Pearson method given various observed numbers of responders among 12 patients or 18 patients, respectively, in Arm F or Arm G. The minimum sample size, 12 patients, will provide reasonably reliable estimates for hypothesis generation in the expansion stage in Arms F and G. Any additional patients will strengthen the evidence by reducing estimate uncertainty.

Table 13 Estimated Pathologic Complete Response Rate and Its 95% CI for 12 Patients in Arm F or Arm G

Number of Responders	pCR Rate (%) (n = 12)	95% CI (%)
7	58.33	27.67, 84.83
8	66.67	34.89, 90.08
9	75.00	42.81, 94.51
10	83.33	51.59, 97.91
11	91.67	61.52, 99.79

pCR = pathologic complete response.

Table 14 Estimated Pathologic Complete Response Rate and Its 95% CI for 18 Patients in Arm F or Arm G

Number of Responders	pCR Rate (%) (n = 18)	95% CI (%)
12	66.67	40.99, 86.66
13	72.22	46.52, 90.31
14	77.78	52.36, 93.59
15	83.33	58.58, 96.42
16	88.89	65.29, 98.62

pCR = pathologic complete response.

6.1.5 Cohort 4

No formal statistical hypothesis testing is planned in this study. Patients from Cohort 4 (approximately 50 patients with PD-L1–positive tumors) will be pooled with approximately 40 patients with PD-L1–positive tumors in Cohort 1. The total sample size for this pooled analysis is expected to be approximately 90 patients, which will provide a reasonably reliable estimate for the ORR in the PD-L1–positive population compared with historical data in this population. Table 15 shows the estimated ORR and its 95% CI given various observed numbers of responders among patients with PD-L1–positive tumors in Cohorts 1 and 4.

Table 15 Estimated Objective Response Rate and Its 95% CI for 90 PD-L1–Positive Patients in Cohorts 1 and 4

Number of Responders	ORR (%) (n = 90)	95% CI (%)
64	71.11%	[60.60, 80.18]
65	72.22%	[61.78, 81.15]
66	73.33%	[62.97, 82.11]
67	74.44%	[64.16, 83.06]
68	75.56%	[65.36, 84.00]

ORR = objective response rate.

6.2 SUMMARIES OF CONDUCT OF STUDY

Patient enrollment, study discontinuation, and discontinuation reasons will be summarized by treatment arm and by cohorts when applicable. In addition, major protocol violations, including violations of inclusion and/or exclusion criteria, will be summarized as well.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographics summaries, patient treatment history, and other baseline disease characteristics will be summarized by treatment arms and by cohorts when applicable.

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 FOR COHORT 1 AND COHORT 4

All efficacy analyses, except for duration of response (DOR), will be based on efficacy evaluable patient population, which is defined as all enrolled patients who received at least one dose of study treatment, regardless of treatment allocation. DOR analysis will include all patients with an objective response (i.e., a confirmed complete response or partial response). Patients will be analyzed according to the treatment they receive. The treatment arms for Cohort 1 efficacy analyses are as follows:

- Arm A: Ipat + Atezo + Pac
- Arm B: Ipat + Atezo + Nab-Pac
- Arm C: Ipat + Pac alone for 2 weeks, then + Atezo
- Arm D: Atezo + Pac alone for 2 weeks, then + Ipat
- Arm A and B combined: Ipat + Atezo + taxane

For Cohort 4, efficacy analyses will be carried out on the pooled data from PD-L1−positive patients in Arms A, B, and H (ipatasertib + atezolizumab + paclitaxel).

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.

6.4.1 Primary Efficacy Endpoint

6.4.1.1 Objective Response Rate

ORR is defined as the proportion of patients with a confirmed complete response or partial response on two consecutive occasions ≥4 weeks apart, as determined by the investigator according to RECIST v1.1 (see Appendix 10). Patients without a postbaseline tumor assessment will be considered as non-responders. ORR is defined as the proportion of patients who have an objective response; an estimate of ORR will be calculated for each treatment arm, and its 95% CI will be calculated using the Clopper−Pearson method.

6.4.1.2 Duration of Response

DOR will be analyzed to support ORR. DOR is defined as the time from the first occurrence of a documented objective response to disease progression, as determined by the investigator according to RECIST v1.1, or death from any cause, whichever occurs first. Patients who have not progressed or died at the time of analysis will be censored at the last disease assessment date.

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Progression-Free Survival

PFS is defined as the time from enrollment to the date of the first recorded 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 receiving first treatment, the data will be censored at the date of first treatment plus 1 day.

6.4.2.2 Clinical Benefit Rate

Clinical benefit rate (CBR) is defined as the proportion of patients who have an objective response (complete or partial), or stable disease for at least 24 weeks, as determined by the investigator according to RECIST v1.1. For each arm, 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 enrollment 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 postbaseline information will be censored at the first treatment date plus 1 day.

6.4.3 Exploratory Efficacy Endpoints

The potential relationship between the presence of *PIK3CA/AKT1/PTEN* genetic alterations in tumors and anti-tumor activity (including ORR, DOR, PFS, CBR, and OS) of ipatasertib in combination with atezolizumab and paclitaxel or nab-paclitaxel in Cohort 1 and of ipatasertib in combination with atezolizumab in Cohort 2 will be explored as data allow.

6.5 EXPLORATORY EFFICACY ANALYSES FOR COHORT 2

Efficacy analyses for Cohort 2 will be performed on endpoints ORR, DOR, CBR, PFS, and OS using the methods described in Section 6.4.

6.6 EFFICACY ANALYSES FOR COHORT 3

The efficacy analyses will be based on the efficacy evaluable patient population, which is defined as all enrolled patients who received at least one dose study treatment, regardless of treatment allocation.

The primary efficacy objective for Cohort 3 is to evaluate the efficacy of neoadjuvant Ipat + Atezo + AC (ipatasertib dose of 300 mg) followed by Ipat + Atezo + Pac (ipatasertib dose of 400 mg) (Arm F) or neoadjuvant Ipat + Atezo + AC (ipatasertib dose of 400 mg) followed by Ipat + Atezo + Pac (ipatasertib dose of 400 mg) (Arm G) in patients with locally advanced T2–4 TNBC, as measured by pCR rate, defined as the proportion of patients who have no residual invasive cancer in the breast and no residual disease in the lymph nodes (ypT0/Tis ypN0). The primary efficacy endpoint will be established following completion of neoadjuvant therapy and surgery.

