Official Title: A Phase Ib/II, Open-Label, Multicenter, Randomized Umbrella Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-Based Treatment Combinations in Patients with Hormone Receptor-Positive HER2-Negative Breast Cancer (Morpheus-HR + Breast Cancer)

NCT Number: NCT03280563

Document Date: Protocol Version 6: 07-Feb-2023

PROTOCOL

PROTOCOL TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE IMMUNOTHERAPY-BASED TREATMENT COMBINATIONS IN PATIENTS WITH HORMONE RECEPTOR–POSITIVE HER2-NEGATIVE BREAST CANCER (MORPHEUS-HR+ BREAST CANCER)**
PROTOCOL NUMBER:	CO39611
VERSION NUMBER:	6
TEST COMPOUNDS:	Atezolizumab (RO5541267), Ipatasertib (RO5532961), Bevacizumab (RO4876646), Entinostat, Abemaciclib
STUDY PHASE:	Ib/II
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 134,288 EudraCT Number: 2017-000335-14 EU Trial Number: Not applicable Clinical Investigation Identification Number (CIV ID): Not applicable NCT Number: NCT03280563
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and data stamp on the final page of this document.

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
6	See electronic date stamp on the final page of this document.
5	2 March 2022
4	14 February 2020
3	2 May 2019
2	4 June 2018
1	8 May 2017

PROTOCOL AMENDMENT, VERSION 6: RATIONALE

Protocol CO39611 has been amended primarily to align the protocol with recent updates to the Atezolizumab Investigator's Brochure (Version 19 and addendums). Substantive changes to the protocol, along with a rationale for each change, are summarized below:

- The synopsis has been simplified to align with Clinical Trial Regulation (CTR) requirements and other guidelines.
- A section describing the duration of participation for individual patients has been added to align with CTR requirements. Subsequent sections have been renumbered (Section 3.3).
- The medical term "Wegener granulomatosis" has been replaced by the term "granulomatosis with polyangiitis" to align with the updated preferred term in the MedDRA (Section 4.1.2.2 and Appendix 4).
- Reports for exploratory analyses from Foundation Medicine are not available, so this language has been removed (Section 4.5.6).
- Text has been revised to clarify the intended use of Research Biosample Repository samples (Section 4.5.9.1).
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 4.5.9.6).
- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (Section 5.4.1). Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites.
- Text has been revised to clarify that the [redacted] (Section 6.4.1).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with Roche practices (Section 8.4).
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Section 9.5).
- Appendix 4 has been revised to include autoimmune myelitis. Appendix 4 has also been revised to indicate that caution should be used when considering atezolizumab for patients who have previously experienced a pericardial disorder while receiving another immunostimulatory anti cancer agent.
- The adverse event management guidelines have been updated to align with the Atezolizumab Investigator's Brochure, Version 19 and Addendums 1 and 2 (Appendix 6).

- Hemophagocytic lymphohistiocytosis has been updated from a potential risk to an identified risk associated with atezolizumab and language has been revised accordingly (Appendices A8–6.1.1, A9–6.1.1, A11–6.1.1, A12–6.1.1, and A13–6.1.1).
- The list of identified risks for atezolizumab has been revised to include pericardial disorders, myelitis, and facial paresis (Appendices A8–6.1.1, A9–6.1.1, A11–6.1.1, A12–6.1.1, and A13–6.1.1).
- The responsibilities of the investigator and the role of the Medical Monitor during study conduct have been clarified (Appendices A8–6.1.4.3, A9–6.1.4.2, A11–6.1.5.2, A12–6.1.7.2, and A13–6.1.5.2; Tables A11–4 and A13–4).
- The list of adverse events of special interest has been revised to include myelitis and facial paresis (A8–6.2, A9–6.2, A11–6.2, A12–6.2, and A13–6.2).

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE Ib/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE IMMUNOTHERAPY-BASED TREATMENT COMBINATIONS IN PATIENTS WITH HORMONE RECEPTOR–POSITIVE HER2-NEGATIVE BREAST CANCER (MORPHEUS-HR+ 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 as instructed by Covance.

PROTOCOL SYNOPSIS

PROTOCOL TITLE:	**A PHASE IB/II, OPEN-LABEL, MULTICENTER, RANDOMIZED UMBRELLA STUDY EVALUATING THE EFFICACY AND SAFETY OF MULTIPLE IMMUNOTHERAPY-BASED TREATMENT COMBINATIONS IN PATIENTS WITH HORMONE RECEPTOR–POSITIVE HER2-NEGATIVE BREAST CANCER (MORPHEUS-HR+ BREAST CANCER)**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 134,288 EudraCT Number: 2017-000335-14 EU Trial Number: Not applicable Clinical Investigation Identification Number (CIV ID): Not applicable NCT Number: NCT03280563

STUDY RATIONALE

This study will evaluate the efficacy, safety, and pharmacokinetics of immunotherapy-based treatment combinations in patients with inoperable locally advance or metastatic hormone receptor-positive (HR+) HER2-negative breast cancer. Given the observed emergence of acquired resistance to CDK4/6i, patients who had disease progression during or following first- or second-line treatment with CDK4/6i are considered appropriate for trials of novel therapeutic candidates to identify effective post-CDK4/6i treatment regimens, including immunotherapies. The study will assess the importance of simultaneously targeting multiple mechanisms of immune escape through immune cell priming and activation, tumor infiltration, and/or recognition of tumor cells for elimination.

OBJECTIVES AND ENDPOINTS

Table 1 Objectives and Corresponding Endpoints for Stage 1

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	• OR, defined as a complete response or partial response, as determined by the investigator according to RECIST v1.1
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	• PFS, defined as the time from randomization [a] to the date of the first recorded occurrence of disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1 • CBR, defined as proportion of patients with stable disease ≥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 randomization [a] to death from any cause • OS at specific timepoints (e.g., 18 months) • DOR, defined as the time from the first occurrence of a documented OR to the first date of recorded disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1

Table 1 Objectives and Corresponding Endpoints for Stage 1 (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of immunotherapy-based treatment combinations during Stage 1	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in vital signs and ECG parameters • Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective	**Corresponding Endpoints**
• To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 1	• Plasma or serum concentration of each drug (as appropriate) at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to drugs that are administered as part of an immunotherapy-based treatment combination during Stage 1	• For drugs for which ADA formation is measured: presence of ADAs during the study relative to the presence of ADAs at baseline

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

[a] For the mandatory serial biopsy arms, PFS and OS will be determined from the time of treatment initiation (rather than the time of randomization).

Table 2 Objectives and Corresponding Endpoints for Stage 2

Safety Objective	Corresponding Endpoints
• To evaluate the safety of immunotherapy-based treatment combinations during Stage 2	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in vital signs and ECG parameters • Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2	• Plasma or serum concentration of each drug at specified timepoints
Immunogenicity Objective	**Corresponding Endpoint**
• To evaluate the immune response to drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2	• For drugs for which ADA formation is measured: presence of ADAs during the study relative to the presence of ADAs at baseline

Table 2 Objectives and Corresponding Endpoints for Stage 2 (cont.)

ADA = anti-drug antibody; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; PK = pharmacokinetic.

OVERALL DESIGN AND STUDY POPULATION

This is a Phase Ib/II, open-label, multicenter, randomized umbrella study in patients with inoperable locally advanced or metastatic HR+ breast cancer who had disease progression during or following treatment with a CDK4/6 inhibitor (e.g., palbociclib, ribociclib, abemaciclib) in the first- or second-line setting. The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, or modify the patient population (e.g., with regard to prior anti-cancer treatment or biomarker status). Eligible patients will initially be assigned to one of several treatment arms (Stage 1). Patients who experience disease progression, loss of clinical benefit, or unacceptable toxicity during Stage 1 may be eligible to continue treatment with a different treatment regimen (Stage 2).

During Stage 1, patients will be randomly assigned to a control arm (fulvestrant) or to one of the experimental arms consisting of doublet combinations of atezolizumab in combination with either entinostat (Atezo + Entino) or fulvestrant (Atezo + Fulvestrant), and endocrine therapy (ET)-containing triplet combinations of atezolizumab in combination with ipatasertib+fulvestrant (Atezo + Ipat + Fulvestrant) or abemaciclib + fulvestrant (Atezo + Abema + Fulvestrant). Enrollment for all experimental arms will take place in two phases: a preliminary phase followed by an expansion phase.

During Stage 1, patients in the control arm who experience disease progression per the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and patients in an experimental arm who experience loss of clinical benefit as determined by the investigator will be given the option of receiving a different treatment combination during Stage 2, provided they meet eligibility criteria and a Stage 2 arm is open for enrollment. Patients in the control arm who experience unacceptable toxicity and patients in an experimental arm who experience unacceptable toxicity not related to atezolizumab may be eligible for Stage 2 treatment. The Stage 2 treatment regimen consists of atezolizumab plus bevacizumab plus one of the following ETs based on physician's choice: fulvestrant, exemestane, or tamoxifen.

Several key aspects of the study design and study population are summarized below.

Phase:	Phase Ib/II	**Population Type:**	Postmenopausal women
Control Method:	Standard of Care Active comparator	**Population Diagnosis or Condition:**	Invasive HR+ HER2- negative breast cancer: metastatic or inoperable locally advanced
Interventional Model:	Parallel	**Population Age:**	≥ 18 years
Test Compound{s}:	Atezolizumab (RO5541267), Ipatasertib (RO5532961), Bevacizumab (RO4876646), Entinostat, Abemaciclib	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Fulvestrant	**Study Intervention Assignment Method:**	Randomization
Number of Arms:	6	**Number of Participants to Be Enrolled:**	Approximately 126–276 patients

STUDY TREATMENT

Table 3 Study Treatments

Treatment Group	Administration Method and Schedule [a]
Control Arm	
Fulvestrant 28-day cycles	• Cycle 1: fulvestrant 500 mg IM on Days 1 and 15 • Cycle ≥ 2: fulvestrant 500 mg IM on Day 1
Stage 1	
Atezolizumab plus Entinostat (Atezo + Entino) 21-day cycles	• Entinostat 5 mg by mouth once a week on Days 1, 8, and 15 • Atezolizumab 1200 mg by IV infusion on Day 1
Atezolizumab plus Fulvestrant (Atezo + Fulvestrant) 28-day cycles	• Fulvestrant 500 mg by IM injection on Days 1 and 15 of Cycle 1 followed by 500 mg by IM injection on Day 1 of every cycle thereafter • Atezolizumab 840 mg by IV infusion on Days 1 and 15
Atezolizumab plus Ipatasertib plus Fulvestrant (Atezo + Ipat + Fulvestrant) 28-day cycles	• Ipatasertib 400 mg by mouth once a day on Days 1–21 • Fulvestrant 500 mg by IM injection on Days 1 and 15 of Cycle 1 followed by 500 mg by IM injection on Day 1 of every cycle thereafter • Atezolizumab 840 mg IV infusion on Days 1 and 15
Atezolizumab plus Abemaciclib plus Fulvestrant (Atezo + Abema + Fulvestrant) 28-day cycles	• Abemaciclib 150 mg by mouth twice daily during each 28-day cycle • Fulvestrant 500 mg by IM injection on Days 1 and 15 of Cycle 1 followed by 500 mg by IM injection on Day 1 of every cycle thereafter • Atezolizumab 840 mg by IV infusion on Days 1 and 15

Table 3 Study Treatments (cont.)

Treatment Group	Administration Method and Schedule [a]
Stage 2	
Atezolizumab plus Bevacizumab plus Fulvestrant (Atezo + Bev + Fulvestrant) 28-day cycles	• Fulvestrant 500 mg IM injection on Days 1 and 15 of Cycle 1 followed by 500 mg IM injection on Day 1 of every cycle thereafter • Atezolizumab 840 mg by IV infusion on Days 1 and 15 • Bevacizumab 10 mg /kg by IV infusion on Days 1 and 15
Atezolizumab plus Bevacizumab plus Exemestane (Atezo + Bev + Exemestane) 21-day cycles	• Exemestane 25 mg by mouth once a day • Atezolizumab 1200 mg by IV infusion on Day 1 • Bevacizumab 15 mg/kg by IV infusion on Day 1
Atezolizumab plus Bevacizumab plus Tamoxifen (Atezo + Bev + Tamoxifen) 21-day cycles	• Tamoxifen 20 mg by mouth once a day • Atezolizumab 1200 mg by IV infusion on Day 1 • Bevacizumab 15 mg/kg by IV infusion on Day 1

Abema = abemaciclib; Atezo = atezolizumab; Bev = bevacizumab; CIT = cancer immunotherapy; Entino = entinostat; ET = endocrine therapy; IM = intramuscular; Ipat = ipatasertib; IV = intravenous

[a] Drugs are listed in order of administration.

DURATION OF PARTICIPATION

Study treatment will continue until disease progression per RECIST v1.1. The duration of study participation for each individual is expected to range from [redacted]

COMMITTEES

Independent Committees:	Not applicable
Other Committees:	Internal Monitoring Committee; Scientific Oversight Committee

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Abema	abemaciclib
ALP	alkaline phosphatase
ADA	anti-drug antibody, also known as anti-therapeutic antibody (ATA)
ASCO	American Society of Clinical Oncology
Atezo	atezolizumab
Bev	bevacizumab
BP	blood pressure
CAP	College of American Pathologists
CBR	clinical benefit rate
CDK4/6i	cyclin-dependent kinase 4/6 inhibitors
CIT	cancer immunotherapy
COVID-19	coronavirus 2019
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
EC	Ethics Committee
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
Entino	entinostat
ESMO	European Society for Medical Oncology
ET	endocrine therapy
FDA	(U.S.) Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
FSH	follicle-stimulating hormone
GI	gastrointestinal
GFR	glomerular filtration rate
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HR+	hormone-receptor positive

Abbreviation	Definition
HR+ breast cancer	HR+ HER2-negative breast cancer
ICH	International Council for Harmonisation
IHC	immunohistochemistry
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (application)
Ipat	ipatasertib
IRB	Institutional Review Board
ISH	in situ hybridization
IxRS	interactive voice or web-based response system
LH	luteinizing hormone
LHRH	luteinizing hormone–releasing hormone
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE v4.0	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0
NGS	next-generation sequencing
OCT	optical coherence tomography
OR	objective response
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria in Solid Tumors
RVO	retinal vein occlusion
SARS CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	Scientific Oversight Committee
ULN	upper limit of normal
WGS	*whole genome sequencing*
WES	whole exome sequencing

1. BACKGROUND

1.1 TREATMENT FOR HR+ BREAST CANCER

Breast cancer is the most frequent cancer diagnosed in women, with an estimated global incidence of 1.67 million new cases reported in 2012 (Ferlay et al. 2013). Breast cancer accounts for approximately 15% (approximately 522,000 cases) of all cancer deaths. Breast cancer mortality rates differ by geographical region, with more favorable survival rates observed in more developed regions of the world (Ferlay et al. 2013).

Hormone receptor–positive (HR+) HER2-negative breast cancer (hereafter referred to as HR+ breast cancer) accounts for over 70% of all breast cancer subtypes. The standard-of-care treatment for patients with HR+ breast cancer takes several prognostic and predictive factors into account, including tumor histology, clinical and pathologic characteristics of the primary tumor, axillary lymph node status, tumor hormone receptor (estrogen receptor/progesterone receptor) content, multi-gene testing, presence or absence of detectable metastatic disease, patient comorbid conditions, patient age, and menopausal status.

In the early breast cancer setting, adjuvant systemic therapy should be considered in addition to local treatment with surgery with or without radiation therapy. The decision to use systemic adjuvant therapy requires considering and balancing risk for disease recurrence with local therapy alone, the magnitude of benefit from applying adjuvant therapy, toxicity of the therapy, and comorbidity. Given the favorable benefit–risk ratio of available endocrine therapies, both National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend the use of endocrine therapy (ET) for the majority of patients with HR+ breast cancer. The choice of agent is primarily determined by the patient's menopausal status; differences in efficacy and side-effect profiles are also factors that influence a treatment decision (NCCN 2014; ESMO 2016). Adjuvant tamoxifen with consideration for ovarian ablation or suppression is recommended in premenopausal women (Senkus et al. 2013). The administration of aromatase inhibitors as initial treatment or as a sequential treatment following tamoxifen has been recommended for postmenopausal women (Burstein et al. 2010; Senkus et al. 2013).

Treatment for patients whose disease recurs following adjuvant treatment may include continued ET or chemotherapy. Chemotherapy is indicated in patients with symptomatic visceral disease or in patients with disease progression after demonstration of endocrine resistance (Cardoso et al. 2017). The appropriate endocrine agent used in the metastatic setting is dependent on the menopausal status of the patients. In premenopausal women, tamoxifen is often used, although ovarian ablation or suppression along with aromatase inhibitors is also acceptable.

Endocrine therapy options in the treatment of postmenopausal women whose cancer has recurred after adjuvant therapy include nonsteroidal aromatase inhibitors (anastrozole, letrozole), steroidal aromatase inhibitors (exemestane), estrogen receptor down-regulators (fulvestrant), and estrogen receptor modulators (tamoxifen, toremifene). Meta-analyses suggest that aromatase inhibitors may be superior to tamoxifen in prolonging the time to disease progression in this treatment setting (Bonneterre et al. 2000; Nabholtz et al. 2000; Paridaens et al. 2008; Gibson et al. 2009). Treatment with fulvestrant offers a PFS benefit (Robertson et al. 2016) and may have a survival advantage over anastrozole (Gibson et al. 2009). Very little evidence is available to support an optimal ET sequence in the metastatic setting (NCCN 2014). The choice agent, sequence of agents, and duration of treatment should be guided by practical considerations such as prior endocrine treatment response and each agent's safety profile.

Not all HR+ breast cancers respond optimally to ET. Mechanisms that can lead to primary and/or secondary hormonal resistance in HR+ breast cancer include a decrease or loss of hormone receptor expression or an upregulation of growth factor signaling pathways, such as the epidermal growth factor receptor (EGFR) or HER2, the MAPK, or the PI3K/Akt/mTOR pathways (Johnston et al. 2009; Musgrove and Sutherland 2009). Recently, mutations in the gene that encodes estrogen receptor (ESR1) have been identified in metastatic estrogen receptor–positive tumors and are associated with resistance to anti-estrogen therapies (Robinson et al. 2013; Toy et al. 2013; Jeselsohn et al. 2014).

Cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) have shown both nonclinical and clinical activity in HR+ breast cancer. Three CDK4/6i have been approved for treatment of advanced HR+ breast cancer patients based on significant improvements in PFS: palbociclib, ribociclib, and abemaciclib.

Positive results from several Phase II and III studies (PALOMA 1, 2, and 3 studies) have resulted in the U.S. Food and Drug Administration (FDA) and European Union approval of CDK4/6 inhibitor, palbociclib, as first- or second-line treatment of HR+ breast cancer in combination with ET. In the first-line setting of metastatic HR+ breast cancer, the combination of palbociclib with letrozole increased the median PFS and overall response rate of letrozole therapy alone (PFS: 20.2 months vs. 10.3 months; overall response rate: 55.4% vs. 39.4%), providing a significant improvement in therapy options for HR+ breast cancer patients. Another CDK4/6 inhibitor, ribociclib, is also approved by the FDA for the initial treatment of HR+ advanced or metastatic breast cancer in combination with an aromatase inhibitor. Abemaciclib is the most potent of the three inhibitors. In patients with advanced HR+ breast cancer, both ORR and PFS were significantly improved after initial therapy in postmenopausal women (MONARCH 3) and in combination with fulvestrant in patients previously treated with endocrine therapy (MONARCH 2) (Goetz et al. 2017; Sledge et al. 2017). Strikingly, abemaciclib also demonstrated significant activity as a single agent. In the Phase II single-arm

MONARCH 1 trial, abemaciclib monotherapy yielded an ORR of 19.7% and CBR of 42.4% in a heavily pretreated population with HR+ metastatic breast cancer (Dicker et al. 2017).