In the primary analysis, patients whose pCR assessment is missing will be counted as not achieving a pCR. An estimate of the pCR rate and its 95% CI will be calculated for each treatment arm through use of the Clopper–Pearson method (Clopper and Pearson 1934).

6.7 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 incidence, 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 treatment 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.

6.8 PHARMACOKINETIC ANALYSES

Sparse or intensive samples will be collected for PK analyses of atezolizumab (patients who receive at least one dose of atezolizumab) and ipatasertib and its metabolite G-037720 (patients who receive at least one dose of the respective drug) as described in Appendix 4, Appendix 5, and Appendix 6. Serum or plasma concentrations of the various study drugs and PK markers (coproporphyrin I and III) will be summarized (mean, standard deviation, coefficient of variation) by treatment arm, and by cycle and day when appropriate and as data allow. Individual and median serum or plasma concentrations of the various study drugs will be plotted by treatment arm and cycle and day. Non-compartmental analysis will be conducted when the data allow for it (e.g., during the intensive sampling). Analyte concentration data for ipatasertib (and its metabolite, G-037220) and atezolizumab may be pooled with data from other studies using an established popPK model to derive PK parameters such as clearance, volume of distribution, and area under the curve as appropriate to assist in comparison with historical data. 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 may be tested for significance on PK parameters of interest, if data allow.

The PK data will be analyzed with the safety and/or efficacy (e.g., PFS) data for exposure–response modeling as data permit. PK and pharmacodynamic analyses may be reported in separate standalone reports.

Additional PK analyses will be conducted as appropriate.

6.9 IMMUNOGENICITY ANALYSES

Immunogenicity will be assessed for atezolizumab. The immunogenicity analyses will include all patients with at least one anti-drug antibody (ADA) assessment. Patients will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

For atezolizumab, the numbers and proportions of ADA-positive patients and ADA-negative patients at baseline (baseline prevalence) and after baseline (postbaseline incidence) will be summarized by treatment group. When determining

postbaseline incidence, patients are considered to be ADA positive if they are ADA negative or are missing data at baseline but develop an ADA response following study drug exposure (treatment-induced ADA response), or if they are ADA positive at baseline and the titer of one or more postbaseline samples is at least 0.60 titer unit greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all postbaseline samples are negative, or if they are ADA positive at baseline but do not have any postbaseline samples with a titer that is at least 0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

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

6.10 BIOMARKER ANALYSES

In Cohorts 1, 2, and 4, the exploratory biomarker endpoints, including the effects of breast intrinsic subtypes, genetic alterations, and expression of tumor suppressors, will be evaluated for their association with drug response.

Additionally, for patients in Cohorts 2 and 3, tumor, plasma, and blood samples will be evaluated for changes in immune cell infiltration and activation as well as molecular tumor biomarkers and circulating immune cell repertoires, from ipatasertib and ipatasertib + atezolizumab treatment. These analyses will be done using appropriate statistical methods.

For Cohort 3, pCR analyses similar to that described in Section 6.6 will be run in the subgroup of patients with *PIK3CA/AKT1/PTEN* genetic alterations and/or subgroups of patients by PD-L1 status.

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 IMP, including eCRFs, 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 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 9.7).

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

8.4 CONFIDENTIALITY

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

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

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.6).

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 *MANAGEMENT OF STUDY QUALITY*

The Sponsor has implemented a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor identified potential risks associated with critical trial processes and data and implemented plans for evaluating and controlling these risks. Risk evaluation and control included the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed.

Details on the establishment and monitoring of quality tolerance limits areprovided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

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

9.5 ADMINISTRATIVE STRUCTURE

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

Up to 25 sites in the United States, Spain, France, the United Kingdom, and Australia will participate to enroll approximately 202 patients. Sequential enrollment into Arms A1, B1, A2, and B2 will be employed. To further explore tolerability of the triplet combination, additional arms (Arms C and D), with stepwise introduction of the treatment drugs, will be opened. Sequential enrollment order in Cohort 1 will then be as follows: A1 → B1 → A2 → B2/C1 → D1 → C2 → D2. Both Arms B2 and Arms C or D can be open simultaneously, but priority for filling of arms will go to Arms C and D. To further investigate the tolerability and efficacy of the triplet combination regime used in Arm A in first-line metastatic TNBC, Arm A will be further extended to include another expansion phase (Stage 3, Arm A3). Arm A3 will open after Arms C2 and D2 have been filled. Enrollment into the biopsy cohort (Cohort 2) will be gated by encouraging efficacy as described in Section 3.1.6. To explore tolerability of the triplet combination in the locally advanced TNBC setting, Cohort 3, with two additional arms (Arms F and G), will be opened. Enrollment order in Cohort 3 will be as follows: F1 → G1 → F2 and/or G2. Cohort 4 will further evaluate the triplet combination of Ipat + Atezo + Pac in patients with PD-L1–positive tumors.

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.

The Study Medical Monitor and the Study Team (see Internal Safety Monitoring, Section 3.1.11) will monitor and evaluate patient safety throughout the study.

9.6 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. 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.

9.7 PROTOCOL AMENDMENTS

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

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

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Appendix 1
Schedule of Activities: Cohorts 1 and 4

	Screening (Day –28 to Day –1)	Treatment Cycles (28-Day Cycles) [a]												Treatment Discon. [b]	Disease Follow-Up	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			
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]															
Plasma sample for biomarkers [f]		x [g]		x												
Blood sample for WGS [h]		x														
Complete physical examination [i]	x													x		
Limited physical examination		x	x	x	x		x	x		x	x					
Weight	x	x			x			x			x					
Height	x															
Vital signs [j]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
ECOG Performance Status	x	x			x			x			x			x		
ECHO or MUGA scan	x [k]															
12-Lead ECG [l]	x													x		
Hematology [m]	x	x [n]	x [n]	x [n]	x [n]	x [n]	x [n]	x [n]	x [n]	x [n]	x [n]	x [n]	x [n]	x		

Appendix 1
Schedule of Activities: Cohort 1 and 4 (cont.)

	Screening (Day –28 to Day –1)	Treatment Cycles (28-Day Cycles) [a]												Treatment Discon. [b]	Disease Follow-Up	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			
INR and PTT (or aPTT)	x													x		
Fasting serum chemistry [o]	x	x [n]	x [n]	x [n]	x [n]	x [n]	x [n]	x [n]	x [n]	x [n]	x [n]	x [n]	x [n]	x		
TSH, free T3 (or total T3), free T4 [p]	x	x						x			x [p]			x		
Fasting lipid profile, amylase, lipase	x				x [q]						x [q]			x		
HbA_{1c}	x				x [q]						x [q]			x		
Urinalysis	x	As clinically indicated												x		
Pregnancy test [r]	x	x [r]			x			x			x			x		x [r]
Tumor assessments [s]	x				x [t]						x [t]			x [u]	x [u]	
Bone scan	x [v]	See footnote "v"												x [t]	x [u]	
Head scan (CT or MRI scan)	x [w]															
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 Section 5.1.9.4; anti-diarrheal treatment should also be resumed with loperamide prophylaxis as needed.														

Appendix 1
Schedule of Activities: Cohort 1 and 4 (cont.)

	Screening (Day –28 to Day –1)	Treatment Cycles (28-Day Cycles) [a]												Treatment Discon. [b]	Disease Follow-Up	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			
Stool sample (optional)		Samples will be used for fecal calprotectin assay when patients experience any diarrhea. Test diarrhea sample at nearest Cycle and day clinic visit associated with diarrhea onset. This test should only be done on patients reporting diarrhea; do not request stool sample if patient has no complaints of diarrhea. Take voluntary stool sample at each clinic visit where patient continues to report event of diarrhea.														
Ipatasertib distribution/ accountability		x [x]			x			x			x					
Atezolizumab administration		x [x]		x	x		x	x		x	x		x			
Paclitaxel or nab-paclitaxel administration [y]		x [x]	x	x	x	x	x	x	x	x	x	x	x			
Record cancer-related medications and surgical procedures	x													x		
Concomitant medications [z]	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Adverse events [aa]	x	x	x	x	x	x	x	x	x	x	x	x	x	x [bb]	x [bb]	x [bb]
PK and ADA samples [cc]		x		x [dd]	x		x	x						x [ee]		
Tumor tissue sample obtained at time of progression (optional) [ff]														x [ff]		

Appendix 1
Schedule of Activities: Cohort 1 and 4 (cont.)

	Screening (Day –28 to Day –1)	Treatment Cycles (28-Day Cycles) [a]												Treatment Discon. [b]	Disease Follow-Up	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			
Patient diary (medication, dosing log, Kit ID)		x	x	x	x	x	x	x	x	x	x	x	x	x		
Survival follow-up and anti-cancer treatment																x [gg]

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 28 days after the last administration of ipatasertib, atezolizumab, paclitaxel or nab-paclitaxel, whichever is discontinued last, or prior to initiation of another therapeutic regimen.

[c] The Informed Consent Form needs to be re-signed if patient is treated beyond progression.

[d] HIV, HBsAg, total HBcAb, and HCV antibody. Additional tests for HBV DNA or HCV RNA will be required to confirm eligibility in patients with a positive antibody result.

Appendix 1
Schedule of Activities: Cohort 1 and 4 (cont.)

[e] Archival tissue (either formalin-fixed, paraffin-embedded tumor specimens or a minimum of 20 unstained serial paraffin slides [or 15 slides for Cohort 4]) 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] Plasma sample collection for cytokine analysis; applies only to Arms C and D. Plasma from one 6-mL blood draw collected prior to receiving study treatment on Cycle 1 Day 1, Cycle 1 Day 15, and Cycle 2 Day 15.

[g] Plasma sample does not need to be collected on Cycle 2 Day 1.

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

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

[j] 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 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.

[k] Performed within 12 weeks prior to Day 1, 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.

[l] A single 12-lead ECG measurement at screening and at the treatment discontinuation visit, and as clinically indicated (refer to Section 4.5.8).

[m] 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.

[n] 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.

[o] Includes sodium, potassium, bicarbonate, glucose, 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.

Appendix 1
Schedule of Activities: Cohort 1 and 4 (cont.)

[p] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every third cycle thereafter (i.e., Cycles 4, 7, 10, etc.).

[q] Fasting lipid profile, amylase, lipase, and HbA_{1c} will be assessed at screening, every three cycles starting on Day 1 of Cycle 3, and at treatment discontinuation visit.

[r] For women of childbearing potential. A serum pregnancy test is to be performed at screening (must be performed within 48 hours prior to Cycle 1, Day 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. During follow-up, urine pregnancy tests will be performed at 3 and 6 months after the final dose of study treatment. 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.

[s] 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 $\geq$ 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 blinded independent central review when needed.

[t] Tumor assessments performed every 8 weeks starting on Days 21–28 of Cycle 2 and every 8 weeks thereafter until documented disease progression per RECIST v1.1 or until loss of clinical benefit. Tumor assessments should be performed and reviewed $\leq$7 days prior to continuation of study treatment on Day 1 of the subsequent cycle. Images for tumor assessments will be collected to enable retrospective blinded independent central review when needed.

[u] At treatment discontinuation visit, tumor assessments should be performed only if not performed within the previous 6 weeks and bone scans (if applicable) should be performed only if not performed within the previous 12 weeks. If a patient discontinues from the study for any reason other than disease progression per RECIST v1.1, every effort should be made to obtain follow-up CT scans to assess disease response approximately every 8–12 weeks and obtain bone scans (if applicable) approximately every 16 weeks until documented progressive disease per RECIST v1.1. Images for tumor assessments and bone scans will be collected to enable retrospective blinded independent central review when needed.

[v] 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 treatment discontinuation visit.

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

Appendix 1
Schedule of Activities: Cohort 1 and 4 (cont.)

[x] 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. If patient is in Arms C1 or C2, atezolizumab dose on Day 1 of Cycle 1 should not be administered (refer to Section 3 and Figure 2). If patient is in Arms D1 or D2, ipatasertib 400 mg will be administered orally QD on Days 15–21 of the first cycle. In all subsequent treatment cycles (Cycles ≥2), ipatasertib 400 mg will be administered orally once a day (QD) on Days 1–21 (refer to Section 3 and Figure 2).

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

[z] 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.

[aa] 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 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 last dose of study treatment or until initiation of new systemic 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.

[bb] 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). 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.

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

[dd] Cycle 2 is applicable to Arms C and D only.

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

[ff] 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 1
Schedule of Activities: Cohort 1 and 4 (cont.)