However, mechanisms of acquired resistance to CDK4/6 inhibitors, as well as anecdotal evidence suggesting poor patient outcomes following CDK4/6i treatments, highlight the need for identifying new therapeutic regimens for these patients. Still, based on the results of these trials, the 2016 American Society of Clinical Oncology (ASCO) and ESMO guidelines state that palbociclib in combination with ET can be considered for treatment of HR+ metastatic breast cancer in the first- or second-line setting (Rugo et al. 2016; Cardoso et al. 2017).

1.2 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

This study will enroll patients with locally advanced or metastatic HR+ breast cancer who had disease progression during or following first- or second-line treatment with CDK4/6i, such as palbociclib, in combination with an ET not including fulvestrant. Given the observed emergence of acquired resistance to CDK4/6i (O'Leary et al. 2016), this population is considered appropriate for trials of novel therapeutic candidates to identify effective post-CDK4/6i treatment regimens, including immunotherapies. Furthermore, recent tissue analysis from a Phase II trial studying the effects of the CDK4/6i abemaciclib in combination with anastrozole (neoMONARCH) revealed an upregulation of inflammatory and activated tumor-infiltrating lymphocytes (Hurvitz et al. 2018), providing a rationale for immunotherapy in this patient population.

Cancer immunotherapy (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.

This Phase Ib/II umbrella study is designed to accelerate the development of CIT combinations by identifying early signals and establishing proof-of-concept clinical data in patients with HR+ breast cancer. The study is designed with the flexibility to open new treatment arms as new treatment combinations become available and to close treatment arms that demonstrate minimal clinical activity or unacceptable toxicity. The study will assess the importance of simultaneously targeting multiple mechanisms of immune escape through immune cell priming and activation, tumor infiltration, and/or

recognition of tumor cells for elimination. To improve the confidence of clinical signal detection in the experimental arms, this study will include a control arm in which patients will receive fulvestrant. Moreover, patients who experience disease progression with the initial treatment regimen (Stage 1) may be eligible to continue treatment with a different treatment regimen (Stage 2), which may advance the scientific understanding of immune escape mechanisms in patients who fail to respond to, or experience disease progression during, treatment with a CIT or ET regimen.

The target and proposed mechanism-of-action classification for each investigational medicinal product (IMP) is summarized in Table 1. The control and experimental treatment regimens are described in Section 3.1.1 (see Table 4 and Table 6). Background information and a rationale for each treatment combination, including a benefit–risk assessment for experimental agents, are provided in the respective appendix for that treatment arm, as outlined in Table 4 and Table 6.

Table 1 Target and Proposed Mechanism-of-Action Classification for Investigational Medicinal Products

IMP	Target	Proposed MoA Classification
Atezolizumab	PD-L1	Checkpoint inhibitor
Ipatasertib	Akt	Kinase inhibitor, tumor cell death, reversal of T cell–mediated IT resistance [a]
Bevacizumab	VEGF	Angiogenesis inhibitor, recruitment of T cells to the tumor microenvironment [b]
Entinostat	HDAC	Histone deacetylase inhibitor, induction of terminal differentiation and/or apoptosis, inhibition of MDSCs and Tregs [c]
Abemaciclib	CDK4/6	CDK4/6 inhibitor, induces cell cycle arrest [d]
Fulvestrant	Estrogen receptor	Selective estrogen receptor degrader
Exemestane	Aromatase	Aromatase inhibitor
Tamoxifen	Estrogen receptor	Selective estrogen receptor modulator

CDK = cyclin-dependent kinase; HDAC = histone deacetylase inhibitor; IMP = investigational medicinal product; IT = immunotherapy; MoA = mechanism of action; Treg = T regulatory (cell); VEGF = vascular endothelial growth factor.

[a] Peng et al. 2016.
[b] Wallin et al. 2016.
[c] Kim et al. 2014.
[d] Ortega et al. 2002.

1.3 COVID-19 BENEFIT–RISK ASSESSMENT

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

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

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

There may be potential synergy or overlap in clinical and radiologic features for immune mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for SARS-CoV-2 infection–related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms. Given the mechanism of action for atezolizumab and other immunostimulatory agents, immune-mediated adverse events are potential overlapping toxicities associated with combination use of these agents.

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

Per recommendations of the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients (NCCN 2021). Given the lack of clinical data, currently no recommendations can be

made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy (SITC 2020). For patients enrolling in this study and receiving cancer immunotherapy, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

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

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When administered, COVID-19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such (see Section 4.4).

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of immunotherapy-based treatment combinations in patients with inoperable locally advanced or metastatic HR+ breast cancer. Specific objectives and corresponding endpoints for the study are outlined below for Stage 1 (see Table 2) and Stage 2 (see Table 3).

Table 2 Objectives and Corresponding Endpoints for Stage 1

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	• OR, defined as a complete response or partial response, as determined by the investigator according to RECIST v1.1
Secondary Efficacy Objective	**Corresponding Endpoints**
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 1	• PFS, defined as the time from randomization [a] to the date of the first recorded occurrence of disease progression or death from any cause (whichever occurs first) in Stage 1, as determined by the investigator according to RECIST v1.1 • CBR, defined as proportion of patients with stable disease ≥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 randomization [a] to death from any cause • OS at specific timepoints (e.g., 18 months) • DOR, defined as the time from the first occurrence of a documented OR to the first date of recorded disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of immunotherapy-based treatment combinations during Stage 1	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in vital signs and ECG parameters • Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 1	• Plasma or serum concentration of each drug (as appropriate) at specified timepoints
Exploratory Pharmacokinetic Objective	**Corresponding Endpoints**
• To evaluate potential relationships between drug exposure during Stage 1 and the efficacy and safety of immunotherapy-based treatment combinations	• Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and efficacy endpoints • Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and safety endpoints

Table 2 Objectives and Corresponding Endpoints for Stage 1 (cont.)

Immunogenicity Objective	Corresponding Endpoint
• To evaluate the immune response to drugs that are administered as part of an immunotherapy-based treatment combination during Stage 1	• For drugs for which ADA formation is measured: 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 during Stage 1	• For drugs for which ADA formation is measured: relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To identify biomarkers during Stage 1 that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (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	• Relationship between biomarkers in blood and tumor tissue (listed in Section 4.5.6) and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

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

[a] For the mandatory serial biopsy arms, PFS and OS will be determined from the time of treatment initiation (rather than the time of randomization).

Table 3 Objectives and Corresponding Endpoints for Stage 2

Exploratory Efficacy Objective	Corresponding Endpoints
• To evaluate the efficacy of immunotherapy-based treatment combinations during Stage 2	• OR, defined as a complete response or partial response during Stage 2, as determined by the investigator according to RECIST v1.1 • PFS after initiation of Stage 2, defined as the time from initiation of Stage 2 treatment to the first recorded disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • DOR, defined as the time from the first occurrence of a documented OR during Stage 2 to disease progression or death from any cause (whichever occurs first), as determined by the investigator according to RECIST v1.1 • CBR, defined as proportion of patients with stable disease ≥24 weeks or with confirmed complete or partial response, as determined by the investigator according to RECIST v1.1 • DCR, defined as proportion of patients with stable disease for ≥12 weeks or a complete or partial response, as determined by the investigator according to RECIST v1.1
Safety Objective	**Corresponding Endpoints**
• To evaluate the safety of immunotherapy-based treatment combinations during Stage 2	• Incidence, nature, and severity of adverse events and laboratory abnormalities, with severity determined according to NCI CTCAE v4.0 • Change from baseline in vital signs and ECG parameters • Change from baseline in targeted clinical laboratory test results
Pharmacokinetic Objective	**Corresponding Endpoint**
• To characterize the PK profile of drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2	• Plasma or serum concentration of each drug at specified timepoints
Exploratory Pharmacokinetic Objective	**Corresponding Endpoints**
• To evaluate potential relationships between drug exposure during Stage 2 and the efficacy and safety of immunotherapy-based treatment combinations	• Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and efficacy endpoints • Relationship between plasma or serum concentration or PK parameters for each drug (as appropriate on the basis of available data) and safety endpoints

Table 3 Objectives and Corresponding Endpoints for Stage 2 (cont.)

Immunogenicity Objective	Corresponding Endpoint
• To evaluate the immune response to drugs that are administered as part of an immunotherapy-based treatment combination during Stage 2	• For drugs for which ADA formation is measured: 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 during Stage 2	• For drugs for which ADA formation is measured: relationship between ADA status and efficacy, safety, or PK endpoints
Exploratory Biomarker Objective	**Corresponding Endpoint**
• To identify biomarkers during Stage 2 that are predictive of response to study treatment (i.e., predictive biomarkers), are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with resistance to study treatment, are associated with susceptibility to developing adverse events (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	• Relationship between biomarkers in blood, tumor tissue, and efficacy, safety, PK, immunogenicity, or other biomarker endpoints

ADA=anti-drug antibody; CBR=clinical benefit rate; DCR=disease control rate; DOR=duration of response; NCI CTCAE v4.0=National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; OR=objective response; PFS=progression-free survival; PK=pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors.

3. STUDY DESIGN

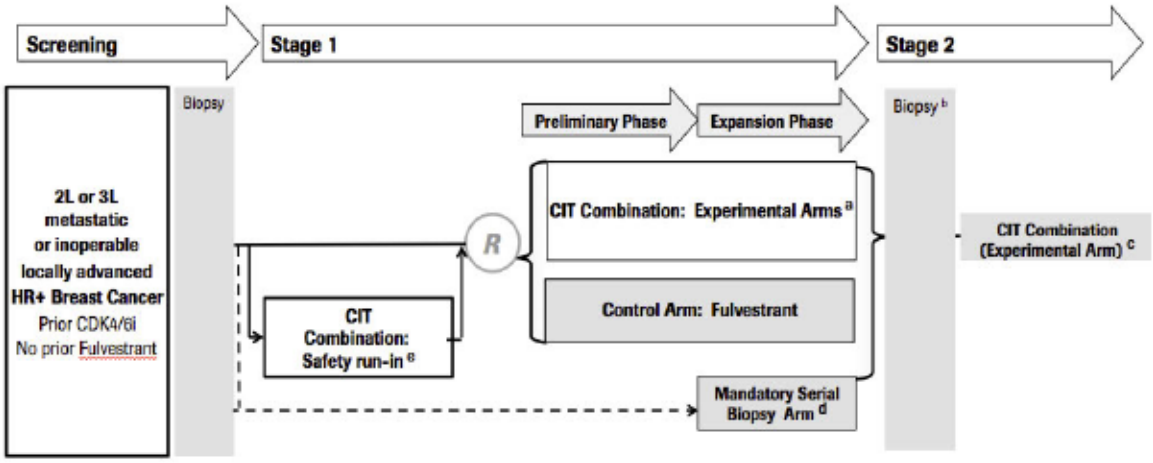
3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase Ib/II, open-label, multicenter, randomized umbrella study in patients with inoperable locally advanced or metastatic HR+ breast cancer who had disease progression during or following treatment with a CDK4/6 inhibitor (e.g., palbociclib, ribociclib, abemaciclib) in the first- or second-line setting. The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, or modify the patient population (e.g., with regard to prior anti-cancer treatment or biomarker status). Eligible patients will initially be assigned to one of several treatment arms (Stage 1; see Section 3.1.1.1). Patients who experience disease progression, loss of clinical benefit, or unacceptable toxicity during Stage 1 may be

eligible to continue treatment with a different treatment regimen (Stage 2; see Section 3.1.1.2).

Figure 1 Study Schema



2L = second-line; 3L = third-line; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; CIT = cancer immunotherapy; HR+ = hormone receptor positive; HR+ breast cancer = HR+ HER2-negative breast cancer; R = randomization; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Refer to Table 4 for a summary of available Stage 1 treatment regimens.

[b] A biopsy (if clinically feasible) will be performed for patients who discontinue Stage 1 because of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator (see details on tissue sample collection in Section 4.5.6).

[c] Refer to Table for a summary of available Stage 2 treatment regimens.

[d] The Sponsor may open enrollment in separate mandatory serial biopsy arms to enable patients who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase of Stage 1. If a site has not been granted IRB/EC approval for mandatory serial biopsies, these arms will not be opened at that site (see Section 3.1.1.1).

[e] Enrollment in arms that include safety run-in will start with safety run-in phase for that experimental arm.

3.1.1.1 Stage 1

During Stage 1, patients will be randomly assigned to a control arm (fulvestrant) or to one of the experimental arms consisting of doublet combinations of atezolizumab in combination with either entinostat (Atezo + Entino) or fulvestrant (Atezo + Fulvestrant), and ET-containing triplet combinations of atezolizumab in combination with ipatasertib+fulvestrant (Atezo + Ipat + Fulvestrant) or abemaciclib + fulvestrant (Atezo + Abema + Fulvestrant) as outlined in Table 4. Details on the treatment regimens are in Appendix 7 through Appendix 11 and Appendix 13, as specified in Table 4. Table 5 lists Stage 1 treatment arms for which enrollment and patient follow-up has been completed.

Enrollment for all experimental arms will take place in two phases: a preliminary phase followed by an expansion phase.

Approximately 126–276 patients will be enrolled during Stage 1. Up to 6 patients will be enrolled during the safety run-in phase. [redacted] Approximately 15 patients will be enrolled in all other arms during the preliminary phase. If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25 additional patients may be enrolled in that arm during the expansion phase. The Sponsor may also decide to open enrollment in separate mandatory serial biopsy arms to enable patients who are willing to undergo serial biopsies to receive treatment with an experimental combination that has qualified for the expansion phase (see Section 3.1.1.1.1 for details). Experimental arms with minimal clinical activity or unacceptable toxicity will not undergo expansion. Additional patients may be randomized to ensure balance among treatment arms with respect to demographic and baseline characteristics, including potential predictive biomarkers, to enable further subgroup analyses. New experimental arms may be added during the study by amending the protocol (see Section 9.6). The Sponsor may decide to delay or suspend enrollment within a given treatment arm.

The randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the preliminary phase), with the stipulation that no more than 35% of patients will be randomized to the control arm at a given time. Randomization will take into account arm-specific exclusion criteria. Patients will be ineligible for a specific arm if they meet any of the exclusion criteria outlined for that arm (see Section 4.1.2). Details on randomization are provided in Section 4.2.

Table 4 Stage 1 Treatment Regimens

Treatment	Number of Patients (Sponsor Assignment) [a]	Number of Patients (Random Assignment) [b]		Appendix
	Safety Run-In Phase	Preliminary Phase	Expansion Phase [c, d]	
Control arm: Fulvestrant	—	Variable		Appendix 7
Atezolizumab plus entinostat (Atezo+Entino)	—	15	25	Appendix 8
Atezolizumab plus fulvestrant (Atezo + Fulvestrant)	—	15	25	Appendix 9
Atezolizumab plus ipatasertib plus fulvestrant (Atezo + Ipat + Fulvestrant)	—	30 [e]	25	Appendix 11
Atezolizumab plus abemaciclib plus fulvestrant (Atezo + Abema + Fulvestrant)	—	15	25	Appendix 13

Abema = abemaciclib; Atezo = atezolizumab; Entino = entinostat; Ipat = ipatasertib.

[a] During the safety run-in phase, patients will be assigned to available treatment arms.

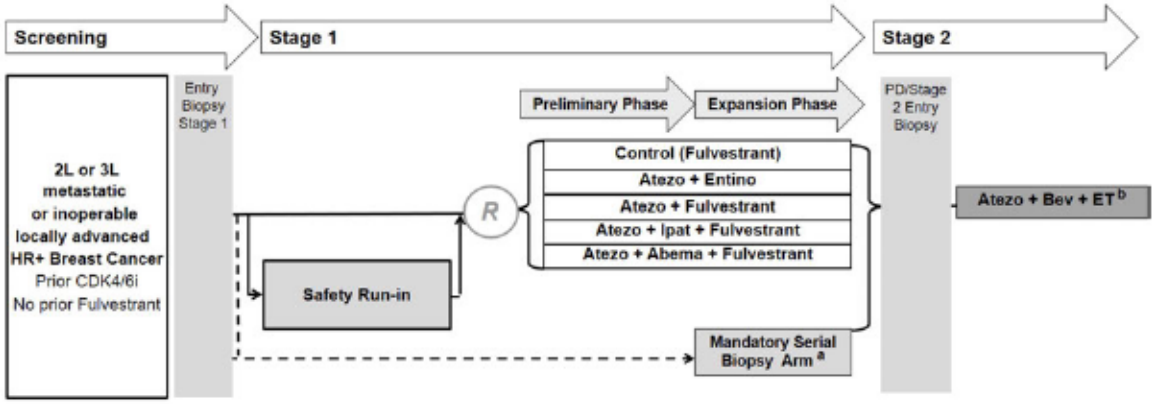
[b] The randomization ratio will depend on the number of experimental arms that are open for enrollment (e.g., if an arm is added or enrollment in an arm is suspended pending analysis of results from the preliminary phase), with the stipulation that no more than 35% of patients will be randomly allocated to the control arm at a given time (see Section 4.2 for details).

[c] If clinical activity is observed in an experimental arm during the preliminary phase, approximately 25 additional patients may be enrolled in that arm during the expansion phase.

[d] The Sponsor may decide to open enrollment in separate mandatory serial biopsy arms to enable patients who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase (see Section 3.1.1.1.1 for details).

[e] [redacted]

Figure 2 Overall Study Design



2L=second-line; 3L=third-line; Abema=abemaciclib; Atezo=atezolizumab; Bev=bevacizumab; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; Entino=entinostat; ET=endocrine therapy; HR+=hormone receptor positive; HR+ breast cancer=HR+ HER2-negative breast cancer; Ipat=ipatasertib; PD=progressive disease; R=randomization.

[a] The Sponsor may decide to open enrollment in separate mandatory serial biopsy arms to enable patients who are willing to undergo serial biopsies to receive treatment with an experimental combination that has demonstrated clinical activity during the preliminary phase (see Section 3.1.1.1 for details).

[b] Physician's choice of fulvestrant, exemestane, or tamoxifen will be given in combination with atezolizumab and bevacizumab.

Table 5 Treatment Arms with Completed Enrollment and Patient Follow-Up

Stage	Arm Name	Treatment	Number of Patients Enrolled		Protocol Versions Describing Arm
			Preliminary Phase	Expansion Phase	
1	Atezo + Ipat	Atezolizumab plus ipatasertib	30	25	1–4

Patients in the control arm will continue to receive treatment until unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). Patients in the experimental arms will continue to receive treatment 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 treatment

with a CIT combination will be permitted to continue treatment 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 Eastern Cooperative Oncology Group (ECOG) Performance Status 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
- Patient's written consent to acknowledge deferring other treatment options in favor of continuing study treatment at the time of initial apparent disease progression

3.1.1.1.1 Mandatory Serial Biopsy Arms

If an experimental combination demonstrates clinical activity during the preliminary phase, the Sponsor may decide to test that same combination in a mandatory serial biopsy arm consisting of patients who are willing to undergo an on-treatment biopsy.

The opening of mandatory serial biopsy arms is contingent upon the review and approval of the protocol and the mandatory serial biopsy 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 mandatory serial biopsies, these arms will not be opened at that site.

The objective of the mandatory serial biopsy arms is to analyze serial tissue samples (including pretreatment, on-treatment, and post-progression samples) in an effort to better understand potential biological changes that occur during treatment with CIT combinations (including immune escape), provide evidence of pharmacodynamic effects, or confirm hypothesized mechanisms of action. Patients entering Stage 1 who are determined by the investigator to be eligible for serial biopsies may be enrolled in a mandatory serial biopsy arm rather than undergo random assignment to other arms that are open for enrollment. If more than one mandatory serial biopsy arm is open, patients will be assigned to one of the available arms by the Sponsor.

Approximately 15 patients with serial biopsy samples may be enrolled in each mandatory serial biopsy arm. However, the number of patients may be reduced if optional on-treatment biopsies have been collected (and determined to be evaluable) from consenting patients treated with that same CIT combination during the preliminary phase, to limit on-treatment biopsy collection to approximately 15 patients per CIT combination.