[gg] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Appendix 2
Schedule of Activities: Cohort 2 (Biopsy)

	Screening (Day −28 to Day −1)	Treatment Cycle (35-Day Cycle) [a]				Treatment Cycle (28-Day Cycle) [a]												Treatment Discon. [b]	Disease FU	Post-Treat. FU
		Cycle 1				Cycle 2			Cycle 3			Cycle 4			Cycles ≥ 5					
		D1	D8	D15	D22	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15			
Signed informed consent(s)	x																			
Viral serology [c]	x																			
Demographics, medical history, prior cancer treatment	x																			
Tumor biopsy [d]	x [d]		x [d]					x [d]												
Plasma sample for biomarkers [e]	x [e]		x [e]					x [e]	x [e]									x [e]		
Blood sample for biomarkers [f]	x [f]		x [f]					x [f]	x [f]									x [f]		
Blood sample for WGS [g]		x																		
Complete physical examination [h]	x																	x		
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	x		
ECOG Performance Status	x	x				x						x			x			x		
ECHO or MUGA scan	x [j]																			

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

	Screening (Day −28 to Day −1)	Treatment Cycle (35-Day Cycle) [a]				Treatment Cycle (28-Day Cycle) [a]												Treatment Discon. [b]	Disease FU	Post-Treat. FU
		Cycle 1				Cycle 2			Cycle 3			Cycle 4			Cycles ≥ 5					
		D1	D8	D15	D22	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15			
12-Lead ECG [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		
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		
TSH, free T3 (or total T3), free T4 [o]	x	x										x			x [o]			x		
Fasting lipid profile, amylase, lipase	x								x [p]						x [p]			x		
HbA_{1c}	x								x [p]						x [p]			x		
Urinalysis	x	As clinically indicated																x		
Pregnancy test [q]	x	x [q]				x			x			x			x			x		x [q]
Tumor assessments [r]	x								x [s]						x [s]			x [t]	x [s]	
Bone scan	x [u]	See footnote "u"																x [u]	x [s]	
Head scan (CT or MRI scan)	x [v]																			

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

	Screening (Day −28 to Day −1)	Treatment Cycle (35-Day Cycle) [a]				Treatment Cycle (28-Day Cycle) [a]												Treatment Discon. [b]	Disease FU	Post-Treat. FU
		Cycle 1				Cycle 2			Cycle 3			Cycle 4			Cycles ≥ 5					
		D1	D8	D15	D22	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15			
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 Section 5.1.9.4; anti-diarrheal treatment should also be resumed with loperamide prophylaxis as needed.																		
Stool sample (optional)		Samples will be used for fecal calprotectin assay when patients experience any diarrhea. Test diarrhea sample at nearest Cycle and day clinic visit associated with diarrhea onset. This test should only be done on patients reporting diarrhea; do not request stool sample if patient has no complaints of diarrhea. Take voluntary stool sample at each clinic visit where patient continues to report event of diarrhea.																		
Ipatasertib distribution/ accountability		x [w]				x			x			x			x					
Atezolizumab administration			x		x	x		x	x		x	x		x	x		x			
Record cancer-related medications and surgical procedures	x																	x		
Concomitant medications [y]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Adverse events [z]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [aa]	x [aa]	x [aa]

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

	Screening (Day −28 to Day −1)	Treatment Cycle (35-Day Cycle) [a]				Treatment Cycle (28-Day Cycle) [a]												Treatment Discon. [b]	Disease FU	Post-Treat. FU
		Cycle 1				Cycle 2			Cycle 3			Cycle 4			Cycles ≥ 5					
		D1	D8	D15	D22	D1	D8	D15	D1	D8	D15	D1	D8	D15	D1	D8	D15			
PK and ADA samples [bb]		x [cc]	x			x			x			x						x[dd]		
Tumor tissue sample obtained at time of progression (optional)[ee]																		x[ee]		
Patient diary (medication, dosing log, Kit ID)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Survival follow-up and anti-cancer treatment																				x [ff]

ADA = anti-drug antibody; BID = twice a day; CT = computed tomography; ctDNA = circulating tumor DNA; D = day; Discon. = discontinuation; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; FU = follow up; 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; 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 28 days after the last administration of ipatasertib, atezolizumab, whichever is discontinued last, or prior to initiation of another therapeutic regimen.

[c] HIV, HBsAg, total HBcAb, and HCV antibody. Additional tests for HBV DNA or HCV RNA will be required to confirm eligibility in patients with a positive antibody result.

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

[d] The predose specimen will be obtained after eligibility criteria have been fulfilled and prior to Day 1 of Cycle 1. A subsequent biopsy will be performed on either Day 7 or 8 of Cycle 1, prior to the administration of atezolizumab. An additional biopsy will be collected on Day 15 of Cycle 2. See the laboratory manual for details.

[e] Plasma will be collected for ctDNA and cytokine analysis at screening, on either Day 7 or 8 of Cycle 1, prior to the administration of atezolizumab, on Day 15 of Cycle 2, Day 1 of Cycle 3, and at the study drug discontinuation visit.

[f] Blood will be collected for assessment of circulation biomarkers at screening, either Day 7 or 8 of Cycle 1, prior to the administration of atezolizumab, on Day 15 of Cycle 2, Day 1 of Cycle 3, and at the study drug discontinuation visit.

[g] Samples will be collected only at sites with local regulatory authority approval.

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

[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). 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, 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.

[k] A single 12-lead ECG measurement at screening and at the treatment discontinuation visit, and as clinically indicated (refer to Section 4.5.8).

[l] Includes WBC count, WBC differential count (including ANCs, 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.

[n] Includes sodium, potassium, bicarbonate, glucose, 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 $\geq$ 3 non-hematologic toxicity should be monitored at least weekly.

[o] 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.).

[p] Fasting lipid profile, amylase, lipase, and HbA_{1c} will be assessed at screening, every three cycles starting on Day 1 of Cycle 3, and at the treatment discontinuation visit.

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

[q] For women of childbearing potential. A serum pregnancy test is to be performed at screening (must be performed within 48 hours prior to Cycle 1, Day 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. During follow-up, urine pregnancy tests will be performed at 3 and 6 months after the final dose of study treatment. 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.

[r] 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 $\geq$ 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 blinded independent central review when needed.

[s] Tumor assessments performed every 8 weeks starting on Days 21–28 of Cycle 2 and every 8 weeks thereafter until documented disease progression per RECIST v1.1 or until loss of clinical benefit. Tumor assessments should be performed and reviewed $\leq$7 days prior to continuation of study treatment on Day 1 of the subsequent cycle. Images for tumor assessments will be collected to enable retrospective blinded independent central review when needed.

[t] At the treatment discontinuation visit, tumor assessments should be performed only if not performed within the previous 6 weeks and bone scans (if applicable) should be performed only if not performed within the previous 12 weeks. If a patient discontinues from the study for any reason other than disease progression per RECIST v1.1, every effort should be made to obtain follow-up CT scans to assess disease response approximately every 8–12 weeks and obtain bone scans (if applicable) approximately every 16 weeks until documented progressive disease per RECIST v1.1. Images for tumor assessments and bone scans will be collected to enable retrospective blinded independent central review when needed.

[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, follow-up bone scans should be performed during Days 16–28 of every fourth cycle (every 16 weeks) and at the treatment discontinuation visit.

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

[w] 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.

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

[y] 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.

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

[z] 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 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 last dose of study treatment or until initiation of new systemic 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.

[aa] 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). 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.

[bb] See Appendix 5 for schedule of PK assessments.

[cc] Plasma sample collection to measure coproporphyrin I and III concentrations only.

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

[ee] 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 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.

[ff] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Sponsor terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

Appendix 3
Schedule of Activities: Cohort 3

	Screening [a]	Neoadjuvant Treatment (28-Day Cycles) (Cycles 1–5; Weeks 1–20)				Pre-Surgery Visit [b]	Study Completion Visit [c] or Early Termination Visit [d]	Follow-Up
	Days –28 to –1	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)	Day 22 (±3 days)			
Informed consent	x [e]							
Baseline tumor tissue sample	x [f]							
Demographic data	x							
Medical history and baseline conditions	x							
Vital signs [g]	x	x	x	x	x	x	x	
Weight	x	x	x	x	x		x	
Height	x							
Complete physical examination [h]	x							
Limited physical examination [i]		x				x	x	
ECOG Performance Status [j]	x	x				x	x	
Disease status assessment [k, l]	x	x [k]				x	x	
Lymph node staging	x [m]							
ECG (12-lead) [n]	x	x [n]		x [n]			x [n]	
ECHO or MUGA scan [o]	x	Cycle 3 only [o]					x [o]	
Hematology [p]	x	x [q]	x [q]	x [q]	x [q]	x	x	

Appendix 3
Schedule of Activities: Cohort 3 (cont.)

	Screening [a]	Neoadjuvant Treatment (28-Day Cycles) (Cycles 1–5; Weeks 1–20)				Pre-Surgery Visit [b]	Study Completion Visit [c] or Early Termination Visit [d]	Follow-Up
	Days –28 to –1	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)	Day 22 (±3 days)			
Fasting serum chemistry [r]	x [q]	x [q]	x [q]	x [q]	x [q]	x	x	
Pregnancy test [s]	x [q]	x [s]					x [s]	x [s]
INR and PTT (or aPTT)	x [q]					x	x	
TSH, free T3 (or total T3), and free T4 [t]	x [q]	Cycles 1 and 4 only [t]					x	
Fasting lipid profile, amylase, lipase	x	Cycle 1 only [u]				x		
HbA_{1c}	x	Cycle 1 only [u]				x		
Viral serology [v]	x [q]							
Urinalysis [w]	x [q]	As clinically indicated					x	
Serum PK sample for ipatasertib and atezolizumab		See Appendix 6 for detailed schedule						
Serum ADA sample for atezolizumab		See Appendix 6 for detailed schedule						
Blood and plasma samples for biomarkers		See Appendix 6 for detailed schedule						
Blood sample for RBR (optional) [x]		Cycle 1 only [x]						
Tumor tissue from surgical resection						x [y]		

Appendix 3
Schedule of Activities: Cohort 3 (cont.)

	Screening [a]	Neoadjuvant Treatment (28-Day Cycles) (Cycles 1–5; Weeks 1–20)				Pre-Surgery Visit [b]	Study Completion Visit [c] or Early Termination Visit [d]	Follow-Up
	Days −28 to −1	Day 1 (±3 days)	Day 8 (±3 days)	Day 15 (±3 days)	Day 22 (±3 days)			
Bilateral mammogram	x [z, aa]	As clinically indicated				x [aa]		
Other radiographic assessments (e.g., CT scan, MRI, PET scan)	x [l, aa, bb, cc]	As clinically indicated [l, aa, bb]						
Ultrasound of breast and axilla	x [aa]					x [aa]		
Concomitant medications	x [dd]	x	x	x	x	x	x	x
Adverse events [ee]	x [ee]	x	x	x	x	x	x [ee]	x [ee]
Dispense ipatasertib		x						
Review diary and collect unused medication		x	x	x	x	x		
Prophylactic treatment administration		x [ff]						
Study treatment administration [hh]		x	x [gg]	x	x [gg]			

Appendix 3
Schedule of Activities: Cohort 3 (cont.)

AC = doxorubicin + cyclophosphamide; ADA = anti-drug antibody; CT = computed tomography; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L = EuroQoL 5-Dimension, 5-Level; ER = estrogen receptor; FACT-G = Functional Assessment of Cancer Therapy-General; FVC = forced vital capacity; FEV_1 = forced expiratory volume 1; FEF_{25-75} = forced expiratory flow 25%–75%; FFPE = formalin-fixed, paraffin-embedded; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition; PD-L1 = programmed death–ligand-1; PET = positron emission tomography; PgR = progesterone receptor; PK = pharmacokinetic; PRO = patient-reported outcome; QD = once daily; RBR = Research Biosample Repository; T3 = triiodothyronine; T4 = thyroxine; Term. = termination; TSH = thyroid-stimulating hormone.

Notes: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. 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.

Assessments shaded in gray should be performed as scheduled, but the associated data do not need to be recorded on the eCRF (except in the case of an adverse event).

[a] 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 prior to Day 1 of Cycle 1 unless otherwise noted. Patients must have adequate hematologic and organ function within 14 days prior to Day 1 of Cycle 1, as defined in Section 4.1.1.

[b] The pre-surgery visit and associated assessments should occur within 14 days prior to surgery. Surgery should be conducted between 2 and 6 weeks after the final dose of neoadjuvant therapy. Pre-operative laboratory tests should be performed as per institutional practice.

[c] The study completion visit should occur after all surgical pathology reports are available and not more than 60 days after the final dose of study treatment.

[d] Patients who discontinue the study prematurely will return to the clinic for an early termination visit not more than 60 days after the final dose of study treatment.

[e] 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.

Appendix 3
Schedule of Activities: Cohort 3 (cont.)