All patients enrolled in a mandatory serial biopsy arm will undergo the same assessments as other patients receiving the same treatment combination but will have

an additional mandatory on-treatment biopsy at Week 4 (±7 days) after initiation of CIT combination treatment (if deemed clinically feasible by the investigator). Details about the timing of biopsy sample collection are provided in the schedule of activities for each arm (see Appendix 7 through Appendix 11 and Appendix 13).

To be eligible for a mandatory serial biopsy arm, a patient should have at least two accessible tumors that are amenable to excisional, punch, or core-needle biopsy (a minimum of three cores, 18-gauge needle or larger [16-gauge needle preferred]) without unacceptable risk of a major procedural complication. If it is planned that more than one biopsy will be obtained from a single lesion, the lesion should be large enough to permit successive biopsies ≥1 cm apart.

Patients enrolled in a mandatory serial biopsy arm for whom three evaluable tissue samples cannot be obtained may continue to receive study treatment as scheduled.

The Informed Consent Form will contain a separate section that addresses the mandatory serial biopsy arms. A separate, specific signature will be required to document a patient's agreement to participate in one of these arms.

3.1.1.2 Stage 2

During Stage 1, patients in the control arm who experience disease progression per RECIST v1.1 and patients in an experimental arm who experience loss of clinical benefit as determined by the investigator (as described above) will be given the option of receiving a different treatment combination during Stage 2, as outlined in Table 6, provided they meet eligibility criteria (see Section 4.1) and a Stage 2 arm is open for enrollment. Patients in the control arm who experience unacceptable toxicity and patients in an experimental arm who experience unacceptable toxicity not related to atezolizumab may be eligible for Stage 2 treatment. The Medical Monitor is available to advise as needed.

Details on the Stage 2 treatment regimen are provided in Table 6 and Appendix 12.

Stage 2 treatment must begin within 3 months after the patient has experienced disease progression per RECIST v1.1 (control arm), loss of clinical benefit (experimental arms), or unacceptable toxicity and will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator. It is recommended that patients begin Stage 2 treatment as soon as possible but no earlier than 2 weeks after the last dose of treatment in Stage 1.

Table 6 Stage 2 Treatment Regimen

Arm	Treatment	Appendix
Atezo + Bev + ET	Atezolizumab plus bevacizumab plus one of the following ETs based on physician's choice • Fulvestrant • Exemestane • Tamoxifen	Appendix 12

Atezo = atezolizumab; Bev = bevacizumab; ET = endocrine therapy.

The Sponsor may also decide to hold or discontinue enrollment in Stage 2 treatment arms on the basis of a review of safety data, preliminary efficacy data, and supportive information (e.g., biomarker research data), as appropriate.

3.1.1.3 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).

Patients will undergo tumor assessments every 6 weeks (±1 week) from Day 1 of Cycle 1 during the first 24 weeks, then every 8 weeks (±1 week) from Week 25 to Week 48, and then every 12 weeks (±2 weeks) thereafter, regardless of dose delays until radiographic progression according to RECIST v1.1 (see Appendix 1), except in the case of atezolizumab-treated patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 4.5.5 and Appendix 7 through Appendix 13 for details). If clinical activity is demonstrated in an experimental arm, the Sponsor may request that tumor assessment scans for that arm and the corresponding control arm be submitted for evaluation by an independent reading facility.

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. It is preferred 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 Stage 1 because of unacceptable toxicity, disease progression per RECIST v1.1 (control arm), or loss of clinical benefit as determined by the investigator (experimental arms). For patients enrolled in a mandatory serial biopsy arm, an additional tumor tissue sample 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 3.4.3 and details on tissue sample collection in Section 4.5.6).

To characterize the pharmacokinetic (PK) properties and/or immunogenicity of atezolizumab and the other therapeutic agents, blood samples will be taken at various timepoints before and during study treatment administration.

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 each arm is presented in Appendix 7 through Appendix 13.

3.1.2 Internal Monitoring Committee and Scientific Oversight Committee

An Internal Monitoring Committee (IMC) will monitor patient safety throughout the study. The IMC will include representatives from Clinical Science, Safety Science, and Biostatistics. 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 investigator and the Medical Monitor, the IMC will review all necessary cumulative data at regular intervals during the study. At the time of each review, the IMC will make appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, a treatment regimen should be modified, the protocol should be amended, enrollment should be held pending further safety evaluations). Decisions will be made in consideration of the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities will be detailed in an IMC Charter.

A Scientific Oversight Committee (SOC) will act as a consultative body to the Sponsor, providing external expert opinions on the safety data collected during the study. This committee will consist of an external group of at least three oncology experts in CIT who will advise the Sponsor on the interpretation of study data. For this purpose, the SOC will evaluate aggregate safety data on a periodic basis, approximately every 6 months from the time the first patient is enrolled in the study. Members will follow a charter that outlines their roles and responsibilities. Data being evaluated by the SOC will include demographic, adverse event, serious adverse event, and relevant laboratory data. The Scientific Oversight Committee may review efficacy data if safety concerns necessitate benefit–risk assessments. The Sponsor will retain all decision-making authority for this study.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient completes the last visit (LPLV), including survival follow-up visits conducted by telephone or in the clinic.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 5–6 years.

3.3 *DURATION OF PARTICIPATION*

Study treatment will continue until disease progression per RECIST v1.1. The duration of study participation for each individual is expected to range from [redacted]

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Patient Population

HR+ breast cancer accounts for over 70% of breast cancer subtypes, with current treatment regimens for metastatic disease only prolonging survival of these patients. Until the recent emergence of selective CDK4/6 inhibitors, ET remained the standard-of-care treatment for metastatic disease through multiple lines of therapy followed by chemotherapy in the late metastatic, ET-resistant setting. However, despite recent improvements with next generation CDK4/6 inhibitors, the emergence of acquired resistance to CDK4/6 inhibitors highlights the continued unmet need to identify new treatment regimens for second- and third-line, inoperable locally advanced or metastatic HR+ breast cancer patients following such treatment (O'Leary et al. 2016). Despite the benefits from current ET and chemotherapies, HR+ metastatic breast cancer remains an incurable disease; patients will eventually progress and die from the disease. Furthermore, recent evidence indicating activation of tumor-infiltrating lymphocytes in CDK4/6i plus ET-treated HR+ breast cancer patients provides a rationale for investigating immunotherapy treatment regimens in this patient population.

3.4.2 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 randomized to immunotherapy-based treatment arms 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 (see Section 3.1.1.1 for details).

3.4.3 Rationale for Biomarker Assessments

Blood samples for biomarker assessments will be collected at baseline and during the study. Changes in biomarkers in blood may provide evidence of biologic activity of the specific treatment combinations. Correlations between surrogate biomarkers in blood (such as tumor burden markers, cytokines, chemokines, immune cell subpopulations, gene expression, and circulating tumor DNA) and drug dose and efficacy and safety endpoints may allow for the development of a blood-based biomarker to help define future treatments and predict which patients are more likely to benefit from specific treatment combinations.

Baseline tumor tissue samples will be collected from all patients, preferably by means of a biopsy performed at study entry. If deemed clinically feasible by the investigator, tumor tissue will also be collected for patients who discontinue Stage 1 because of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details), to enable analysis of tumor tissue biomarkers related to resistance, disease progression, and clinical benefit of study treatments. If deemed clinically feasible by the investigator, tumor tissue will also be collected at least once from patients who are receiving treatment at Week 8.

Tumor samples will be evaluated for biomarkers such as tumor-infiltrating immune cells, PD-L1, CD8, and expression of targets specific to each drug combination. Evaluation of the tumor microenvironment in response to treatment within each arm, including changes in the number and functional status of tumor-infiltrating immune cells, could provide validation of the postulated mechanism of action and confirmation that an appropriate dose and exposure for the specific treatment combination have been achieved.

Tumor tissue and blood samples may be analyzed through use of next-generation sequencing (NGS) and whole exome sequencing (WES) to identify 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.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Inclusion Criteria

Patients must meet all of the criteria outlined in Sections 4.1.1.1 and 4.1.1.2 to qualify for Stage 1. Patients must meet all of the criteria outlined in Sections 4.1.1.2 and 4.1.1.3 to qualify for Stage 2.

4.1.1.1 Inclusion Criteria for Stage 1

Patients must meet all of the following criteria to qualify for Stage 1:

- Age ≥ 18 years at the time of signing Informed Consent Form
- Female
- ECOG Performance Status of 0 or 1 (see Appendix 3)
- Histologically or cytologically confirmed invasive HR+ HER2-negative breast cancer (determined by local testing): metastatic or inoperable locally advanced breast cancer
- Patients for whom ET (e.g., fulvestrant) is recommended and treatment with cytotoxic chemotherapy is not indicated at time of entry into the study, as per national or local treatment guidelines.
- Radiologic/objective evidence of recurrence or progression after the most recent systemic therapy for breast cancer
- Disease progression during or after first- or second-line hormonal therapy for locally advanced or metastatic disease

  Note: At least one line of therapy must have contained a CDK4/6i administered for a minimum of 8 weeks prior to disease progression.
- Postmenopausal status for women, defined as one of the following:
  - Age ≥ 60 years
  - Age < 60 years and postmenopausal as defined by documented follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol in the postmenopausal ranges in addition to being amenorrheic for 12 months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression
  - Age < 60 years and on luteinizing hormone–releasing hormone (LHRH) agonist for ovarian suppression, provided that:

    Estradiol level must be in postmenopausal range while on LHRH agonist.

    The patient remains on LHRH agonist for duration of the study if she does not proceed with definitive ovarian ablation (surgical or radiation).
  - Prior ovarian ablation (≥ 28 days prior to Cycle 1, Day 1) with FSH, LH, and estradiol in the postmenopausal range or prior bilateral oophorectomy (≥ 14 days prior to Cycle 1, Day 1) with recovery to baseline
- Life expectancy ≥ 3 months, as determined by the investigator
- Availability of a representative tumor specimen that is suitable for determination of PD-L1 and/or additional biomarker status via central testing

  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. It is preferred 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.

A formalin-fixed, paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least 18 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report. See Section 4.5.6 for additional information on tumor specimens collected at screening.

4.1.1.2 Inclusion Criteria for Stage 1 and Stage 2

Patients must meet all of the following criteria to qualify for Stage 1 and to qualify for Stage 2:

- Signed Informed Consent Form
- Able to comply with the study protocol, in the investigator's judgment
- Measurable disease (at least one target lesion) according to RECIST v1.1

  Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC $\geq 1.5 \times 10^9$/L (1500/μL) without granulocyte colony-stimulating factor support within 14 days prior to screening laboratory test
  - WBC count $\geq 2.5 \times 10^9$/L (2500/μL)
  - Lymphocyte count $\geq 0.5 \times 10^9$/L (500/μL)
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion within 7 days prior to screening laboratory test
  - Hemoglobin ≥90 g/L (9.0 g/dL)

    Patients may be transfused to meet this criterion after discussion with the Medical Monitor.
  - AST, ALT, and alkaline phosphatase (ALP) $\leq 2.5 \times$ upper limit of normal (ULN), with the following exceptions:

    Patients with documented liver metastases: AST and ALT $\leq 5 \times$ ULN

    Patients with documented liver or bone metastases: ALP $\leq 5 \times$ ULN
  - Bilirubin $\leq 1.5 \times$ ULN with the following exception:

    Patients with known Gilbert disease: bilirubin level $\leq 3 \times$ ULN
  - Creatinine clearance ≥50 mL/min (calculated using the Cockcroft-Gault formula)

    Patients with normal serum or plasma creatinine but <50 mL/min creatinine clearance, may be eligible. The Medical Monitor is available to advise as needed.
  - Albumin ≥25 g/L (2.5 g/dL)
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN

- For patients receiving therapeutic anticoagulation: stable anticoagulant regimen

4.1.1.3 Inclusion Criteria for Stage 2

Patients who participated in Stage 1 must meet all of the following criteria to qualify for Stage 2:

- ECOG Performance Status of 0, 1, or 2 (see Appendix 3)
- Patients randomly allocated to the control arm during Stage 1: ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity or disease progression per RECIST v1.1 while receiving control treatment
- Patients randomly allocated to an experimental arm during Stage 1: ability to initiate Stage 2 treatment within 3 months after experiencing unacceptable toxicity not related to atezolizumab or loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details) while receiving Stage 1 treatment
- Availability of a tumor specimen from a biopsy performed upon discontinuation of Stage 1 because of unacceptable toxicity to drugs other than atezolizumab, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator.

  If a biopsy is not deemed feasible by the investigator, they may consult with the Medical Monitor.

4.1.2 Exclusion Criteria

Patients will be excluded from enrollment in specific arms during Stage 1 or enrollment during Stage 2 if they meet any of the criteria outlined in subsequent sections, as specified by treatment arm below. If a patient is eligible only for the control arm, the patient will not be enrolled in the study.

Treatment Arm and Stage	Applicable Exclusion Criteria
Control (Stage 1)	Sections 4.1.2.1 and 4.1.2.2
Atezo + Entino (Stage 1)	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.3
Atezo + Fulvestrant (Stage 1)	Sections 4.1.2.1 and 4.1.2.2
Atezo + Ipat + Fulvestrant (Stage 1)	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.4
Atezo + Abema + Fulvestrant (Stage 1)	Sections 4.1.2.1, 4.1.2.2, and 4.1.2.6
Atezo + Bev + ET (Stage 2)	Sections 4.1.2.2 and 4.1.2.5

Abema=abemaciclib; Atezo=atezolizumab; Bev=bevacizumab; Entino=entinostat; ET=endocrine therapy (physician's choice of fulvestrant, exemestane, or tamoxifen); Ipat=ipatasertib.

4.1.2.1 Exclusion Criteria for Stage 1

Patients who meet any of the following criteria will be excluded from Stage 1:

- Known HER2-positive breast cancer as defined by ASCO/CAP guidelines:
  - >10% of contiguous and homogenous tumor cells showing protein expression (3+) on circumferential membrane staining that is complete and intense by immunohistochemistry (IHC)
    - In situ hybridization (ISH) positive based on counting at least 20 cells within the area of >10% contiguous and homogenous tumor cells showing:

      Single-probe average *HER2* copy number ≥6.0 signals/cell

      Dual-probe *HER2*/CEP17 ratio ≥2.0, with an average HER2 copy number ≥4.0 signals/cell

      Dual-probe *HER2*/CEP17 ratio ≥2.0, with an average HER2 copy number <4.0 signals/cell (in rare cases such as chromosome 17 monosomy)

      Dual-probe *HER2*/CEP17 ratio <2.0, with an average HER2 copy number ≥6.0 signals/cell

  If results are equivocal, reflex testing should be performed using the alternative assay (IHC or ISH).
- Prior treatment with fulvestrant
- Prior treatment with cytotoxic chemotherapy for metastatic breast cancer
- Concurrent hormone replacement therapy
- Prior treatment with any of the protocol-specified study treatments

  Patients previously treated with a CDK4/6 inhibitor (e.g., palbociclib, ribociclib, or abemaciclib) are allowed.
- Prior treatment with T-cell co-stimulating or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Treatment with investigational therapy within 28 days prior to initiation of study treatment
- Systemic treatment for HR+ breast cancer within 2 weeks of Cycle 1, Day 1 or 5 half-lives of the drug (whichever is longer) prior to Cycle 1, Day 1

  For patients treated with an endocrine therapy, an earlier initiation of study treatment may be possible after discussion with Medical Monitor.
- Adverse events from prior anti-cancer therapy that have not resolved to Grade ≤1 or better with the exception of alopecia of any grade and Grade ≤2 peripheral neuropathy
- Eligibility only for the control arm

4.1.2.2 Exclusion Criteria for Stage 1 and Stage 2

Patients who meet any of the following criteria will be excluded from Stage 1 and from Stage 2:

- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (monthly or more frequently)
- Uncontrolled tumor-related pain

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

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

  Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not presently associated with spinal cord compression) should be considered for loco-regional therapy, if appropriate, prior to initiation of study treatment.
- Uncontrolled or symptomatic hypercalcemia (ionized calcium > 1.5 mmol/L, calcium > 12 mg/dL or corrected serum calcium > ULN)
- Symptomatic, untreated, or actively progressing CNS metastases

  Patients with a history of treated CNS metastases are eligible, provided that all the following criteria are met:

  - Measurable disease, per RECIST v1.1, must be present outside the CNS.
  - The patient has no history of intracranial hemorrhage or spinal cord hemorrhage.
  - Metastases are limited to the cerebellum or the supratentorial region (i.e., no metastases to the midbrain, pons, medulla, or spinal cord).
  - There is no evidence of interim progression between completion of CNS-directed therapy and the initiation of study treatment.
  - The patient has not received stereotactic radiotherapy within 7 days prior to initiation of study treatment or whole-brain radiotherapy within 14 days prior to initiation of study treatment or neurosurgical resection within 28 days prior to initiation of study treatment.
  - The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anti-convulsant therapy at a stable dose is permitted.
  - Asymptomatic patients with CNS metastases newly detected at screening are eligible for the study after receiving radiotherapy or surgery, with no need to repeat the screening brain scan.
- History of leptomeningeal disease
- 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, *granulomatosis with polyangiitis*, Sjögren's syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 4 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the following exceptions:

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

Patients with controlled Type 1 diabetes mellitus who are on a stable insulin regimen are eligible for the study with the exception of patients randomized to any of the ipatasertib-containing arms.

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, or 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.

- Positive HIV test at screening or at any time prior to screening

  Patients without a prior positive HIV test result will undergo an HIV test at screening, unless not permitted per local regulations.

- Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test at screening

  Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test followed by a quantitative HBV DNA <500 IU/mL at screening, are eligible for the study.

- Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test followed by a positive HCV RNA test at screening

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

- Active tuberculosis
- 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, or any active infection that, in the opinion of the investigator, could impact patient safety

- Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment

  Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.

- Significant cardiovascular disease, such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident within 3 months prior to initiation of study treatment, unstable arrhythmia or unstable angina
- Grade ≥3 hemorrhage or bleeding event within 28 days prior to initiation of study treatment
- Prior allogeneic stem cell or solid organ transplantation
- Major surgical procedure other than for diagnosis within 4 weeks prior to initiation of study treatment or anticipation of need for a major surgical procedure during the course of the study

  Placement of a central venous access catheter (e.g., port or similar) is not considered a major surgical procedure and is therefore permitted.

- History of malignancy other than breast cancer within 2 years prior to screening, with the exception of those with a negligible risk of metastasis or death (e.g., 5-year overall survival [OS] >90%), such as adequately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer
- Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications
- 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
- Known allergy or hypersensitivity to any of the study drugs or any of their excipients
- 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–α 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.

- For patients entering Stage 2: Recovery from all immunotherapy-related adverse events to Grade 1 or better or to baseline at the time of consent

  Note: Patients with ongoing endocrine events that are adequately managed with supplemental therapy are eligible.

4.1.2.3 Exclusion Criteria for Atezo+Entino Arm

Patients who meet any of the following criteria will be excluded from the Atezo + Entino arm during Stage 1:

- Inability to swallow medication or malabsorption condition that would alter the absorption of orally administered medications
- Prior treatment with HDAC inhibitor
- Allergy to benzamide or inactive components of entinostat

4.1.2.4 Exclusion Criteria for Ipatasertib-Containing Arms

Patients who meet any of the following criteria will be excluded from the Atezo + Ipat + Fulvestrant arm during Stage 1:

- Prior treatment with an Akt inhibitor

  Note: Prior treatment with PI3K or mTOR inhibitor is allowed.
- Inability to swallow medication or malabsorption condition that would alter the absorption of orally administered medications
- Grade ≥2 uncontrolled or untreated hypercholesterolemia or hypertriglyceremia
- History of Type 1 or Type 2 diabetes mellitus requiring insulin

  Patients who are on a stable dose of oral diabetes medication ≥2 weeks prior to initiation of study treatment are allowed.