[f] The most recently collected tumor tissue sample will be submitted for HER2, ER, and PgR determination and exploratory biomarker research. Retrieval and submission of tissue sample can occur more than 28 days prior to initiation of study treatment, provided it occurs after signing of the Informed Consent Form. Tumor tissue should be of good quality based on total and viable tumor content (sites will be informed if the quality of the submitted specimen is inadequate). An FFPE block of at least 15 unstained slides and an associated pathology report must be confirmed to be available prior to entry into the study. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core-needle biopsy specimens, at least three cores should be submitted for evaluation. Refer to Section 4.5.7 for details on tumor tissue samples.

[g] Includes respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. For the first atezolizumab infusion, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated, every 15 (±5) minutes during and 30 (±10) minutes after the infusion. For subsequent atezolizumab infusions, vital signs should be measured within 60 minutes prior to the infusion and, if clinically indicated or if symptoms occurred during the previous infusion, during and 30 (±10) minutes after the infusion.

[h] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

[i] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints.

[j] See Appendix 7.

[k] Assessment of primary tumor and regional lymph nodes should be done by physical examination during screening, within 3 days prior to each treatment cycle, within 14 days prior to surgery, and at the study completion or early termination visit. Assessments should include measurement of tumors in the breast, preferably through use of calipers or a ruler or tape measure.

[l] Additional disease assessments (e.g., liver function tests, radiographs) may be performed when clinically indicated to exclude metastatic disease, as per current institutional practice. Whenever possible, disease recurrence should be confirmed pathologically.

[m] Patients who have enlarged or suspicious axillary nodes by physical examination or by any radiographic imaging (e.g., cortical thickness >2 mm) at screening should undergo fine-needle aspiration or core-needle biopsy prior to enrollment. Lymph nodes will be staged as described in Section 4.5.6.6.

[n] ECG recordings will be obtained during screening*, at each doxorubicin administration (Days 1 and 15 of Cycles 1–2), at study completion/early termination visit,* and as clinically indicated. *Screening ECG assessments obtained ≤48 hours before Day 1 of Cycle 1 do not have to be repeated on Day 1 of Cycle 1.* Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[o] ECHO or MUGA scans will be performed on all patients enrolled in the study. ECHO is the preferred method. The same method used for a given patient at screening should be used throughout the study. ECHO or MUGA scans should be performed at screening, at Day 1 of Cycle 3, and at the study completion or early termination visit if not performed within the previous 6 weeks.

Appendix 3
Schedule of Activities: Cohort 3 (cont.)

[p] Includes WBC count, WBC differential count (including ANCs, lymphocytes), hemoglobin, hematocrit, and platelet count.

[q] 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. *Screening local laboratory assessments obtained ≤48 hours before Day 1 of Cycle 11 do not have to be repeated on Day 1 of Cycle 1. Note that hematology and fasting serum chemistry laboratories are not required on Days 8 and 22 during Cycles 1–2 because no chemotherapy infusions are being given on these days.*

[r] Includes sodium, potassium, bicarbonate, glucose, 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.

[s] All women of childbearing potential will have a serum pregnancy test at screening (must be performed within 48 hours prior to initiation of study treatment). Urine or serum pregnancy tests will be performed at specified subsequent visits. During follow-up, urine pregnancy tests will be performed at 3, 6, 9, and 10 months after the final dose of study treatment. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[t] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed on Day 1 of Cycles 1 and 4.

[u] Fasting lipid profile, amylase, lipase, and HbA_{1c} will be assessed at screening, on Day 1 of Cycle 1, and within 14 days prior to surgery.

[v] Includes HIV, HBsAg, total HBcAb, and HCV antibody. Additional tests for HBV DNA or HCV RNA will be required to confirm eligibility in patients with a positive antibody result.

[w] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted, with microscopic examination performed is clinically indicated.

[x] Not applicable for a site that has not been granted approval for RBR sampling. Performed only for patients at participating sites who have provided written informed consent to participate. Blood sample will be collected on Day 1 of Cycle 1.

[y] An FFPE tumor tissue block with at least three core biopsies should be obtained during scheduled surgical resection.

[z] The unaffected breast should be imaged within 60 days prior to initiation of study treatment. The affected breast should be imaged within 28 days prior to initiation of study treatment.

[aa] Tumors should be measured at screening and within 14 days prior to surgery. Tumors should be accurately measured in at least one dimension (longest diameter to be recorded) through use of conventional techniques (most commonly mammogram, but may be supplemented as clinically indicated with other radiologic assessments such as PET scan, CT scan, MRI, ultrasound, or X-ray).

[bb] Additional breast imaging such as MRI is not mandated but may be performed at the investigator's discretion per local practice. If MRI is conducted, suggested timelines for MRI are within 28 days prior to treatment initiation, after completion of Cycle 2, and 14 days prior to surgery. Results from optional MRIs or other breast imaging (other than mammograms) should be entered into the eCRF.

Appendix 3
Schedule of Activities: Cohort 3 (cont.)

[cc] Baseline distant-site tumor staging procedures should be performed as clinically indicated in alignment with National Comprehensive Cancer Network (NCCN) or national guidelines (see Section 4.5.6.4).

[dd] 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.

[ee] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new 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 last dose of study treatment or until initiation of new anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Section 5.6). 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 treatment or trial-related procedures until a final outcome can be reported.

[ff] Prophylactic treatment should be administered as described in Section 4.3.3.

[gg] Patients will be treated for five cycles of 28 days each. Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Days 1 and 15 of Cycles 1–5. Doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 will be administered by IV infusion on Days 1 and 15 of Cycles 1 and 2. Paclitaxel 80 mg/m^2 will be administered by IV infusion on Days 1, 8, 15, and 22 of Cycles 3–5. In Arm F, ipatasertib will be administered orally QD at a dose of 300 mg on Days 1–21 of Cycles 1 and 2 and at a dose of 400 mg on Days 1–21 of Cycles 3–5. In Arm G, ipatasertib will be administered orally QD at a dose of 400 mg on Days 1–21 of Cycles 1–5.

Appendix 4
Schedule of Pharmacokinetic and Immunogenicity Samples: Cohorts 1 and 4

Table 1 Schedule of Pharmacokinetic and Immunogenicity Samples for Cohort 1 (Arms A and B) and Cohort 4 (Arm H)

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)
Day 15 of Cycle 1	Prior to ipatasertib dose	• Ipatasertib PK (plasma)
	1 hour after ipatasertib dose	• Ipatasertib PK (plasma)
	2 hours after ipatasertib dose	• Ipatasertib PK (plasma)
	4 hours after ipatasertib dose	• Ipatasertib PK (plasma)
	6 hours after ipatasertib dose	• Ipatasertib PK (plasma)
Day 15 of Cycle 1	Prior to start of atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
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	1–3 hours after ipatasertib dose	• Ipatasertib PK (plasma)
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.

Appendix 4
Schedule of Pharmacokinetic and Immunogenicity Samples: Cohorts 1 and 4 (cont.)

Table 2 Schedule of Pharmacokinetic and Immunogenicity Samples for Cohort 1 (Arms C and D)

Visit	Time	Sample
Day 1 of Cycle 1	Prior to start of first atezolizumab infusion (Arm D only)	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
	30 (±10) minutes after end of atezolizumab infusion (Arm D only)	• Atezolizumab PK (serum)
Day 15 of Cycle 1	Prior to start of atezolizumab infusion Prior to start of ipatasertib dose (Arm C only)	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Ipatasertib PK (plasma)
	30 (±10) minutes after end of atezolizumab infusion (Arm C only)	• Atezolizumab PK (serum)
	2 hours (±30) after ipatasertib dose (Arm D only)	• Ipatasertib PK (plasma)
Day 1 of Cycle 2	Prior to start of atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 15 of Cycle 2	Prior to ipatasertib dose	• Ipatasertib PK (plasma)
	1 hour after ipatasertib dose	• Ipatasertib PK (plasma)
	2 hours after ipatasertib dose	• Ipatasertib PK (plasma)
	4 hours after ipatasertib dose	• Ipatasertib PK (plasma)
	6 hours after ipatasertib dose	• Ipatasertib PK (plasma)
Day 15 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	1–3 hours after ipatasertib dose	• Ipatasertib PK (plasma)
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.

Appendix 5
Schedule of Pharmacokinetic and Immunogenicity Samples: Cohort 2 (Biopsy Cohort)

Visit	Time	Sample
Day 1 of Cycle 1	Prior to ipatasertib dose [a]	• Coproporphyrin I and III sample (plasma)
Day 8 of Cycle 1	Prior to ipatasertib dose	• Ipatasertib PK (plasma) • Coproporphyrin I and III sample (plasma)
	1 hour after ipatasertib dose	• Ipatasertib PK (plasma) • Coproporphyrin I and III sample (plasma)
	2 hours after ipatasertib dose	• Ipatasertib PK (plasma) • Coproporphyrin I and III sample (plasma)
	Prior to start of first atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
	30 (±10) minutes after end of atezolizumab infusion	• Atezolizumab PK (serum)
Day 1 of Cycle 2	Prior to atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 3	Prior to atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 4	Prior to 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; Atezo + Ipat = atezolizumab plus ipatasertib; PK = pharmacokinetic.

Notes: 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.

PK sampling should be conducted on the day of dosing and adapted based on actual date of dosing.

Dose time on the day before and day of PK sampling should be accurately reported. Ipatasertib dosing on the day of PK sampling should be taken in the clinic.

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.

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

Appendix 6
Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples: Cohort 3

Visit	Time	Sample
Day 1 of Cycle 1	Prior to the first dose	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (blood and plasma)
	30 (±10) minutes after completion of atezolizumab infusion	• Atezolizumab PK (serum)
Day 15 of Cycles 1 and 4 [a]	Prior to dose	• Ipatasertib and G-037720 PK (plasma)
	2 to 4 hours after dose	• Ipatasertib and G-037720 PK (plasma)
Day 1 of Cycles 2, 3, 4, and 5	Prior to dose	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Surgical intervention	Prior to surgery	• Biomarkers (blood and plasma)
Study completion visit or early termination visit (≤60 days after final dose of study treatment)	NA	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma)
At disease recurrence	NA	• Biomarkers (blood and plasma)

ADA = anti-drug antibody; NA = not applicable; PK = pharmacokinetic; RBR = Research Biosample Repository; WGS = whole genome sequencing.

Notes: 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.

If treatment is withheld (e.g., due to adverse events), the pharmacokinetic, immunogenicity, and biomarker samples during the neoadjuvant phase should be taken during the same cycle as shown in the table above (e.g., if the dose on Day 1 of Cycle 2 is delayed, the atezolizumab PK [serum] sample and atezolizumab ADA [serum] sample scheduled for predose should still be taken on Day 1 of Cycle 2). The only exception is on Day 1 of Cycle 1 when the sample should only be taken on the day of the patient's first dose of the study.

Biomarker (blood) sample may include whole blood WGS (i.e., at sites with local regulatory authority approval). Please see lab manual for detailed collection instructions.

[a] Day 15 of Cycle 1 for Arm F; Day 15 of Cycles 1 and 4 for Arm G.

Appendix 7
Eastern Cooperative Oncology Group
Scale of Performance Status

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

Oken MM, Creech RH, Tormey DC, et al: Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol 1982;5:649–55.

Appendix 8
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 8
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 http://www.cap.org/web/home/resources/cap-guidelines/current-cap-guidelines/er-pgr-guideline.

Appendix 9
ASCO/CAP HER2 Test Guideline Recommendations

Table 1. Summary of All Recommendations (original recommendations and focused update recommendations)

Topic	2013 Recommendations	2018 Focused Update Recommendations
Specimens to be tested	All newly diagnosed patients with breast cancer must have a HER2 test performed. Patients who then develop metastatic disease must have a HER2 test performed in a metastatic site, if tissue sample is available.	No change.
Optimal algorithm for HER2 testing	Must report HER2 test result as positive for HER2 if: 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 9
ASCO/CAP HER2 Test Guideline Recommendations (cont.)

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

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Appendix 9
ASCO/CAP HER2 Test Guideline Recommendations (cont.)

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 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.

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

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

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

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

(those with short axis $\geq$ 10 mm but $<$ 15 mm) should be considered non-target lesions. Nodes that have a short axis of $<$ 10 mm are considered non-pathological and should not be recorded or followed.

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

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

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.)

<u>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.</u>

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 timepoints specified in the protocol.

- CR: disappearance of all non-target lesions and (if applicable) normalization of tumor marker level
  - All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Non-CR/Non-PD: persistence of one or more non-target 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 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.

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

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.

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.

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

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.

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.

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

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

Subjects should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Subjects with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be subjects 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.* Contact the Medical Monitor regarding any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • Autoimmune myocarditis • Autoimmune oophoritis • Autoimmune orchitis • Autoimmune thrombocytopenic purpura • Behçet disease • Bullous pemphigoid • Chronic fatigue syndrome • Chronic inflammatory demyelinating polyneuropathy • Churg-Strauss syndrome • Crohn disease	• Dermatomyositis • 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 cirrhosis • 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 as required by patient status and directed by the physician in charge.
4. Continue to observe the patient and document observations.