  Diabetic patients with fasting total serum glucose >8.3 mmol/L (150 mg/dL) and/or HbA_{1c} >7.5 are not eligible for enrollment.
- 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, evidence of prior myocardial infarction
- Treatment with strong CYP3A4 inducers and inhibitors within 4 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study drug

4.1.2.5 Exclusion Criteria for Bevacizumab-Containing Arm

Patients who meet any of the following criteria will be excluded from the Atezo + Bev + ET arm during Stage 2:

- Inability to tolerate atezolizumab during Stage 1
- Inadequately controlled hypertension (defined as systolic blood pressure [BP] > 150 mmHg and/or diastolic BP > 100 mmHg), based on an average of ≥ 3 BP readings on ≥ 2 sessions

  Anti-hypertensive therapy to achieve these parameters is allowable.
- Prior history of hypertensive crisis or hypertensive encephalopathy
- Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1 of Cycle 1
- History of hemoptysis (≥ 2.5 mL of bright red blood per episode) within 1 month prior to Day 1 of Cycle 1
- Evidence of bleeding diathesis or significant coagulopathy (in the absence of therapeutic anticoagulation)
- Current or recent (within 10 days of first dose of study treatment) use of aspirin (> 325 mg/day) or clopidogrel (> 75 mg/day)

  Use of full-dose oral or parenteral anticoagulants for therapeutic purpose is permitted as long as the INR and/or aPTT is within therapeutic limits (according to institution standards) within 7 days prior to initiation of study treatment and the patient has been on a stable dose of anticoagulants for ≥ 2 weeks prior to initiation of study treatment. Prophylactic use of anticoagulants is allowed.
- Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 3 days prior to the first dose of bevacizumab
- History of abdominal or tracheoesophageal fistula, GI perforation, or intra-abdominal abscess within 6 months prior to Day 1 of Cycle 1
- History of intestinal obstruction and/or clinical signs or symptoms of GI obstruction, including subocclusive or occlusive syndrome related to the underlying disease, within 6 months prior to initiation of study treatment, or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding within 6 months prior to Day 1 of Cycle 1

  Patients with signs and/or symptoms of subocclusive or occlusive syndrome or with intestinal obstruction at the time of initial diagnosis may be enrolled if they had received definitive (surgical) treatment for symptom resolution.

- Evidence of abdominal free air that is not explained by paracentesis or recent surgical procedure
- Serious, non-healing or dehiscing wound, active ulcer, or untreated bone fracture
- Grade ≥2 proteinuria, as demonstrated by ≥2+ protein on urine dipstick and ≥1.0 g of protein in a 24-hour urine collection

  All patients with ≥2+ protein on dipstick urinalysis at screening must undergo a 24-hour urine collection for protein. Patients with <2+ protein on dipstick urinalysis are eligible for the study.
- Metastatic disease that involves major airways or blood vessels, or centrally located mediastinal tumor masses (<30 mm from the carina) of large volume
- History of intra-abdominal inflammatory process within 6 months prior to Day 1 of Cycle 1, including but not limited to peptic ulcer disease, diverticulitis, or colitis
- Radiotherapy within 28 days or abdominal/pelvic radiotherapy within 60 days prior to Day 1 of Cycle 1, except palliative radiotherapy to bone lesions within 7 days prior to Day 1 of Cycle 1
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 1 of Cycle 1, or abdominal surgery, abdominal interventions or significant abdominal traumatic injury within 60 days prior to Day 1 of Cycle 1, or anticipation of need for major surgical procedure during the course of the study or non-recovery from side effects of any such procedure

4.1.2.6 Exclusion Criteria for Abemaciclib-Containing Arm

Patients who meet any of the following criteria will be excluded from the Atezo+Abema+Fulvestrant arm during Stage 1:

- Interstitial lung disease or severe dyspnea at rest or requiring oxygen therapy
- History of major surgical resection involving the stomach or small bowel, or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea
- History of syncope of cardiovascular etiology, ventricular arrhythmia, or sudden cardiac arrest

4.2 METHOD OF TREATMENT ASSIGNMENT

This is a randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and Stage 1 treatment assignment from the interactive voice or web-based response system (IxRS). Patients who enroll in Stage 2 will be assigned to treatment through use of the IxRS and will retain the same patient identification number that was assigned in Stage 1.

This study will employ a permuted-block randomization method with dynamically changing randomization ratios to account for fluctuation in the number of treatment arms that are open for enrollment during the study. The randomization ratio will depend on

the number of experimental arms that are open for enrollment, with the stipulation that the likelihood of being allocated to control arm is no more than 35% (subsequent randomization scheme).

Randomization will take into account general exclusion criteria and arm-specific exclusion criteria as outlined in Section 4.1.2. If a patient is eligible only for the control arm, the patient will not be enrolled in the study.

If more than one mandatory serial biopsy arm is open for enrollment at a time, eligible patients will be assigned to one of the available cohorts by the Sponsor.

In Stage 1, patients who do not receive at least one dose of each drug for their assigned treatment regimen will not be included in the efficacy analyses. Additional patients may be randomized to reach the target number of treated patients planned for analysis.

4.3 STUDY TREATMENT

Details on the therapeutic agents for each treatment arm are provided in the respective appendix for that treatment arm, as outlined in Table 4 for Stage 1 and Table 6 for Stage 2.

4.3.1 Investigational Medicinal Product Accountability

For Stage 1 of the study, the IMPs are atezolizumab, ipatasertib, fulvestrant, entinostat, and abemaciclib. All IMPs required for completion of Stage 1 except fulvestrant will be provided by the Sponsor where required by local practices. Fulvestrant will either be provided by the Sponsor where required by local health authority regulations or sourced locally with reimbursement by the Sponsor where required. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

For Stage 2, in addition to atezolizumab, the IMPs are bevacizumab, fulvestrant, exemestane, and tamoxifen. As the choice of using fulvestrant, exemestane, or tamoxifen is left to the physician's discretion, these Stage 2 IMPs will either be provided by the Sponsor where required by local health authority regulations or sourced locally with reimbursement by the Sponsor where required.

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 (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

4.3.2 Non-Investigational Medicinal Product

The non-investigational medicinal product for this study is loperamide. Loperamide will be sourced locally. Details regarding dosing of loperamide for the management of adverse events in the ipatasertib- and abemaciclib-containing treatment arms can be found in Appendix 11 and Appendix 13. For information on the formulation and handling of loperamide, please refer to the local prescribing information.

4.3.3 Post-Trial Access to Study Treatment

Currently, the Sponsor does not have any plans to provide study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing study treatments in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following web site:

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

4.4 CONCOMITANT THERAPY AND PROHIBITED FOOD

Details on concomitant therapy, prohibited food, and additional restrictions for each treatment arm are provided in the respective appendix for that treatment arm, as outlined in Appendix 7 through Appendix 13.

4.5 STUDY ASSESSMENTS

A schedule of activities to be performed during the study is provided for each treatment arm in Appendix 7 through Appendix 13. 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

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

Written informed consent must also be obtained before performing screening evaluations for Stage 2.

Screening evaluations are to be performed within 28 days prior to initiation of study treatment in Stage 1 or Stage 2 (Day 1). All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. Patients who fail their first screening for study eligibility (Stage 1 or Stage 2) may qualify for two re-screening opportunities (for a total of three screenings per patient) at the investigator's discretion. Patients must re-sign the consent form prior to re-screening.

Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 (within 14 days prior to Day 1 for laboratory tests) may be used; such tests do not need to be repeated for screening or re-screening.

4.5.2 Medical History, Molecular Profile, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol, will be recorded at baseline. The patient's molecular profile for HR+ breast cancer, if available, will be recorded at screening and whenever updated information becomes available during the study. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within a specified period of time prior to initiation of study treatment (see Appendix 7 through Appendix 13) 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.

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, GI, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions electronic Case Report Form (eCRF).

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

4.5.4 Vital Signs

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

Vital signs should be measured within 60 minutes prior to each study treatment and, if clinically indicated, during or after the infusion. In addition, vital signs should be measured at other specified timepoints as outlined in the schedule of activities (see Appendix 7 through Appendix 13).

4.5.5 Tumor and Response Evaluations

Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 24 weeks following initiation of combination treatment, then every 8 weeks

(±1 week) from Week 25 to Week 48, and then every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of atezolizumab-treated patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new, non–protocol-specified anti-cancer therapy. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected.

Baseline tumor assessments for Stage 2 must be performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). For patients eligible for Stage 2, tumor assessments performed prior to or at the time of unacceptable toxicity, disease progression per RECIST v1.1 (control arm) or loss of clinical benefit (experimental arm) during Stage 1 may serve as baseline assessments for Stage 2, provided that the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment.

All measurable and evaluable lesions should be assessed and documented at screening (in both Stage 1 and Stage 2). Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening.

Screening assessments must include CT scans (with IV contrast; with or without oral contrast) or magnetic resonance imaging (MRI) scans (with IV contrast) of the chest, abdomen, pelvis, and head with one exception: a head scan is not required at Stage 2 screening. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans (with IV contrast, if feasible) of the abdomen, pelvis, and head should be performed. A CT scan with contrast or MRI scan with contrast of the head must be done at Stage 1 screening to evaluate CNS metastasis in all patients (MRI scan must be performed if contrast is contraindicated). CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

Bone scans, positron emission tomography (PET) scans, and/or skeletal survey should be performed at screening to assess bone lesions. Bone lesions identified at baseline should continue to be assessed following the tumor assessment schedule described above. Additional bone scans, PET scans, or skeletal surveys should be performed if clinically indicated.

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

All measurable and evaluable lesions identified at baseline should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans). To facilitate evaluation of post-progression tumor changes while treatment is ongoing, tumor assessments must be continued after disease progression per RECIST v1.1 for patients who receive treatment beyond progression. This includes continued measurement of target lesions, evaluation of non-target lesions (including monitoring for further worsening of any non-target lesions that have shown unequivocal progression), and evaluation of any newly identified lesions (including measurements, if lesions are measurable) at all subsequent assessments).

Response will be assessed by the investigator using RECIST v1.1 (see Appendix 1). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

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

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): CPK (as needed), sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, ALP, ALT, AST
- Coagulation: INR, aPTT
- FSH, LH, and estradiol (at screening for patients who are ≤60 years old and in postmenopausal state or had prior ovarian ablation); estradiol is also needed for patients who are ≤60 years old and in postmenopausal state and on LHRH agonist for ovarian suppression
- Thyroid function testing: TSH, T3 (or total T3 for sites where free T3 is not performed), and T4
- HIV serology, unless not permitted per local regulations
- HBV serology: HBsAg, total HBcAb, and (if HBsAg test is negative and total HBcAb test is positive) HBV DNA

  If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection.

- HCV serology: HCV antibody and (if HCV antibody test is positive) HCV RNA

  If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.
- C-reactive protein
- LDH
- Urinalysis (pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted

  For Stage 2 patients receiving bevacizumab: If urinary protein is ≥2+ on dipstick at screening, a 24-hour urine collection is required to check the total urinary protein.

Refer to Appendix 7 through Appendix 13 for arm-specific local laboratory requirements.

Samples for the following laboratory test will be sent to a central laboratory or to the study site's local laboratory for analysis:

- Blood cystatin C and calculated glomerular filtration rate (GFR) of cystatin C as needed

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

- Serum sample for analysis of autoantibodies: anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody

  These analyses will be performed using validated assays.
- Plasma or serum samples for PK analysis (see Appendix 8 through Appendix 13)
- Plasma or serum samples for immunogenicity analysis (see Appendix 8 through Appendix 13)
- Plasma, serum, and peripheral blood mononuclear cell (PBMC) samples for exploratory research on biomarkers (see Appendix 7 through Appendix 13)
- Archival or fresh tumor tissue sample collected at baseline for determination of PD-L1 expression and for exploratory research on biomarkers

  Baseline tumor tissue samples from the primary lesion or a metastatic lesion 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. It is preferred 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.

  A representative FFPE tumor specimen in a paraffin block (preferred) or at least 18 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report.

  Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 50 viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method.

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. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases is not acceptable.

Remaining archival tumor tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first.

- Tumor tissue sample collected during Stage 1, at the time of unacceptable toxicity, disease progression per RECIST v1.1, or loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details), if deemed clinically feasible by the investigator, for exploratory research on biomarkers

  Biopsies should be performed within 40 days after determination of unacceptable toxicity, disease progression, or loss of clinical benefit, 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 are preferred.

- Mandatory serial biopsy arm: tumor tissue samples collected 4 weeks (±7 days) after initiation of Stage 1 treatment, if deemed clinically feasible by the investigator, for exploratory research on biomarkers

  Patient should have at least two accessible tumors that are amenable to excisional, punch, or core-needle biopsy (a minimum of three cores, 18-gauge needle or larger [16-gauge needle preferred]) without unacceptable risk of a major procedural complication. If it is planned that more than one biopsy will be obtained from a single lesion, the lesion should be large enough to permit successive biopsies ≥1 cm apart.

Refer to Appendix 7 through Appendix 13 for arm-specific central laboratory requirements.

Exploratory biomarker research may include, but will not be limited to, analysis of genes or gene signatures associated with tumor microenvironment and immunobiology, PD-L1, cytokines associated with T-cell activation, T-cell receptor repertoire, or density, localization, activation status of immune cells and their subsets, and *PIK3CA/AKT1/PTEN* alterations. Research may involve extraction of DNA, cell-free DNA, or RNA; analysis of mutations, single nucleotide polymorphisms, and other genomic variants; and genomic profiling through use of NGS of a comprehensive panel of genes. DNA extracted from blood may be compared with DNA extracted from tissue to identify somatic variants by distinguishing germline variants from somatic variants. NGS methods may include whole genome sequencing (WGS) or WES of tissue and blood samples, but WGS or WES of blood samples will be performed only at participating sites.

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

Unless the patient gives specific consent for his or her remaining samples to be stored for optional exploratory research (see Section 4.5.9), biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Plasma and/or serum samples collected for PK analysis or immunogenicity analysis may be needed for additional immunogenicity characterization and PK and immunogenicity assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Plasma, serum, PBMC, and tumor tissue samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed, with the exception of samples that undergo WES, which will be stored until they are no longer needed or until they are exhausted. However, the storage period for the WES samples will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

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

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

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 Sponsor policy on study data publication.

4.5.7 Electrocardiograms

An ECG is required at screening and when clinically indicated. Patients in arms that require additional ECG monitoring (e.g., Ipat-containing arms) will undergo ECG monitoring at specified timepoints during the study. ECGs for each patient should be obtained from the same machine wherever possible. Lead placement should be as consistent as possible. It is recommended that patients be resting in a supine position for at least 10 minutes prior to the 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. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

4.5.8 Optional Tumor Tissue Samples

Consenting patients will undergo optional tumor biopsy sample collection, if deemed clinically feasible by the investigator, 4 weeks (±7 days) after treatment initiation (see Appendix 7 through Appendix 13 for details) and may undergo additional on-treatment biopsies at any other time at the investigator's discretion. Samples collected by means of resection, core-needle biopsy (at least three cores preferred), or excisional, incisional, punch, or forceps biopsy are preferred. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

The Informed Consent Form will contain a separate section that addresses optional biopsies. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of collecting optional biopsies. 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 biopsies. 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 Optional Biopsy Sample Informed Consent eCRF.

Samples may be used for exploratory biomarker research as described in Section 4.5.6. Refer to Section 4.5.6 for details on sample storage, use of samples after patient withdrawal, confidentiality standards for data, and availability of data derived from WES.

4.5.9 Optional Samples for Research Biosample Repository

4.5.9.1 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 *biomarker assays*, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR *samples* will be 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 assays and establish the performance characteristics of these assays

4.5.9.2 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 4.5.9) will not be applicable at that site.

4.5.9.3 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 cancer immunotherapy or diseases:

- Blood samples collected on Day 1 of Cycle 1, during Stages 1 and 2
- Remaining blood, serum, plasma, PBMC, and tumor tissue samples (with the exception of remaining archival FFPE blocks, which will be returned to sites) and any derivatives thereof (e.g., DNA, RNA, proteins, and peptides), including remaining tissue samples from medically indicated procedures (e.g., bronchoscopy, esophagogastroduodenoscopy, colonoscopy) performed at the investigator's discretion during the course of the study

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

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.

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).

4.5.9.4 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.

4.5.9.5 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.

4.5.9.6 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 specimens 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 CO39611 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 CO39611.

If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

4.5.9.7 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 if they experience 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 may jeopardize the patient's safety if she continues study treatment
- Investigator or Sponsor determines it is in the best interest of the patient
- Use of another non–protocol anti-cancer therapy
- Experimental arms: 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) (see Section 3.1.1.1 for details)
- Control arm: radiographic disease progression per RECIST v1.1

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

Patients will return to the clinic for a treatment discontinuation visit ≤ 30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments as outlined in the schedule of activities (see Appendix 7 through Appendix 13).

After treatment discontinuation, information on survival follow-up and initiation of new anti-cancer therapy 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 study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from 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:

- 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. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients who withdraw from the study will not be replaced.

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

A safety plan, including a summary of risks and management guidelines for patients who experience specific adverse events, is provided for each treatment arm in Appendix 7 through Appendix 12 as outlined in Table 4 for Stage 1 and Table 6 for Stage 2.

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

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

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

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

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

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

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

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

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

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest are listed for each treatment arm in Appendix 7 through Appendix 13.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study treatment, all adverse events will be reported until 30 days after the 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 135 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 study treatment, 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 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 study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of study treatment, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to study treatment; and/or the adverse event abates or resolves upon discontinuation of study treatment or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than study treatment (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment).

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions and Cytokine Release Syndrome

There may be significant overlap in signs and symptoms of IRRs and CRS. While IRRs occur during or within 24 hours after treatment administration, time to onset of CRS may vary. Differential diagnosis should be applied, particularly for late-onset CRS (occurring more than 24 hours after treatment administration), to rule out other etiologies such as

delayed hypersensitivity reactions, sepsis or infections, hemophagocytic lymphohistiocytosis (HLH), tumor lysis syndrome, early disease progression, or other manifestations of systemic inflammation.

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

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 associated signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF or Cytokine Release Syndrome eCRF.

In recognition of the challenges in clinically distinguishing between IRRs and CRS, consolidated guidelines for medical management of IRRs and CRS are provided in Appendix 6.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Laboratory Values

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

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

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

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST (> 3 × baseline value) in combination with either an elevated total bilirubin (> 2 × ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury

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

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

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

5.3.5.8 Deaths

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

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

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of HR+ Breast Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

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

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

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

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

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

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Overdoses, medication errors, drug abuse, or drug misuse (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

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours per day, 7 days per week. Details will be provided separately.

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 Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Treatment Initiation

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 135 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 Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur > 135 days after the last dose of study treatment are provided in Section 5.6.

5.4.3 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, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For atezolizumab, ipatasertib, bevacizumab, entinostat, and abemaciclib 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 atezolizumab, ipatasertib, bevacizumab, entinostat, and abemaciclib, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Special situations should be recorded 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.

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 135 days after the last dose of study treatment or until initiation of new, non–protocol-specified systemic anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

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

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

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

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

- Atezolizumab Investigator's Brochure
- Entinostat Investigator's Brochure
- Ipatasertib Investigator's Brochure
- Bevacizumab Investigator's Brochure
- Summary of Product Characteristics for fulvestrant, exemestane, and tamoxifen
- Abemaciclib Investigator's Brochure

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The final study analysis will be based on patient data collected through study discontinuation. If not otherwise specified, efficacy analyses will be based on the efficacy-evaluable population, defined as all patients who receive at least one dose of each drug for their assigned treatment regimen, and other analyses will be based on the safety-evaluable population, defined as all patients who receive any amount of study treatment.