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab

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

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

The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. In patients who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered if the patient is deriving benefit and has fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

PULMONARY EVENTS

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

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 6 in Section 5.1.9.4.

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

HEPATIC EVENTS

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 6 in Section 5.1.9.4.

GASTROINTESTINAL EVENTS

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 6 of Section 5.1.9.4.

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 below. For events of hyperglycemia, see Table 6 of Section 5.1.9.4.

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

Appendix 13
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 weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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]
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.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 1 Management Guidelines for Endocrine Events (cont.)

Event	Management
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 agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 2 below.

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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 agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

IMMUNE-MEDIATED MYOCARDITIS

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

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

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 3 below.

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 3 Management Guidelines for Immune-Mediated Myocarditis

Event	Management
Immune-mediated myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated myocarditis, Grade 3–4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

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

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 13
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 COVID-19 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 COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

Guidelines for medical management of IRRs during Cycle 1 are provided in Table 4 below. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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.* [e] • *Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact Medical Monitor.* [e] • *If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS.* • *If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact Medical Monitor.*

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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.* [f] • *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.* [f] • *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.* [e] *For patients who are refractory to anti-cytokine therapy, experimental treatmentsg may be considered at the discretion of the investigator and in consultation with the Medical Monitor.* • *Hospitalize patient until complete resolution of symptoms.*

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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 ℃ 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] *There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.*

[f] *Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor. 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 consulting the Medical Monitor and considering the benefit–risk ratio.*

[g] *Refer to Riegler et al. (2019) for information on experimental treatments for CRS.*

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

PANCREATIC EVENTS

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 5 below.

Table 5 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	• Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. [c]

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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 agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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 are provided in Table 6 below.

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.
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]

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 9 Management Guidelines for Dermatologic Events (cont.)

Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	***Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:*** • *Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis.* • *Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy.* • *Follow the applicable treatment and management guidelines above.* • *If Stevens-Johnson syndrome or toxic epidermal necrolysis 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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

NEUROLOGIC DISORDERS

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 7 below.

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness.

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 8 below.

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. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

RENAL EVENTS

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. 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 below.

Table 9 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

IMMUNE-MEDIATED MYOSITIS

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the

most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 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 agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 10 Management Guidelines for Immune-*Mediated* Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

Table 10 Management Guidelines for Immune-*Mediated* Myositis (cont.)

Event	Management
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS AND MACROPHAGE ACTIVATION SYNDROME

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS)*, 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.

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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 $\leq 181 \times 10^9$/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.

Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

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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Appendix 13
Risks Associated with Atezolizumab and Guidelines for Management of Adverse Events Associated with Atezolizumab (cont.)

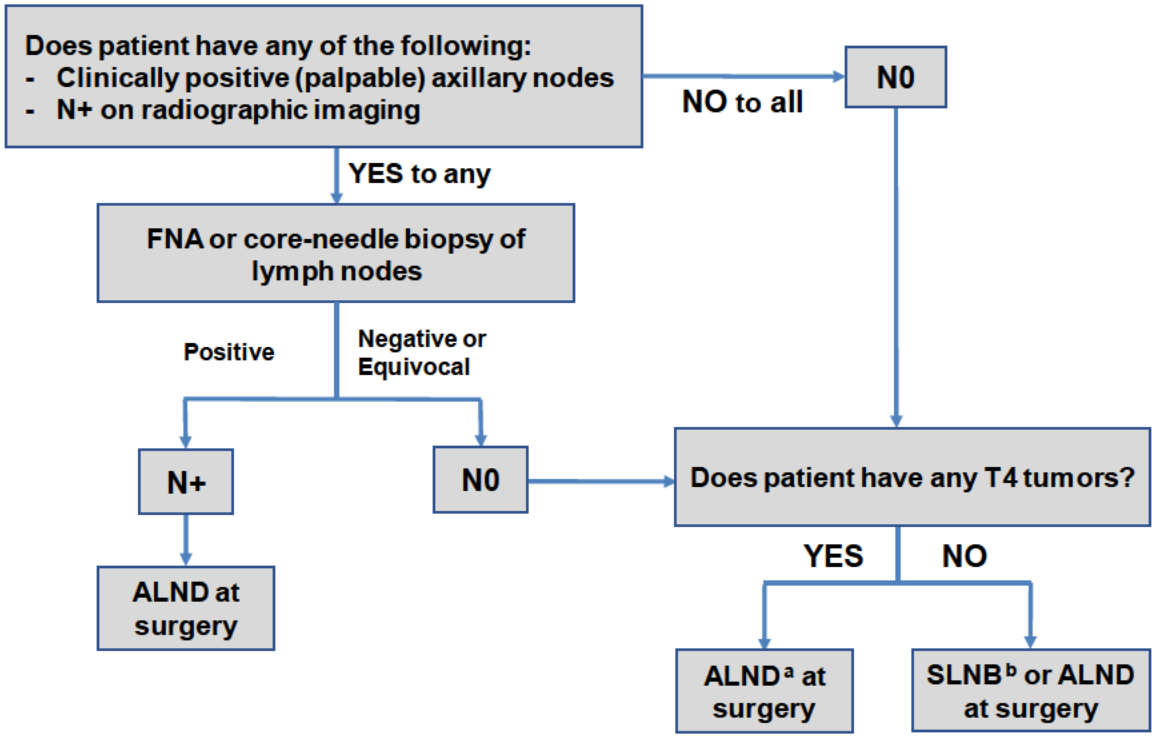
Ravelli A, Minoia F, Davi S, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Ann Rheum Dis 2016;75:481–9.

Riegler LL, Jones GP, Lee DW. Current approaches in the grading and management of cytokine release syndrome after chimeric antigen receptor T-cell therapy. Ther Clin Risk Manag 2019;15:323–35.

Rotz SJ, Leino D, Szabo S, et al. Severe cytokine release syndrome in a patient receiving PD-1-directed therapy. Pediatr Blood Cancer 2017;64:e26642.

Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood 2015;125:2908–14.

Appendix 14
Axillary Lymph Node Staging and Management



ALND = axillary lymph node dissection; FNA = fine-needle aspiration; SLNB = sentinel lymph node biopsy.

[a] ALND should be performed unless not aligned with institutional guidelines.

[b] If SLNB is conducted, it is strongly recommended that more than one lymph node (two to three minimum) be removed and that all patients with positive macrometastases in sentinel nodes undergo ALND regardless of the number of positive nodes.