The analysis results will be summarized by the treatment that patients actually received, and as well as by stage (Stage 1 or Stage 2). Data will be described and summarized as warranted by sample size. Continuous variables will be summarized through use of means, standard deviations, medians, and ranges. Categorical variables will be summarized through use of counts and percentages. Listings will be used in place of tables in the event of small sample sizes.

New baseline values will be established for the Stage 2 efficacy and safety analyses. For evaluation of tumor response, new baseline tumor assessments will be established as described in Section 4.5.5. For other endpoints (e.g., change from baseline in vital

signs or laboratory test results), the last non-missing value prior to the patient's first dose during Stage 2 will serve as the new baseline.

6.1 DETERMINATION OF SAMPLE SIZE

This study is not designed to make explicit power and Type I error considerations for a hypothesis test. Instead, this study is designed to obtain preliminary efficacy, safety, and PK data on immunotherapy-based treatment combinations when administered to patients with inoperable locally advanced or metastatic HR+ breast cancer who had disease progression during or following first-line metastatic treatment with a CDK4/6 inhibitor (e.g., palbociclib, ribociclib, abemaciclib) in combination with an ET not including fulvestrant.

Approximately 126–276 patients will be randomized in the control and experimental arms during the study.

[redacted] Thus, enrollment may be increased beyond the initially planned sample size of 126–276 patients.

[redacted]

[redacted]

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment will be summarized by region, country, and investigator by treatment arm within the two stages. Patient disposition will be summarized by treatment arm within each stage. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, and reasons for discontinuation from the study will be summarized by treatment arm within each stage.

For safety-evaluable patients, study drug administration data will be tabulated or listed by treatment arm within each stage, and any dose modifications will be flagged. Means and standard deviations will be used to summarize the total dose and dose intensity for each study drug. The reasons for discontinuation of study treatment will also be tabulated.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race/ethnicity, weight, malignancy duration, metastatic disease site, and baseline ECOG Performance Status) will be summarized overall and by treatment arm within each stage.

6.4 EFFICACY ANALYSES

The efficacy-evaluable populations will be defined as follows:

- All patients who received at least one dose of each drug for their assigned treatment regimen

Efficacy endpoints will be summarized by actual treatment arm.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is ORR (defined as the proportion of patients with an objective response [complete or partial response]) during Stage 1, as defined in

Section 2 (see Table 2). Patients with missing or no response assessments will be classified as non-responders.

ORR will be calculated for each arm, along [redacted] The difference in ORR between the experimental arms and the control arm will also be calculated, along [redacted]

6.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are PFS, clinical benefit rate (CBR), OS, OS at specific timepoints (e.g., 18 months), and duration of response (DOR) during Stage 1, as defined in Section 2 (see Table 2). DOR and CBR are determined by the investigator according to RECIST v1.1.

DOR will be derived for efficacy-evaluable patients with a complete or partial response.

For patients who do not have documented disease progression or death in a study stage, PFS and DOR will be censored at the day of the last tumor assessment.

Patients who are still alive at the time of OS analysis will be censored at the last date they were known to be alive.

The Kaplan-Meier method will be used to estimate the median for PFS, OS, and DOR, with 95% confidence intervals constructed through use of the Brookmeyer and Crowley method. OS rate at specific timepoints will also be estimated using the Kaplan-Meier method, with 95% confidence intervals calculated on the basis of Greenwood's estimate for the variance.

CBR, the proportion of patients with stable disease for ≥24 weeks, a partial response, or a complete response, will be calculated for each treatment arm, with [redacted]

6.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints ORR, PFS, DOR, CBR, and DCR during Stage 2, as determined by the investigator according to RECIST v1.1 (see Table 3).

ORR, PFS, DOR, CBR, and DCR will be analyzed through use of the same methods described in Sections 6.4.1 and 6.4.2. DOR will be assessed for efficacy-evaluable patients with a complete or partial response.

6.5 SAFETY ANALYSES

Verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v4.0.

Safety will be assessed through summaries of adverse events, changes in laboratory test results, changes in vital signs and ECGs, and exposure to study drugs. Exposure to combination treatment and length of safety follow-up will be summarized by treatment arm within each stage.

Treatment-emergent adverse events occurring after initiation of treatment will be summarized. For each patient, the maximum reported severity of each adverse event will be used in the summaries by severity grade. All treatment-emergent adverse events, serious adverse events, adverse events leading to withdrawal of study treatment, Grade ≥3 adverse events, deaths, and causes of death will be listed and summarized by mapped term, appropriate thesaurus level, and NCI CTCAE severity grade.

Relevant laboratory, vital signs (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum post-baseline severity grade. Changes in vital signs and ECGs will be summarized.

6.6 PHARMACOKINETIC ANALYSES

Sparse samples will be collected for PK analyses of atezolizumab (patients who receive at least one dose of atezolizumab) and drugs given in combination with atezolizumab (patients who receive at least one dose of the drug). Serum or plasma concentrations of the various study drugs will be reported as individual values and summarized (mean, standard deviation, coefficient of variation, median, range, geometric mean, and geometric mean 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. Pharmacokinetic data for combination drugs may be compared with available historical data from internal and published previous studies. Atezolizumab concentration data may be pooled with data from other studies using an established population PK model to derive PK parameters such as clearance, volume of distribution, and area under the curve.

6.7 IMMUNOGENICITY ANALYSES

Immunogenicity will be assessed for atezolizumab (both stages) and bevacizumab (Stage 2). 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

(post-baseline incidence) will be summarized by treatment group. When determining post-baseline 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 post-baseline samples is at least 0.60 titer units greater than the titer of the baseline sample (treatment-enhanced ADA response). Patients are considered to be ADA negative if they are ADA negative or have missing data at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 0.60 titer units greater than the titer of the baseline sample (treatment unaffected).

For bevacizumab, ADA positivity will be determined according to standard methods established for previous studies of these drugs.

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

6.8 BIOMARKER ANALYSES

Exploratory biomarker analyses will be performed in an effort to understand the association of these biomarkers with response to study drugs, taking into account efficacy and safety endpoints (see Section 4.5.6 for more details).

6.9 INTERIM ANALYSES

It is anticipated that interim analyses will be conducted over the course of the study. For Stage 1, the earliest interim analysis is scheduled to take place when at least one experimental arm has completed enrollment in the preliminary phase, approximately 15 patients have been enrolled in the control arm, and patients have been followed for a minimum of 6 weeks. A posterior probability will be used to guide further enrollment based on the interim analysis of clinical activity in the experimental arm compared with the control arm. If the interim analysis suggests that the activity in an experimental arm is higher than that in the control arm, there may be enrollment of an additional 25 patients in the experimental arm.

An interim analysis will also be conducted [redacted]

The interim analyses will be performed and interpreted by Sponsor study team personnel.

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.

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, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMPs, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the 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 Trials Directive (2001/20/EC) *or Clinical Trials Regulation (536/2014)* and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Forms (and ancillary sample Informed Consent Forms such as a Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, they will be provided in a certified translation into the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

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

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

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or

access. In the event of a data security breach, appropriate mitigation measures will be implemented.

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

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring. Screening and enrollment will occur through an IxRS. Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker analyses, and PK analyses), as specified in Section 4.5.6. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker analyses, and PK analyses), as specified in Section 4.5.6. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC will be employed to monitor and evaluate patient safety throughout the study. An SOC will provide external expert opinions on the safety data collected during the study.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, *in clinical trial registries*, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. *Study data may be shared with others who are not participating in this study (see Section 8.4). In addition, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local*

regulation, and 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: *https://www.roche.com/innovation/process/clinical-trials/data-sharing/*

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a Marketing Authorization Application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

10. REFERENCES

Bonneterre J, Thürlimann B, Robertson JF, et al. Anastrozole versus tamoxifen as first line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. J Clin Oncol 2000;18:3748–57.

Burstein HJ, Griggs JJ, Prestrud AA, et al. American society of clinical oncology clinical practice guideline update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Oncol Pract 2010;6:243–6.

Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 3). Ann Oncol 2017; 28:16–33.

Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity 2013;39:1–10.

Dicker MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2– metastatic breast cancer. Clin Cancer Res 2017;23:5218–24.

Ebert PJ, Cheung J, Yang Y, et al. MAP kinase inhibition promotes T cell and anti-tumor activity in combination with PD-L1 checkpoint blockade. Immunity 2016;44:609–21.

[ESMO] European Society for Medical Oncology. ESMO clinical practice guidelines: breast cancer [resource on the Internet]. 2016 [updated 18 February 2016; cited 16 March 2017]. Available from: http://www.esmo.org/Guidelines/Breast-Cancer.

Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374–403.

Frebel H, Nindl V, Schuepbach RA, et al. Programmed death 1 protects from fatal circulatory failure during systemic virus infection of mice. J Exp Med 2012;209:2485–99.

Gibson L, Lawrence D, Dawson C, et al. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. Cochrane Database Syst Rev 2009;4:CD003370.

Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. J Clin Onc 2017;doi: 10.1200/JCO.2017.75.6155.Epub: 2 October 2017.

Hales RK, Banchereau J, Ribas A, et al. Assessing oncologic benefit in clinical trials of immunotherapy agents. Ann Oncol 2010;21:1944–51.

Hurvitz SA, Martin M, Press MF, et al. Treatment with abemaciclib modulates the immune response in gene expression in gene expression analysis of the neoMONARCH neoadjuvant study of abemaciclib in postmenopausal women with HR+, HER2− breast cancer [abstract]. In: San Antonio Breast Cancer Symposium;2018.Abstract PD2−10.

Jeselsohn R, Yelensky R, Buchwalter G, et al. Emergence of constitutively active estrogen receptor-α mutations in pretreated advanced estrogen receptor-positive breast cancer. Clin Cancer Res 2014;20:1757−67.

Johnston S, Pippen J Jr, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor positive metastatic breast cancer. J Clin Oncol 2009;27:5538−46.

Kim K, Skora AD, Li Z, et al. Eradication of metastatic mouse cancers resistant to immune checkpoint blockade by suppression of myeloid-derived cells. Proc Natl Acad Sci USA 2014;111:11774−9.

Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625−38.

Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20:355−62.

Musgrove EA, Sutherland RL. Biological determinants of endocrine resistance in breast cancer. Nat Rev Cancer 2009;9:631−43.

Nabholtz JM, Buzdar A, Pollak M, et al. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. J Clin Oncol 2000; 18:3758−67.

[NCCN] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: breast cancer [resource on the Internet]. 2014 [updated 20 March 2013; cited 16 March 2017]. Available from: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

[NCCN] National Comprehensive Cancer Network. Recommendations of the NCCN COVID-19 Vaccination Advisory Committee [resource on the internet]. 2021 [cited: 28 May 2021]. Available from: https://www.nccn.org/docs/default-source/covid-19/2021_covid-19_vaccination_guidance_v2-0.pdf?sfvrsn=b483da2b_2.

O'Leary B, Finn RS, Turner NC. Treating cancer with selective CDK4/6 inhibitors. Nat Rev Clin Oncol 2016;13:417−30.

Ortega S, Malumbres M, Barbacid M. Cyclin D-dependent kinases, INK4 inhibitors and cancer. Biochim Biophys Acta 2002;1602:73−87.

Paridaens RJ, Dirix LY, Beex LV, et al. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. J Clin Oncol 2008;26:4883–90.

Peng W, Chen JQ, Liu C, et al. Loss of PTEN promotes resistance to T cell-mediated immunotherapy. Cancer Discov 2016;6:202–16.

Robertson JFR, Bondarenko IM, Trishkina E, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. Lancet 2016;388:2997–3005.

Robinson DR, Wu YM, Vats P, et al. Activating ESR1 mutations in hormone-resistant metastatic breast cancer. Nat Genet 2013;45:1446–51.

Rugo HS, Rumble RB, Macrae E, et al. Endocrine therapy for hormone receptor-positive metastatic breast cancer: American Society of Clinical Oncology Guideline. J Clin Onocol 2016;34:3069–103.

Senkus E, Kyriakides S, Penault-Llorca F, et al. Primary breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24(Suppl 6):vi7–23.

Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2– advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol 2017;35:2875–84.

[SITC] Society for Immunotherapy of Cancer. Society for Immunotherapy of Cancer statement on SARS-CoV-2 vaccination and cancer immunotherapy [resource on the internet]. Press release: 23 December 2020 [cited: 28 May 2021]. Available from: https://www.sitcancer.org/aboutsitc/press-releases/2020/sitc-statement-sars-cov-2-vaccination-cancer-immunotherapy.

Toy W, Shen Y, Won H, et al. ESR1 ligand-binding domain mutations in hormone-resistant breast cancer. Nat Genet 2013;45:1439–45.

Wykes MN, Lewin SR. Immune checkpoint blockade in infectious diseases. Nat Rev Immunol 2018;18:91–104.

Wallin JJ, Bendell JC, Funke R. Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma. Nat Commun 2016;7:12624.

Appendix 1
Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

A1–1 TABLE OF CONTENTS

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

A1–2 TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

A1–2.1 DEFINITION OF MEASURABLE LESIONS

A1–2.1.1 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 ≤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

A1–2.1.2 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 ≤5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

A1–2.2 DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter <10 mm or pathological lymph nodes with short axis ≥10 mm but <15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

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

A1–2.3 SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

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

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

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

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

A1–3 METHODS FOR ASSESSING LESIONS

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

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

A1–3.1 CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of

skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is required.

A1–3.2 CHEST X-RAY

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

A1–3.3 CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scans have slice thickness of >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (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 prior studies, if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward</u>. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, because the same lesion may appear to have a different size using a new modality.

A1–3.4 ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

A1–4 <u>ASSESSMENT OF TUMOR BURDEN</u>

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.

A1–4.1 IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and 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 because 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. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

A1–4.2 CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

A1–4.2.1 Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, because a normal lymph node is defined as having a short axis of < 10 mm.

A1–4.2.2 Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes because 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 "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is < 5 mm, and in that case "too small to measure" should not be ticked.

A1–4.2.3 Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining 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.

A1–4.3 EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to < 10 mm in short axis.
Non-target lesions should be noted at baseline and should be identified as "present" or

"absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis < 10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

A1–5 RESPONSE CRITERIA

A1–5.1 CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

A1–5.2 CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions 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

A1–5.3 SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

A1–5.3.1 Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit

discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

A1–5.4 NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

A1–5.5 CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table A1-1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table A1-1 Criteria for Overall Response at a Single Timepoint: 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 all 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.

A1–5.6 MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

A1–5.7 SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as having "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 lesions as shown in Table A1-1.

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.

A1–6 REFERENCES

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

Appendix 2
Placeholder for Future Arm

The Modified RECIST v1.1 for Immune-Based Therapeutics (iRECIST) appendix has been removed as the Sponsor no longer plans to perform these analyses. Appendix 2 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 3
ECOG Performance Status Scale

Grade	Description
0	Fully active; able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours
3	Capable of only limited self-care; confined to a bed or chair >50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

ECOG=Eastern Cooperative Oncology Group.

Appendix 4
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 *or pericardial disorder* while receiving another immunostimulatory anti-cancer agent. The Medical Monitor is available to advise on any uncertainty over autoimmune exclusions.

Autoimmune Diseases and Immune Deficiencies

• Acute disseminated encephalomyelitis • Addison disease • Ankylosing spondylitis • Antiphospholipid antibody syndrome • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune hepatitis • Autoimmune hypoparathyroidism • Autoimmune hypophysitis • *Autoimmune myelitis* • 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 • *Granulomatosis with polyangiitis* • Graves disease • Guillain-Barré syndrome • Hashimoto disease • IgA nephropathy • Inflammatory bowel disease • Interstitial cystitis • Kawasaki disease • Lambert-Eaton myasthenia syndrome • Lupus erythematosus • Lyme disease - chronic • Meniere syndrome • Mooren ulcer • Morphea • Multiple sclerosis • Myasthenia gravis	• Neuromyotonia • Opsoclonus myoclonus syndrome • Optic neuritis • Ord thyroiditis • Pemphigus • Pernicious anemia • Polyarteritis nodosa • Polyarthritis • Polyglandular autoimmune syndrome • Primary biliary cholangitis • Psoriasis • Reiter syndrome • Rheumatoid arthritis • Sarcoidosis • Scleroderma • Sjögren's syndrome • Stiff-Person syndrome • Takayasu arteritis • Ulcerative colitis • Vitiligo • Vogt-Koyanagi-Harada disease

Appendix 5
Anaphylaxis Precautions

A5–1 EQUIPMENT NEEDED

- Oxygen
- Epinephrine for subcutaneous, IV, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

A5–2 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 6
Management of Atezolizumab-Specific Adverse Events

A6–1 TABLE OF CONTENTS

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 following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections in this appendix or the treatment arm-specific appendices.

- *Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.*
- *In general, atezolizumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.*
- *Consider holding atezolizumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.5–1 mg/kg/day of prednisone or equivalent) may be administered.*
- *For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.*
- *Hold atezolizumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1–2 mg/kg/day prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.*
- *In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab treatment, with the exception of endocrinopathies that are controlled by hormonereplacement therapy.*
- The investigator should consider the benefit–risk balance a given patient may be experiencing prior to further administration of atezolizumab. *Resumption* of atezolizumab may be considered *in patients who are* deriving benefit and *have* fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's assessment of *the benefits and risks* and documented by the investigator. The Medical Monitor is available to advise as needed.

A6–2 PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, *chest pain, fever, dyspnea,* fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. 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. *Coronavirus 2019 (COVID-19) evaluation should be performed per institutional guidelines where relevant.* Management guidelines for pulmonary events are provided in Table A6-1.

Table A6-1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For Grade 1 pneumonitis, consider withholding atezolizumab.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL *with or without transbronchial biopsy*. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c, d] • For recurrent events or events with no improvement after 48-72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c, d] • *Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment.* • Bronchoscopy or BAL *with or without transbronchial biopsy* is recommended. • Initiate treatment with *corticosteroids equivalent to* 1–2 mg/kg/day IV methylprednisolone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

Table A6-1 Management Guidelines for Pulmonary Events, Including Pneumonitis (cont.)

BAL = bronchoscopic alveolar lavage.

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

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

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

[d] *In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.*

A6–3 HEPATIC EVENTS

Patients eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases; liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table A6-2.

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

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

Table A6-2 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with *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 the Medical Monitor. [c]
Event	Management
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with *corticosteroids equivalent to* 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal; LFT = liver function test.

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

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

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

Table A6-2 Management Guidelines for Hepatic Events (cont.)

Guidelines for patients with hepatocellular carcinoma	
Event	Management
AST/ALT is within normal limits at baseline and increases to >3× ULN to≤10× ULN or AST/ALT is>ULN to ≤ 3×ULN at baseline and increases to > 5×ULN to ≤ 10×ULN or AST/ALT is > 3×ULN to ≤5× ULN at baseline and increases to >8×ULN to ≤ 10×ULN	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Monitor LFTs more frequently until return to baseline values. • For events of >5 days' duration, consider initiating treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to baseline or to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to baseline or to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
AST or ALT increases to > 10×ULN or total bilirubin increases to > 3×ULN	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to baseline, taper corticosteroids over≥1 month.

GI=gastrointestinal; LFT=liver function test.

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

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

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

A6–4 GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table A6-3.

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

Table A6-3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • *If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis.* • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with *corticosteroids equivalent to* 1–2 mg/kg/day oral prednisone. *If the 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 the Medical Monitor. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with *corticosteroids equivalent to* 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. *If event 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 the Medical Monitor. [c]

GI=gastrointestinal.

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

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

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

Table A6-3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis) (cont.)

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

GI=gastrointestinal.

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

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

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

A6–5 ENDOCRINE EVENTS

Management guidelines for endocrine events are provided in Table A6-4.

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, T3, and T4 levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table A6-4 Management Guidelines for Endocrine Events

Event	Management
Grade 1 hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Grade 2 hypothyroidism	• *Consider withholding atezolizumab.* • *Initiate treatment with thyroid replacement hormone.* • *Monitor TSH closely.* • *Consider patient referral to endocrinologist.* • *Resume atezolizumab when symptoms are controlled and thyroid function is improving.*
Grade 3 or 4 hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • *Refer* to *an* endocrinologist. • *Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status)* • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • *Permanently discontinue atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hypothyroidism.* [c]
Grade 1 hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH < 0.1 mU/L:** • Follow guidelines for *Grade 2* hyperthyroidism. • Consider patient referral to endocrinologist.

MRI = magnetic resonance imaging.

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

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

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

Table A6-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Grade 2 hyperthyroidism	• *Consider withholding 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.*
Grade 3 or 4 hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. • *Refer* to *an* endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact the Medical Monitor for life-threatening immune-mediated hyperthyroidism. [c]
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [b] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with *corticosteroids equivalent to* 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.

MRI = magnetic resonance imaging.

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

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

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

Table A6-4 Management Guidelines for Endocrine Events (cont.)

Event	Management
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
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 *corticosteroids equivalent to* 1–2 mg/kg/day *IV* methylprednisolone *and convert to 1-2 mg/kg/day oral prednisone* or equivalent upon improvement. • Initiate hormone replacement as clinically needed. • 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 the Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with *corticosteroids equivalent to* 1–2 mg/kg/day *IV* methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement as clinically needed.

MRI = magnetic resonance imaging.

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

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

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

A6–6 OCULAR EVENTS

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table A6-5.

Table A6-5 Management Guidelines for Ocular Events

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

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

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

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

A6–7 IMMUNE-MEDIATED CARDIAC EVENTS

Management guidelines for cardiac events are provided in Table A6-6.

A6–8 IMMUNE-MEDIATED MYOCARDITIS

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

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

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-6.

A6–9 IMMUNE-MEDIATED PERICARDIAL DISORDERS

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated

according to the guidelines in Table A6-6. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table A6-6 Management Guidelines for Immune-Mediated *Cardiac Events*

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

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

A6–10 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, *antipyretic medications*, 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 the medical management of IRRs and CRS are provided in Table A6-7.

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

Table A6-7 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, *antipyretic medications*, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors and/or Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	• Immediately interrupt infusion. • Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. • If symptoms recur, discontinue infusion of this dose. • Administer symptomatic treatment. [c] • For hypotension, administer IV fluid bolus as needed. • Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (e.g., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this appendix. • Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy. • Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab, and contact the Medical Monitor. • 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, *antipyretic medications*, 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 the Medical Monitor.

Table A6-7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome (cont.)

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

Table A6-7 Management Guidelines for Infusion-Related Reactions and Cytokine Release Syndrome (cont.)

ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = bi-level positive airway pressure; CAR = chimeric antigen receptor; CPAP = continuous positive airway pressure; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: The management guidelines have been adapted from the NCCN guidelines for the management of CAR T-cell–related toxicities (Version 2.2019).

[a] Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v4.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

[b] Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

[c] Symptomatic treatment may include oral or IV antihistamines, a*ntipyretic medications*, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

[d] Low flow is defined as oxygen delivered at ≤ 6 L/min, and high flow is defined as oxygen delivered at > 6 L/min.

[e] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed. For subsequent infusions, administer oral premedication with antihistamines, *antipyretic medications*, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit-risk ratio.

[f] Refer to Riegler et al. (2019).

A6–11 PANCREATIC EVENTS

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 A6-8.

Table A6-8 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	• Continue atezolizumab for up to 12 weeks after event onset. [a] • 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 *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 the Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact the Medical Monitor. [c]

GI = gastrointestinal.

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

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

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

Table A6-8 Management Guidelines for Pancreatic Events, Including Pancreatitis (cont.)

Event	Management
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with *corticosteroids equivalent to* 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c] • For recurrent events, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to GI specialist. • Initiate treatment with *corticosteroids equivalent to* 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

GI = gastrointestinal.

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

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

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

A6–12 DERMATOLOGIC EVENTS

The majority of cases of rash *reported with the use of atezolizumab* 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 A6-9.

Table A6-9 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and, if indicated, biopsy. • Initiate treatment with *corticosteroids equivalent to* 10 mg/day oral prednisone, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • 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 the 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 based on *the investigator's* benefit-risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

Table A6-9 Management Guidelines for Dermatologic Events (cont.)

Event	Management
Dermatologic event, Grade 4	Permanently discontinue atezolizumab and contact the 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 based on *the investigator's* benefit-risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

A6–13 NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table A6-10, *with specific guidelines to myelitis provided in Table A6-11.*

Table A6-10 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology. • *Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.*
Immune-mediated neuropathy, *including facial paresis,* Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. • *For general immune-mediated neuropathy:* – 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 the Medical Monitor. [c] • *For facial paresis:* – *If event resolves fully, resume atezolizumab* [b] – *If event does not resolve fully while withholding aezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor.* [c]
Immune-mediated neuropathy, *including facial paresis,* Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of *corticosteroids equivalent to* 1–2 mg/kg/day oral or IV prednisone.

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

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

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

Table A6-11 Management Guidelines for Immune-Mediated Myelitis

Event	*Management*
Immune-mediated myelitis, Grade 1	• *Continue atezolizumab unless symptoms worsen or do not improve.* • *Investigate etiology and refer patient to a neurologist.*
Immune-mediated myelitis, Grade 2	• *Permanently discontinue atezolizumab and contact the Medical Monitor.* • *Investigate etiology and refer patient to a neurologist.* • *Rule out infection.* • *Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.*
Immune-mediated myelitis, Grade 3 or 4	• *Permanently discontinue atezolizumab and contact the Medical Monitor.* • *Refer patient to a neurologist.* • *Initiate treatment as per institutional guidelines.*

A6–14 IMMUNE-MEDIATED MENINGOENCEPHALITIS

Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-12.

Table A6-12 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact the Medical Monitor. • Refer patient to neurologist. • Initiate treatment with *corticosteroids equivalent to* 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

A6–15 RENAL EVENTS

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 A6-13.

Table A6-13 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine and urine protein, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the 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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's* benefit-risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

A6–16 IMMUNE-MEDIATED MYOSITIS

Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table A6-14.

Table A6-14 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 the 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 the 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 based on *the investigator's* benefit-risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

Table A6-14 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 the 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 the Medical Monitor. [c] • For recurrent events, treat as a Grade 4 event. *Permanently discontinue atezolizumab and contact the 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 based on *the investigator's* benefit-risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

Table A6-14 Management Guidelines for Immune-Mediated Myositis (cont.)

Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact the 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 ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be based on *the investigator's* benefit-risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

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

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

A6–17 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).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly

- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (< 100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count $< 100 \times 10^9$/L (100,000/μL)
  - ANC $< 1.0 \times 10^9$/L (1000/μL)
- Fasting triglycerides > 2.992 mmol/L (265 mg/dL) and/or fibrinogen < 1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin > 500 mg/L (500 ng/mL)
- Soluble 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 A6-15.

Table A6-15 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact the 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 the 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.

A6–18 REFERENCES

Adashek ML, Feldman M. Cytokine release syndrome resulting from anti–programmed death-1 antibody: raising awareness among community oncologist. J Oncol Practice 2019;15:502–4.

La Rosée P. Treatment of hemophagocytic lymphohistiocytosis in adults. Hematology Am Soc Hematol Educ Protram 2015;1:190–6.

La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. Blood 2019;133:2465–77.

Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625–38.

McClain KL, Eckstein O. Clinical features and diagnosis of hemophagocytic lymphohistiocytosis. Up to Date [resource on the Internet]. 2014 [updated 29 October 2018; cited: 17 May 2019]. Available from: https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-hemophagocytic-lymphohistiocytosis.

Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 2020;20:355–62.

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 7
Study Details Specific to Fulvestrant Control Arm

A7–1 TABLE OF CONTENTS

A7–2 BACKGROUND ON FULVESTRANT

Fulvestrant is an estrogen receptor (ER) antagonist that binds to the ER, disrupting the signaling pathway and leading to ER degradation. Fulvestrant is approved for the treatment of postmenopausal patients with HR+ breast cancer who have disease progression following other anti-estrogen therapy (Faslodex® [fulvestrant] prescribing information). The common adverse events associated with the use of fulvestrant include injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, extremity pain, hot flashes, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, constipation, and increases in liver enzymes (AST, ALT, ALP).

A7–3 A7MATERIALS AND METHODS SPECIFIC TO FULVESTRANT CONTROL ARM

A7–3.1 TREATMENT IN FULVESTRANT CONTROL ARM

A7–3.1.1 Formulation, Packaging, and Handling

For information on the formulation, packaging, and handling of fulvestrant, refer to the local label.

A7–3.1.2 Dosage, Administration, and Compliance

Patients in the control arm will receive fulvestrant (see Table A7-1), until unacceptable toxicity or disease progression per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1). Treatment must be initiated no later than 7 days after randomization. If initiation of treatment has to be delayed, patient may start treatment at the investigator's discretion. The Medical Monitor is available to advise as needed. Treatment will be administered according to institutional standards.

Table A7-1 Treatment Regimen for Control Arm

Treatment Regimen	Cycle Length	Dose, Route, and Regimen
Fulvestrant	28 days	• Cycle 1: fulvestrant 500 mg IM on Days 1 and 15. • Cycles ≥2: fulvestrant 500 mg IM on Day 1.

IM=intramuscular.

Treatment interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed. The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Any dose modification of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.4.3.

A7–3.1.3 Stage 2 Treatment

Patients who experience disease progression per RECIST v1.1 will be given the option of receiving atezolizumab in combination with bevacizumab plus one of three endocrine therapy (ET) options (fulvestrant, exemestane, tamoxifen) on the basis of the physician's choice (Atezo+Bev+ET) during Stage 2 of the study, provided they meet eligibility criteria (see Section 4.1) and a Stage 2 arm is open for enrollment. Patients who experience unacceptable toxicity may also be eligible to receive treatment during Stage 2, provided they meet eligibility criteria. The Medical Monitor is available to advise as needed. Stage 2 treatment must begin within 3 months after the patient has experienced disease progression or unacceptable toxicity. However, it is recommended that patients begin Stage 2 treatment as soon as possible but no earlier than 2 weeks after the last dose of treatment in Stage 1.

Tumor assessments performed prior to or at the time of disease progression according to RECIST v1.1 or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided that the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

A7–3.2 CONCOMITANT THERAPY, PROHIBITED FOOD, AND OTHER RESTRICTIONS FOR FULVESTRANT CONTROL ARM

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 10 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.

For information on permitted, prohibited, or cautionary therapy, prohibited foods, and other restrictions (as applicable) for fulvestrant, refer to the local label.

A7–4 ASSESSMENT OF SAFETY FOR FULVESTRANT CONTROL ARM

A7–4.1 SAFETY PLAN FOR FULVESTRANT CONTROL ARM

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Administration of fulvestrant will be performed according to institutional practice. Adverse events will be reported as described in Sections 5.2–5.6.

A7–4.1.1 Risks Associated with Fulvestrant

Fulvestrant has been associated with risks such as the following: injection site reactions, asthenia, nausea, and increased hepatic enzymes (ALT, AST, ALP). Refer to

the local prescribing information for fulvestrant for a detailed description of all anticipated risks for fulvestrant.

A7–4.1.2 Management of Patients Who Experience Specific Adverse Events in the Fulvestrant Control Arm

Guidelines for dose modification and management of patients who experience specific adverse events can be found in the local prescribing information for fulvestrant.

A7–4.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR FULVESTRANT CONTROL ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the control arm 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 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

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

A7–5 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR FULVESTRANT CONTROL ARM

Table A7-2 Schedule of Activities for Fulvestrant Control Arm

Assessment/Procedure	Screening [a]	Treatment Cycles (28-day cycles) [b]			Stage 2 Scrn. [d] or Treat. Discon. [e]	Follow-Up [e]
		Cycle 1 [c]		Cycles ≥2		
	–28 to –1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)		Every 3 Months
Informed consent	x [f]				x [g]	
Demographic data	x					
Medical history and baseline conditions	x					
Molecular profile of HR+ breast cancer (if available)	x	Whenever updated information becomes available				
Vital signs [h]	x	x	x	x	x	
Weight	x	x [ii]		x [ii]	x	
Height	x					
Complete physical examination [i]	x				x	
Limited physical examination [j]		x [ii]		x [ii]		
ECOG Performance Status	x	x [ii]		x [ii]	x	
ECG [k]	x	Perform as clinically indicated			x [g]	
Hematology [l]	x [m]	x [n]	x	x	x	
Chemistry [o]	x [m]	x [n]	x	x	x	
FSH, LH, and estradiol [p]	x [m]					
Fasting glucose [q]	x [m]					
Fasting lipid panel [q, r]	x [m]					
HbA_{1c} [q]	x [m]					
Amylase and lipase [q]	x [m]					
Coagulation (INR, aPTT)	x [m]				x [g]	
TSH, free T3 (or total T3), free T4 [s]	x [m]				x [g]	
Viral serology	x [m t]				x [g]	

Appendix 7: Study Details Specific to Fulvestrant Control Arm (cont.)

Assessment/Procedure	Screening [a]	Treatment Cycles (28-day cycles) [b]			Stage 2 Scrn. [d] or Treat. Discon. [e]	Follow-Up [e]
		Cycle 1 [c]		Cycles ≥ 2		
	–28 to –1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)		Every 3 Months
C-reactive protein	X				X [g]	
LDH	X [m]				X [g]	
Urinalysis [u]	X [m]	Perform as clinically indicated			X [g]	
Serum autoantibody sample [v]	X [m]	Perform if a patient experiences a suspected immune-mediated adverse event				
Plasma, serum, and PBMC samples for biomarkers		Refer to Table A7-3 below				
Blood sample for RBR (optional) [w]		X				
Tumor biopsy	X [x]	X [y]				
Tumor biopsy (optional)		X [z]				
Tumor response assessments	X [aa]	X [bb, cc, dd]				
Concomitant medications [ee]	X [ee]	X	X	X	X	
Adverse events [ff]	X [ff]	X	X	X	X [ff]	X [ff]
Fulvestrant administration [gg, hh]		X	X	X		
Survival follow-up and anti-cancer treatment						X [ii]

Appendix 7: Study Details Specific to Fulvestrant Control Arm (cont.)

CT = computed tomography; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LH = luteinizing hormone; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; PET = positron emission tomography; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; Scrn. = screening; Treat. = treatment.

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

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window at the investigator's discretion. The Medical Monitor is available to advise as needed.

[c] Treatment must be initiated no later than 7 days after randomization. If initiation of treatment has to be delayed, patient may start treatment at the investigator's discretion. The Medical Monitor is available to advise as needed.

[d] Patients who experience disease progression per RECIST v1.1 and patients who experience unacceptable toxicity will be given the option of participating in Stage 2 of the study and will undergo screening assessments to determine eligibility. The Medical Monitor is available to advise as needed. Study details specific to the Stage 2 treatment regimen is provided in Appendix 12. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[e] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which disease progression is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Patients who do not enter Stage 2 will then undergo follow-up assessments. Note that treatment discontinuation assessments will be performed for all patients, regardless of whether they enter Stage 2.

[f] 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.

[g] Assessments to be performed only for patients undergoing Stage 2 screening.

[h] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, 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.

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

[j] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

Appendix 7: Study Details Specific to Fulvestrant Control Arm (cont.)

[l] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[m] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment (Day 1 of Cycle 1).

[n] If screening laboratory assessments were performed within 96 hours prior to dosing, they do not have to be repeated.

[o] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST.

[p] FSH, LH, and estradiol are all required for patients who are <60 years old and in postmenopausal state or who are <60 years old and have had prior ovarian ablation. Only estradiol is required for patients who are <60 years old and are on a LHRH agonist for ovarian suppression.

[q] Required only if an ipatasertib-containing arm is open for enrollment at the time of patient screening.

[r] Fasting lipid panel should include cholesterol, HDL, LDL, and triglyceride.

[s] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening.

[t] At screening, patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.

[u] Includes pH, specific gravity, glucose, protein, ketones, and blood; dipstick permitted.

[v] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody.

[w] 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.

[x] 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. It is preferred 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. Refer to Section 4.5.6 for tissue sample requirements.

[y] Patients will undergo tumor biopsy sample collection during Stage 1 at the time of unacceptable toxicity or disease progression per RECIST v1.1, if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or disease progression, or prior to the next anti-cancer therapy, whichever is sooner. Refer to Section 4.5.6 for tissue sample requirements.

[z] Patients will undergo optional tumor biopsy sample collection, if deemed clinically feasible by the investigator, 4 weeks (±7 days) after treatment initiation and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[aa] All measurable and evaluable lesions should be assessed and documented at screening (in both Stage 1 and Stage 2). Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with IV contrast; with or without oral contrast) or MRI scans (with IV contrast) of the chest, abdomen, pelvis, and head with one exception: a head scan is not required at Stage 2 screening. In addition, bone

scans, PET scans, and/or skeletal survey should be performed at screening to assess bone lesions. Bone lesions identified at baseline should continue to be assessed following the tumor assessment schedule described above. Additional bone scans, PET scans, or skeletal surveys should be performed if clinically indicated. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans (with IV contrast) of the abdomen and pelvis should be performed. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. Refer to Section 4.5.5 for further details on tumor assessments.

[bb] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 24 weeks following treatment initiation, and every 8 weeks (±1 week) from Week 25 to Week 48, and then every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1. Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression, even if they start new non–protocol-specified anti-cancer therapy.

[cc] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[dd] For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of disease progression per RECIST v1.1 or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided that the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

[ee] 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 10 days prior to initiation of study treatment until the treatment discontinuation visit.

[ff] 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 systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic 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.

[gg] Fulvestrant should be administered intramuscularly into the buttocks slowly (1–2 minutes per injection) as two 5-mL injections, one in each buttock.

[hh] Treatment will continue until unacceptable toxicity or disease progression per RECIST v1.1.

[ii] 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 study, the study staff may use a public information source

(e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

- Assessment may be performed within 24 hours prior to dosing during the treatment period.

Table A7-3 Schedule of Biomarker Samples for Fulvestrant Control Arm

Visit	Time	Sample Type
Day 1 of Cycle 1	Prior to first injection	• Biomarker (plasma, serum, PBMC)
Day 15 of Cycle 1	Prior to injection	• Biomarker (plasma, serum)
Day 1 of Cycle 2	Prior to injection	• Biomarker (plasma, serum, PBMC)
Day 1 of Cycle 4	Prior to injection	• Biomarker (plasma, serum)
Day 1 of Cycle 8	Prior to injection	• Biomarker (plasma, serum)
Treatment discontinuation visit (≤30 days after last dose)	At visit	• Biomarker (plasma, serum)

PBMC=peripheral blood mononuclear cell.

A7–6 REFERENCES

Faslodex® (fulvestrant) prescribing information. Wilmington (DE): AstraZeneca Pharmaceuticals, 2016.

Appendix 8
Study Details Specific to Atezo + Entino Arm

A8–1 TABLE OF CONTENTS

A8–2 BACKGROUND ON ATEZO+ENTINO ARM

A8–2.1 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 cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved for the treatment of urothelial carcinoma, non–small cell lung cancer (NSCLC), *small-cell lung cancer,* triple-negative breast cancer, hepatocellular carcinoma, and melanoma.

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

A8–2.2 BACKGROUND ON ENTINOSTAT

Entinostat is an orally available synthetic pyridylcarbamate licensed from Bayer Schering AG by Syndax Pharmaceuticals (previously named MS-275). Entinostat inhibits histone deacetylases (HDACs). Entinostat promotes hyperacetylation of nucleosomal histones, allowing transcriptional activation of a distinct set of genes. This ultimately leads to the inhibition of cell proliferation, induction of terminal differentiation, and/or apoptosis (Hess-Stumpp et al. 2007).

To date, entinostat has been investigated alone or in combination in more than 1100 patients with cancer in clinical studies. In breast cancer, entinostat has been studied in a Phase II, randomized clinical trial sponsored by Syndax, ENCORE 301, in patients with estrogen receptor–positive (ER+) metastatic breast cancer. ENCORE 301 was a placebo-controlled, double-blind trial of exemestane in combination with entinostat (EE) versus exemestane plus placebo (EP). The primary endpoint of progression-free survival was met, with EE resulting in a median of 4.3 months and EP a median of 2.3 months. Overall survival, an exploratory endpoint, showed a survival benefit of approximately 8 months in favor of EE (28.1 months) versus EP (19.8 months). In 2014, the U.S. Food and Drug Administration granted breakthrough therapy designation for entinostat in combination with exemestane in metastatic hormone receptor–positive

breast cancer in post-menopausal women whose disease had progressed following non-steroidal aromatase inhibitor (AI) therapy based on these results. A Phase III registrational study, E2112, has been designed to confirm the ENCORE 301 results and is currently being conducted by ECOG-ACRIN Research Group under sponsorship by the National Cancer Institutes under a Special Protocol Assessment.

Additional information on the chemistry, pharmacology, toxicology, preclinical findings, and clinical experience to date may be found in the Entinostat Investigator's Brochure.

A8–3 RATIONALE FOR ATEZO+ENTINO ARM

A8–3.1 THE PD-L1 PATHWAY

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 downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and 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 (see Atezolizumab Investigator's Brochure for detailed efficacy results).

PD-L1 expression has been observed in HR+ HER2-negative breast cancer (HR+ breast cancer) tissues. However, clinically significant response to single-agent checkpoint inhibitor therapy is extremely limited in patients with HR+ breast cancer (Dirix et al. 2016; Rugo et al. 2016), indicating that combination therapy may be needed in order to overcome mechanisms of resistance to anti–PD-L1/anti–PD-1 monotherapy.

A8–3.2 HISTONE DEACETYLASE INHIBITORS IN CANCER

Gene transcription and expression are regulated by chromatin conformation. Histone acetyltransferases acetylate the amino terminal ends and neutralize their positive charges, thus leading to a more open chromatin conformation, facilitating DNA transcription. In return, these histones can be deacetylated by HDACs, leading to condensed conformation of the DNA, inhibiting DNA transcription.

Altered activity of HDACs and inactivation of histone acetyltransferases within transformed cells are key events that affect chromatin remodeling. There is evidence that HDACs are associated with a wide range of tumors, including melanomas, neuroblastomas, lymphomas, and lung, breast, prostate, ovarian, bladder, and colon cancers. In a number of in vitro models, HDAC inhibitors triggered growth arrest and induced cell differentiation or apoptosis.

Entinostat (SNDX-275), an orally available synthetic pyridylcarbamate, selectively inhibits class 1 HDACs, specifically HDAC1, 2, and 3. Entinostat promotes hyperacetylation of nucleosomal histones, allowing transcriptional activation of a distinct set of genes. This ultimately leads to the inhibition of cell proliferation, induction of terminal differentiation, and/or apoptosis (Hess-Stump et al. 2007).

Entinostat inhibited HDAC in various tumor cell lines; in vitro studies in a range of human cancer cell lines have demonstrated the anti-proliferative activity of entinostat. In vivo, entinostat inhibited the growth in a range of human tumor xenograft models, including lung, prostate, breast, pancreatic, renal cell, and glioblastoma.

More recently, entinostat has been shown to modify the phenotype of cancer cells from a mesenchymal to an epithelial one, leading to a reduction in the metastatic potential of the cancer cells (Shah et al. 2014). In addition, there is a suggestion that entinostat may have longer term effects on cancer phenotypes, cancer stem cells or progenitor cell pool and potential sensitization to subsequent post-study treatments (Juergen et al. 2011).

A8–3.3 COMBINED INHIBITION OF PD-L1 AND HDAC AS POTENTIAL ANTI-CANCER THERAPY

Targeting the checkpoint pathway has demonstrated activity across multiple tumor types in patients with advanced malignancies who have failed standard-of-care therapies. Despite the promise of single-agent checkpoint inhibition, however, only a small percentage of patients experience benefit, suggesting that additional strategies enhancing the anti-tumor immune response are needed to improve survival for cancer patients (Mahoney et al. 2015; Sharma et al. 2015).

Research to identify the basis for the limited efficacy of recently developed immune therapies has provided investigators with an appreciation for the role that specific immune regulatory cells, such as myeloid-derived suppressor cells (MDSCs) and T-regulatory cells (Tregs), have in dampening the cytotoxic T-cell response (Joyce and

Fearon 2015; Mahoney et al. 2015; Sharma and Allison 2015). MDSCs and Tregs localize in the area surrounding the tumor and, together with the immune checkpoints, play a significant role in helping a tumor evade detection and elimination by the immune system (Adeegbe and Nishkawa 2013; Marvel and Gabrilovich 2015).

MDSCs are immature myeloid cells that are activated by disease or injury and are generally increased in cancer patients. The primary function of MDSCs is to suppress an activated T cell–immune response (Marvel and Gabrilovich 2015). High concentrations of circulating MDSCs in various cancers, including breast, lung, head and neck and melanoma, correspond with a poor prognosis and limited response to cancer therapy (Liu et al. 2010; Solito et al. 2011; Najjar and Finke 2013; Weed et al. 2014; Weber et al. 2015). The data suggest that targeting MDSCs may offer new therapeutic opportunities for enhancing the anti-tumor response to immune checkpoint inhibitors.

Tregs are immune suppressor cells and recruited to sites of active immune response in order to shut down the cytotoxic T-cell response (Adeegbe and Nishikawa 2013; Zhang et al. 2015). Unlike MDSCs, which are found in activated states in circulating blood, Tregs are recruited to the tumor microenvironment and activated by local signals from the cancer cell (Adeegbe and Nishikawa 2013; Zhang et al. 2015). As with MDSCs, an increase in the concentration of activated Tregs correlates with poor prognosis in a number of tumor types, including breast, colorectal, and ovarian cancers (Freiser et al. 2013; Zhang et al. 2015). Inhibiting Tregs may therefore relieve immune suppression in a manner similar and potentially complementary to that of other immune-targeted approaches.

Separate preclinical studies have demonstrated that entinostat is a dual inhibitor of immune suppressor cells and targets both MDSCs and Tregs. Entinostat reduces the growth of MDSCs at concentrations that spare the growth of cytotoxic T cells (Kim et al. 2014; Orillion et al. 2017). Another study showed that entinostat reduces the expression of the FOXP3 protein in Tregs when administered in an animal cancer model, thus demonstrating entinostat's ability to inhibit Treg immune suppressor activity (Shen et al. 2012).

A study conducted with blood samples from a subset of patients in ENCORE 301, a Phase IIb clinical trial in advanced HR+ breast cancer patients, showed statistically significant reduction of circulating MDSCs in patients treated with the combination of entinostat and exemestane, a hormone therapy, but not in patients treated with the combination of placebo and exemestane.

In order to determine whether entinostat could be combined effectively with immune checkpoint inhibitors, entinostat was tested in combination with anti-PD-1 and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) in immune-resistant animal models. The elimination of both primary and metastatic tumors was observed in a 4T1 mouse triple-negative metastatic breast cancer model treated with entinostat

together and dual PD-1/CTLA4 checkpoint inhibition (Kim et al. 2014). These results support the clinical testing of entinostat combined with atezolizumab.

The potential beneficial effects of combining entinostat with a PD-1 or PD-L1 inhibitor were also observed in patients. In a heavily pre-treated metastatic NSCLC population, patients given the combination of entinostat and azacitidine achieved few objective responses and a modest 3% overall response rate (Juergens et al. 2011). However, patients who received the combination of entinostat and azacitidine and subsequently received immune checkpoint therapy demonstrated a higher response rate than expected for this patient population; 5 patients who received either nivolumab or an investigational PD-L1 inhibitor as their next therapy derived durable clinical benefit. Of the 5 patients, 3 patients had durable responses and 2 had durable stable disease. This enhanced response rate was better than the 15% response to nivolumab alone observed in a similar advanced NSCLC population and led investigators to hypothesize that the prior effect of the combination of entinostat and azacitidine therapy was "priming" the tumors to the subsequent immune therapy (Wrangle et al. 2013). Encouraging preliminary data of the combination of entinostat plus pembrolizumab in PD-1 pretreated patients have been reported. In the ENCORE 601 study, an ORR of 31% (4 of 13) was observed in melanoma patients who previously progressed on or after a PD-1/PD-L1 blocking antibody, and an ORR of 10% (3 of 31) was observed in an NSCLC patient population who progressed on PD-1/PD-L1 blocking antibody. Entinostat in combination with pembrolizumab also demonstrated acceptable safety (Gandhi et al. 2017; Johnson et al. 2017). Another clinical trial with the combination of entinostat and pembrolizumab (SNDX-275-0141) continues to show promising activity in patients with heavily pretreated cancers with an ORR of 11.5% (3 of 26) in endometrial cancer, HR+ breast cancer, and uterine leiomyosarcoma; in this study, 19 (73.1%) and 11 (42.3%) patients were on study for 12 and 24 weeks, respectively. Consistent with previous reports, it was observed that entinostat treatment resulted in reduction in circulating MDSCs to potentiate anti-tumor activity from checkpoint blockade antibody (Tolcher et al. 2018).

Based on these findings it is hypothesized that entinostat combined with a PD-L1–blocking antibody, atezolizumab, will result in an improvement in progression-free survival for the combination compared with atezolizumab alone.

A8–3.4 BENEFIT–RISK ASSESSMENT

PD-L1 expression has been observed in HR+ HER2-negative breast cancer (HR+ breast cancer) tissues. However, clinically significant response to single-agent checkpoint inhibitor therapy is extremely limited in patients with HR+ breast cancer (Dirix et al. 2016; Rugo et al. 2016), indicating that combination therapy may be needed in order to overcome mechanisms of resistance to anti–PD-L1/anti–PD-1 monotherapy.

One potential mechanism for converting otherwise resistant cancers is manipulation of the immune system by means of HDAC inhibitors effectively rebalancing the immune environment by decreasing Tregs and MDSCs and restoring T-cell function.

The safety profile of atezolizumab in combination with entinostat continues to be defined. Overlapping toxicities include GI, pulmonary and metabolic adverse events. Aggressive safety monitoring will be put into place to monitor for these adverse events. As of 27 April 2018, 48 patients have been enrolled in the TNBC trial (NCT02708680), a study of combination treatment of atezolizumab and entinostat. Study treatment has been well tolerated and the study is ongoing.

Considering the high therapeutic need for tolerable and effective treatment in HR+ metastatic breast cancer, the compelling immunologic rationale for the combination of atezolizumab and entinostat, and the anticipated safety profile of the combination, the benefit–risk assessment favors moving forward with the evaluation of the combination in the second- and third-line, inoperable locally advanced or metastatic setting.

For the evaluation of the impact of the COVID-19 pandemic on the benefit-risk assessment, please refer to Section 1.3.

A8–4 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO+ENTINO ARM

A8–4.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 1200 mg every 3 weeks (Q3W) (1200 mg on Days 1 of each 21-day cycle). This dose is the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A8–4.2 RATIONALE FOR ENTINOSTAT DOSE AND SCHEDULE

Entinostat will be administered at a fixed dose of 5 mg orally (PO) once a week on Days 1, 8, and 15 of each 21-day cycle. Recent data from a triple-negative breast cancer trial (NCT02708680) of atezolizumab+entinostat supports the above dose.

In this study, the dose of atezolizumab is fixed at 1200 mg. The entinostat dose was determined in a dose determination Phase Ib study. The dose determination phase started with a dose of 5 mg entinostat PO weekly with plans to dose de-escalate if the dose level was not tolerable. To date, 8 patients have been treated with the 5-mg entinostat dose and no dose-limiting toxicities have been observed (data on file).

Enrollment in a larger Phase II trial in triple-negative breast cancer will further assess this dose.

A8–5 SECTION MATERIALS AND METHODS SPECIFIC TO ATEZO+ENTINO ARM

A8–5.1 TREATMENT IN ATEZO +ENTINO ARM

A8–5.1.1 Formulation, Packaging, and Handling

A8–5.1.1.1 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 and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A8–5.1.1.2 Entinostat

Entinostat is an oral drug supplied to sites as pink to light red (1 mg) or yellow (5 mg) coated tablets.

For information on handling of entinostat, see the pharmacy manual and the Entinostat Investigator's Brochure.

A8–5.1.2 Dosage, Administration, and Compliance

Patients in the Atezo + Entino arm will receive treatment as outlined in Table A8–1 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) (see Section 3.1.1.1 for details). Treatment must be initiated no later than 7 days after randomization. If initiation of treatment has to be delayed, patient may start treatment at the investigator's discretion. The Medical Monitor is available to advise as needed.

Table A8-1 Treatment Regimen for Atezo + Entino Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Entinostat 5 mg by mouth once a week on Days 1, 8, and 15 • Atezolizumab 1200 mg by IV infusion on Day 1

Atezo+Entino=atezolizumab plus entinostat.

Refer to Sections A8–6.1.4.2 and A8–6.1.4.3 for information on treatment interruptions for patients who experience toxicities. Atezolizumab or entinostat treatment interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed. The acceptable length of treatment interruption must be based on an assessment of

benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Any dose modification of any of the study treatments 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 5.4.3.

No safety data related to overdosing of atezolizumab and entinostat are available to date.

A8–5.1.2.1 Entinostat

Patients will receive entinostat at a dose of 5 mg (one tablet) PO once a week on Days 1, 8, and 15 of each 21-day cycle. On study days when patients receive both entinostat and atezolizumab, entinostat is to be taken prior to atezolizumab. Entinostat is to be taken on an empty stomach at least 2 hours after a meal and at least 1 hour before the next meal.

If an entinostat dose is missed, it may be taken up to 48 hours after the scheduled dosing time. If it is not taken within the 48-hour window, the dose should not be taken and will be counted as a missed dose. The patient should take the next scheduled dose per protocol. Missed doses should be noted as such in the patient drug diary and on the eCRF. If entinostat is vomited, dosing should not be re-administered but instead the dose should be skipped.

Guidelines for dosage modification and treatment interruption or discontinuation because of toxicities are provided in Sections A8–6.1.4.1, A8–6.1.4.2, and A8–6.1.4.3.

A8–5.1.2.2 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 each 21-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 5. Atezolizumab infusions will be administered per the instructions outlined in Table A8–2.

Table A8-2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion of Atezolizumab	Subsequent Infusions of Atezolizumab
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded 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.	• 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 (± 10) minutes after the infusion.

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

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A8–6.1.4.3 and in Appendix 6.

A8–5.1.3 Stage 2 Treatment

Patients who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1.1) will be given the option of receiving atezolizumab in combination with bevacizumab plus one of three endocrine therapy (ET) options (fulvestrant, exemestane, or tamoxifen) on the basis of the physician's choice (Atezo+Bev+ET) during Stage 2 of the study, provided they meet eligibility criteria (see Section 4.1) and a Stage 2 arm is open for enrollment. Stage 2 treatment must begin within 3 months after a patient has experienced loss of clinical benefit and will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator. However, it is recommended that patients begin Stage 2 treatment as soon as possible but no earlier than 2 weeks after the last dose of treatment in Stage 1.

Tumor assessments performed prior to or at the time of disease progression, loss of clinical benefit, or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided that the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

A8–5.2 CONCOMITANT THERAPY FOR ATEZO+ENTINO ARM

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment from 10 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.

A8–5.2.1 Permitted Therapy for Atezo + Entino Arm

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

- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section 4.1.2.2).
- 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 and mineralocorticoids (e.g., fludrocortisone) administered for orthostatic hypotension or adrenocortical insufficiency
- Bisphosphonates or denosumab at a stable dose
- 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 and entinostat should be withheld during palliative radiotherapy and may be resumed after palliative radiotherapy; patients should be recovered from the effects of radiation.
- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may

receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) 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 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 must be discontinued from study treatment.
- Anti-convulsant therapy, if required, is administered at a stable dose.

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

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 5).

A8–5.2.2 Cautionary Therapy for Atezo+Entino Arm

A8–5.2.2.1 Corticosteroids, *Immunosuppressive Medications,* and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, 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, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab therapy (refer to Section 4.4 for details).

Sensitive substrates of CYP enzymes and drugs known to inhibit or induce P-gP:

- Sensitive substrates of CYP enzymes (see Table A8–3)
- Drugs that are known to inhibit or induce P-gp (see Table A8–4)

In the event the use of these medications is required, the Medical Monitor must be consulted for guidance. Patients will be allowed to administer proton-pump inhibitors if they hold administration for 3 days prior to each entinostat dose.

Table A8-3 Examples of Sensitive In Vivo CYP Substrates and CYP Substrates with Narrow Therapeutic Range

CYP Enzymes	Sensitive Substrate	Substrates with Narrow Therapeutic Range
CYP1A2	Alosetron, duloxetine, melatonin, ramelteon, tacrine, tizanidine	Theophylline, tizanidine
CYP2B6	Bupropion, efavirenz	–
CYP2C8	Repaglinide	Paclitaxel
CYP2C9	Celecoxib	Warfarin, phenytoin
CYP2C19	Clobazam, lansoprazole, omeprazole, S-mephenytoin	S-mephenytoin
CYP3A	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	Alfentanil, astemizole, cisapride7, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine
CYP2D6	Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine	Thioridazine, pimozide

Also refer to the following website for the classification of substrates: Classification of Substrates:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#4)

Table A8-4 P-gp Inhibitors and Inducers

	Inhibitors	Inducers
P-gp, MDR1	Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, felodipine, lopinavir, quercetin, ranolazine, ticagrelor, ritonavir, cyclosporine, verapamil, erythromycin, ketoconazole, itraconazole, quinidine, elacridar (GF120918), zosuqidar (LY335979), valspodar (PSC 833)	Avasimibe, carbamazepine, phenytoin, rifampin, St. John's wort, tipranavir/ritonavir
BCRP	Cyclosporine, elacridar, eltrombopag, gefitinib	Not known
UGT1A4	Probenecid	–

A8–5.2.2.2 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) may be used during the study at the discretion of the investigator.

A8–5.2.3 Prohibited Therapy for Atezo+Entino Arm

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

- Any other HDAC inhibitor, including valproic acid
- DNA methyltransferase inhibitors
- 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 radiotherapy to the brain under circumstances outlined in Section A8–5.2.1
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.

- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

A8–6 ASSESSMENT OF SAFETY FOR ATEZO+ENTINO ARM

A8–6.1 SAFETY PLAN FOR ATEZO+ENTINO ARM

The safety plan for patients in this study is based on clinical experience with atezolizumab and entinostat in completed and ongoing studies. The anticipated important safety risks are outlined below (see Sections A8–6.1.1, A8–6.1.2, and A8–6.1.3). Guidelines for management of patients who experience specific adverse events are provided in Section A8–6.1.4. These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit-risk balance when managing individual cases.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. 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. Adverse events will be reported as described in Sections 5.2–5.6.

A8–6.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, *facial paresis, myelitis,* meningoencephalitis, myocarditis, *pericardial disorders,* nephritis, myositis, and severe cutaneous adverse reactions. *In addition,* immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis *(HLH)*. Refer to Appendix 6 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A8–6.1.2 Risks Associated with Entinostat

Commonly encountered adverse events across clinical studies of entinostat in patients with solid tumors included fatigue, anorexia, nausea, vomiting, diarrhea, abdominal pain, neutropenia, anemia, thrombocytopenia, hyponatremia, hypophosphatemia, hypoalbuminemia, hyperglycemia, and rash.

Additional clinical experience is summarized in the Entinostat Investigator's Brochure.

A8–6.1.3 Risks Associated with Combination Use of Atezolizumab and Entinostat

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab and entinostat: diarrhea, thrombocytopenia, pneumonitis, hypothyroidism, rash, abnormal liver enzymes, hyponatremia and hyperglycemia.

A8–6.1.4 Management of Patients Who Experience Specific Adverse Events in Atezo + Entino Arm

A8–6.1.4.1 Dose Modifications

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

The dose of entinostat can be reduced to 3 mg once per week, and further to 2 mg once per week for management of drug-related toxicities. If further dose reduction is indicated after two dose reductions, the patient must discontinue entinostat but may continue treatment with atezolizumab at the investigator's discretion.

Guidelines for the dose modification of entinostat for non-hematologic toxicities are provided in Table A8–5.

Table A8-5 Non-Hematologic Toxicity: Dose Modifications for Entinostat

Toxicity	Dose Modifications
Grade 4	Administer symptomatic remedies and start prophylaxis. Hold dose [a] until recovery to Grade 1 or baseline under the following directions: • If recovered within 4 weeks of onset (i.e., 3 or fewer missed doses), resume study drug as follows: – If receiving 5 mg, restart study drug at 3 mg. – If receiving 3 mg, restart study drug at 2 mg. – If receiving 2 mg, discontinue study treatment. • If dose is held for 4 consecutive weeks, permanently discontinue study drug.
Grade 3	Administer symptomatic remedies and start prophylaxis. Hold dose [a] until recovery to Grade 1 or baseline under the following directions: • If recovered by next scheduled dose, resume study drug at prior dose. If not recovered by next scheduled dose, continue to hold the dose. • If recovered within 2–4 weeks (i.e., missed 3 or fewer doses), resume study drug as follows: – If receiving 5 mg, restart study drug at 3 mg. – If receiving 3 mg, restart study drug at 2 mg. – If receiving 2 mg, continue study drug at 2 mg. • If dose is held for 4 consecutive weeks, permanently discontinue study drug.
Recurrence of the same Grade 3 toxicity despite dose reduction	Administer symptomatic remedies and start prophylaxis. If receiving 2 mg, permanently discontinue study drug. Otherwise, hold dose [a] until recovery to Grade 1 or baseline. • If recovered within the next 2 scheduled doses, resume study drug as follows: – If receiving 5 mg, restart study drug at 3 mg. – If receiving 3 mg, restart study drug at 2 mg. If the same Grade ≥ 3 event recurs (i.e., three occurrences) despite entinostat dose reduction to 2 mg, as described above, discontinue study drug.
Grade ≤2	Administer symptomatic remedies and start prophylaxis. Dosing of study drug may be interrupted at the investigator's discretion, in consultation with the Medical Monitor. • If dose is held for 4 consecutive weeks, permanently discontinue study drug.[a] If toxicity resolves, resume entinostat at the original dose.

[a] If >50% of doses are missed during any 6-week period, discontinue study drug treatment.

A8–6.1.4.2 Hematologic Toxicity at Least Possibly Related to Entinostat

The guidelines in Table A8–6 will be followed for determining the timing of cycles based on a patient's hematologic status at the time of planned dosing.

Table A8-6 Hematologic Toxicity: Dose Modification for Entinostat

Toxicity	Dose Modifications
Grade ≥3 neutropenia, Grade ≥3 uncomplicated thrombocytopenia, or Grade 2 complicated thrombocytopenia	Administer symptomatic remedies and start prophylaxis. Hold dose[a] until recovery to Grade 1 or baseline under the following directions: • If recovered by next scheduled dose, resume study drug at prior dose. If not recovered by next scheduled dose, continue to hold the dose. • If recovered within 2–4 weeks (i.e., missed 3 or fewer doses), resume study drug as follows: – If receiving 5 mg, restart study drug at 3 mg. – If receiving 3 mg, restart study drug at 2 mg. – If receiving 2 mg, restart study drug at 2 mg. • If not recovered within 4 weeks (i.e., 4 doses missed), permanently discontinue study drug.
Recurrence of the same hematologic toxicity	Administer symptomatic remedies and start prophylaxis. If receiving 2 mg, permanently discontinue study drug. Otherwise, hold dose[a] until recovery to Grade 1 or baseline. • If recovered within the next 2 scheduled doses, resume study drug as follows: – If receiving 5 mg, restart study drug at 3 mg. – If receiving 3 mg, restart study drug at 2 mg. If the same Grade ≥3 event recurs (i.e., third occurrence) despite entinostat dose reduction to 2 mg, as described above, discontinue study drug.

[a] If >50% of doses are missed during any 6-week period, discontinue study drug treatment.

A8–6.1.4.3 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 patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the*

investigator's benefit-risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Entinostat treatment may be temporarily suspended in patients who experience toxicity considered to be related to study treatment. If entinostat has been withheld for >28 days because of toxicity related to entinostat alone, the patient should be discontinued from entinostat. *The decision to re-challenge patients with entinostat should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.* However, if entinostat is held for greater than 28 days with atezolizumab for toxicity related to atezolizumab alone or the combination, entinostat may be restarted at the prior dose when atezolizumab is restarted. The Medical Monitor should be consulted for any major surgery (e.g., involving a body cavity), and entinostat should generally be withheld for 2 days prior to the procedure and for 2 weeks afterwards.

If atezolizumab is discontinued, entinostat should also be discontinued. If entinostat is discontinued, atezolizumab can be continued if the patient is likely to derive clinical benefit, as determined by the investigator.

A8–6.1.4.4 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Appendix 6 and Table A8–7, as outlined below:

- Appendix 6 provides guidelines for the management of patients who experience atezolizumab-associated IRRs and immune-mediated endocrine, pancreatic, neurologic, and meningoencephalitis events. It is recommended that atezolizumab be withheld or discontinued per the guidelines for atezolizumab in Appendix 6 and that entinostat be withheld or discontinued per the guidelines in Table A8–7.
- Table A8–7 provides guidelines for the management of patients who experience the following potential overlapping toxicities: diarrhea, thrombocytopenia, pneumonitis, hypothyroidism, rash, abnormal liver enzymes, hyponatremia and hyperglycemia. It is recommended that study treatments be withheld or discontinued per the guidelines in Table A8–7. For these potential overlapping toxicities, guidelines in Table A8–7 should be followed instead of guidelines for atezolizumab in Appendix 6.
- Table A8–7 provides guidelines for the management of patients who experience adverse events associated with entinostat. It is recommended that atezolizumab and/or entinostat be withheld or discontinued per the guidelines in Table A8–7.
- For cases in which management guidelines are not covered in Table A8–7 or Appendix 6, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Table A8-7 Guidelines for Management of Patients Who Experience Adverse Events in Atezo + Entino Arm

Event	Action to Be Taken
IRRs, CRS, anaphylaxis, and hypersensitivity reaction	
	• Guidelines for management of IRRs and CRS are provided for atezolizumab in Appendix 6. • For anaphylaxis precautions, see Appendix 5. • For severe hypersensitivity reactions, permanently discontinue atezolizumab and entinostat.
Diarrhea/ Colitis	
Diarrhea or colitis, Grade 1 or 2	• Follow atezolizumab-specific guidelines in Appendix 6. • Initiate supportive care and monitor patient closely • Discontinue medications that may exacerbate colitis (e.g., NSAIDs) while investigating etiology. • Continue entinostat • Entinostat may be interrupted at the Investigator's discretion, in consultation with the Medical Monitor. • Investigate etiology, referring patient to GI specialist for evaluation of possible colitis if appropriate. • If event resolves to Grade 1 or better within 28 days, resume entinostat at the original dose. If not, permanently discontinue entinostat.

Diarrhea or colitis, Grade 3	• Follow atezolizumab-specific guidelines in Appendix 6.
	• Administer symptomatic remedies/start prophylaxis
	• Hold entinostat until recovery to Grade 1 or baseline under the following directions:
	  ○ If not recovered by next scheduled dose, skip the dose. If recovered by next scheduled dose, resume study drug at prior dose.
	  ○ If not recovered by either of the next 2 scheduled doses and receiving 2 mg, permanently discontinue study treatment. Otherwise, skip each dose and if recovered by the 4th dose, resume study drug as follows: If receiving 5 mg, restart study drug at 3 mg. If receiving 3 mg, restart study drug at 2 mg.
	  ○ If dose is held for 4 consecutive weeks, permanently discontinue entinostat.

Appendix 8: Study Details Specific to Atezo + Entino Arm (cont.)

Event	Action to Be Taken

Diarrhea or colitis, Grade 4	• Follow atezolizumab-specific guidelines in Appendix 6.
	• Withhold entinostat and contact the 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.
	• Hold entinostat until recovery to Grade 1 or baseline under the following directions:
	  ○ If recovered within 4 weeks of onset (i.e., ≤3 missed doses), resume study drug as follows: If receiving 5 mg, restart study drug at 3 mg. If receiving 3 mg, restart study drug at 2 mg. If receiving 2 mg, discontinue study treatment.
	  ○ If dose is held for 4 consecutive weeks, permanently discontinue entinostat.

Dermatologic toxicity	
General guidance	• A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.
Dermatologic event, Grade 1 or 2	• Follow atezolizumab-specific guidelines in Appendix 6. • Continue entinostat • Initiate supportive care and monitor patient closely

Dermatologic event, Grade 3	• Follow atezolizumab-specific guidelines in Appendix 6.
	• Administer symptomatic remedies/start prophylaxis
	• Hold entinostat until recovery to Grade 1 or baseline under the following directions:
	  ○ If not recovered by next scheduled dose, skip the dose. If recovered by next scheduled dose, resume study drug at prior dose.
	  ○ If not recovered by either of the next 2 scheduled doses and receiving 2 mg, permanently discontinue study treatment. Otherwise, skip each dose and if recovered by the 4th dose, resume study drug as follows: If receiving 5 mg, restart study drug at 3 mg. If receiving 3 mg, restart study drug at 2 mg.
	• If dose is held for 4 consecutive weeks, permanently discontinue entinostat.

Appendix 8: Study Details Specific to Atezo + Entino Arm (cont.)

Event	Action to Be Taken

Dermatologic event, Grade 4	• Follow atezolizumab-specific guidelines in Appendix 6.
	• Withhold entinostat.
	• Hold entinostat until recovery to Grade 1 or baseline under the following directions:
	  ○ If recovered within 4 weeks of onset (i.e., ≤3 missed doses), resume study drug as follows: If receiving 5 mg, restart study drug at 3 mg. If receiving 3 mg, restart study drug at 2 mg. If receiving 2 mg, discontinue study treatment.
	  ○ If dose is held for 4 consecutive weeks, permanently discontinue entinostat.

Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Follow guidelines for atezolizumab in Appendix 6. • Withhold entinostat. • If event resolves to Grade 1 or better, resume entinostat. • Permanently discontinue entinostat if withheld for >4 consecutive weeks or if Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed.
Elevations in ALT, AST, and/or bilirubin	
Grade 1 or 2 (AST/ALT >ULN to ≤5×ULN and/or total bilirubin >ULN to ≤3×ULN)	• Follow atezolizumab-specific guidelines in Appendix 6. • Entinostat may be interrupted at the Investigator's discretion, in consultation with the Medical Monitor. • If event resolves to Grade 1 or better within 28 days, resume entinostat at the original dose. If not, permanently discontinue entinostat.

Grade 3 (AST/ALT >5×ULN to <20×ULN and/or total bilirubin >3×ULN to ≤10×ULN)	• Follow atezolizumab-specific guidelines in Appendix 6.
	• Monitor LFTs at least weekly.
	• Consider patient referral to hepatologist and liver biopsy.
	• Administer symptomatic remedies/start prophylaxis
	• Hold entinostat until recovery to Grade 1 or baseline under the following directions:
	  ○ If not recovered by next scheduled dose, skip the dose. If recovered by next scheduled dose, resume study drug at prior dose.
	  ○ If not recovered by either of the next 2 scheduled doses and receiving 2 mg, permanently discontinue study treatment. Otherwise, skip each dose and if recovered by the 4th dose, resume study drug as follows: If receiving 5 mg, restart study drug at 3 mg. If receiving 3 mg, restart study drug at 2 mg.
	  ○ If dose is held for 4 consecutive weeks, permanently discontinue entinostat

Appendix 8: Study Details Specific to Atezo + Entino Arm (cont.)

Event	Action to Be Taken
Grade 4 (AST/ALT >20 × ULN and/or total bilirubin >10 × ULN)	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Withhold entinostat. • Monitor LFTs 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. • Hold entinostat until recovery to Grade 1 or baseline under the following directions: o If recovered within 4 weeks of onset (i.e., ≤3 missed doses), resume study drug as follows: If receiving 5 mg, restart study drug at 3 mg. If receiving 3 mg, restart study drug at 2 mg. If receiving 2 mg, discontinue study treatment. o If dose is held for 4 consecutive weeks, permanently discontinue entinostat
Pulmonary events	
General guidance	• All pulmonary events should be thoroughly evaluated 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	• May continue atezolizumab and entinostat. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	• Withhold atezolizumab and entinostat. • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL *with or without transbronchial biopsy*. • 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 contact the Medical Monitor. [a, b, c, d] • If event resolves to Grade 1 or better within 28 days, resume entinostat at current dose. • For recurrent events, treat as a Grade 3 or 4 event.

Appendix 8: Study Details Specific to Atezo + Entino Arm (cont.)

Event	Action to Be Taken

Pulmonary event, Grade 3	• Follow atezolizumab-specific guidelines in Appendix 6.
	• Withhold entinostat and contact the Medical Monitor. [c]
	• Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL *with or without transbronchial biopsy*.
	• 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.
	• Hold entinostat until recovery to Grade 1 or baseline under the following directions:
	  ○ If not recovered by next scheduled dose, skip the dose. If recovered by next scheduled dose, resume study drug at prior dose.
	  ○ If not recovered by either of the next 2 scheduled doses and receiving 2 mg, permanently discontinue study treatment. Otherwise, skip each dose and if recovered by the 4th dose, resume study drug as follows: If receiving 5 mg, restart study drug at 3 mg. If receiving 3 mg, restart study drug at 2 mg.
	  ○ If dose is held for 4 consecutive weeks, permanently discontinue entinostat.

Pulmonary event, Grade 4	• Follow atezolizumab-specific guidelines in Appendix 6.
	• Withhold entinostat and contact the Medical Monitor. [c]
	• Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL *with or without transbroncial biopsy*.
	• 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.
	• Hold entinostat until recovery to Grade 1 or baseline under the following directions:
	  ○ If recovered within 4 weeks of onset (i.e., ≤3 missed doses), resume study drug as follows: If receiving 5 mg, restart study drug at 3 mg. If receiving 3 mg, restart study drug at 2 mg. If receiving 2 mg, discontinue study treatment.
	  ○ If dose is held for 4 consecutive weeks, permanently discontinue entinostat.

Endocrine disorders	
Grade 1 hypothyroidism	• Follow guidelines for atezolizumab in Appendix 6. • Continue entinostat.

Appendix 8: Study Details Specific to Atezo + Entino Arm (cont.)

Event	Action to Be Taken
Grade 2, 3 or 4 hypothyroidism	• Follow guidelines for atezolizumab in Appendix 6. • Withhold entinostat. • If the event resolves to Grade 1 or better within 28 days, resume entinostat at current dose. If not, permanently discontinue entinostat.
Hyperglycemia, Grade 1 or 2	• Follow guidelines for atezolizumab in Appendix 6. • Entinostat may be interrupted at the Investigator's discretion, in consultation with the Medical Monitor • If event resolves to Grade 1 or better, resume entinostat. If not, permanently discontinue entinostat
Hyperglycemia, Grade 3	• Follow guidelines for atezolizumab in Appendix 6. • Withhold entinostat • If the event resolves to Grade 1 or better, resume entinostat with dose reduced by one level. If not, permanently discontinue entinostat.
Hyperglycemia, Grade 4	• Follow guidelines for atezolizumab in Appendix 6. • Withhold entinostat and contact the Medical Monitor • Hold entinostat until recovery to Grade 1 or baseline under the following directions: o If recovered within 4 weeks of onset (i.e., ≤3 missed doses), resume study drug as follows: If receiving 5 mg, restart study drug at 3 mg. If receiving 3 mg, restart study drug at 2 mg. If receiving 2 mg, discontinue study treatment. o If dose is held for 4 consecutive weeks, permanently discontinue entinostat.
Grade 3 or 4 or intolerable Grade 2 treatment-related toxicities not described above	• Withhold atezolizumab and entinostat and contact the Medical Monitor. • If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at fixed dose. If not, permanently discontinue atezolizumab and entinostat and contact the Medical Monitor. [a, b, c] • If event resolves to Grade 1 or better within 28 days, resume entinostat with dose reduced by one level. If not, permanently discontinue entinostat.

Atezo + Entino = atezolizumab plus entinostat; CRS = cytokine release syndrome; GI = gastrointestinal; IM = intramuscular; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; 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 *based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with atezolizumb should be based on the investigator's benefit-risk assessment and documented by the investigator.*

[d] *In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.*

A8–6.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + ENTINO ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo + Entino arm include the following:

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

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>10\times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenzalike illness, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, *optic neuritis*)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders
- Vasculitis
- *Myelitis*
- *Facial paresis*

A8–7 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO + ENTINO ARM

Table A8-8 Schedule of Activities for Atezo + Entino Arm

Assessment/Procedure	Screening [a]	Treatment Cycles (21-day cycles) [b]				Stage 2 Scrn. [d] or Treat. Discon. [e]	Follow-Up
		Cycle 1 [c]			Cycles ≥2		
	Days –28 to –1	Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	≤30 Days after Last Dose	Every 3 Months
Informed consent	x [f]					x [g]	
Demographic data	x						
Medical history and baseline conditions	x						
Molecular profile of HR+ breast cancer (if available)	x	Whenever updated information becomes available					
Vital signs [h]	x	x		x	x	x	
Weight	x	x [mm]			x [mm]	x	
Height	x						
Complete physical examination [i]	x					x	
Limited physical examination [j]		x [mm]	x	x	x [mm]		
ECOG Performance Status	x	x [mm]			x [mm]	x	
ECG [k]	x				x [l, mm]	x [g]	
Hematology [m]	x [n]	x [o]	x	x	x	x	
Chemistry [p]	x [n]	x [o]	x	x	x	x	
FSH, LH, and estradiol [q]	x [n]						
Fasting glucose [r]	x [n]						
Fasting lipid panel [r, s]	x [n]						
HbA_{1c} [r]	x [n]						

Appendix 8: Study Details Specific to Atezo + Entino Arm (cont.)

Assessment/Procedure	Screening [a]	Treatment Cycles (21-day cycles) [b]				Stage 2 Scrn. [d] or Treat. Discon. [e]	Follow-Up
		Cycle 1 [c]			Cycles ≥2		
	Days –28 to –1	Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	≤30 Days after Last Dose	Every 3 Months
Amylase and lipase [r]	x [n]						
LDH	x [n]					x [g]	
Coagulation (INR, aPTT)	x [n]					x [g]	
TSH, free T3 (or total T3), free T4 [t]	x [n]		x [t]			x [g]	
Viral serology [u]	x [n]					x [v]	
C-reactive protein	x					x [g]	
Urinalysis [w]	x [n]		Perform as clinically indicated			x [g]	
Serum autoantibody sample [x]	x	Perform if patient experiences a suspected immune-mediated adverse event					
PK sample		Refer to Table A8–9 below					
ADA sample		Refer to Table A8–9 below					
Samples for biomarkers		Refer to Table A8–9 below					
Blood sample for RBR (optional) [y]		x					
Tumor biopsy	x [z]	x [aa]					
Tumor biopsy (optional)		x [bb]					
Tumor response assessments	x [cc]		x [dd, ee, ff]				
Concomitant medications [gg]	x [gg]	x	x	x	x	x	
Adverse events [hh]	x [hh]	x	x	x	x	x [hh]	x [hh]
Entinostat administration [ii]		x	x	x	x		
Atezolizumab administration [ij, kk]		x			x		
Survival follow-up and anti-cancer treatment							x [ll]

Appendix 8: Study Details Specific to Atezo + Entino Arm (cont.)

ADA = anti-drug antibody; Atezo + Entino = atezolizumab plus entinostat; CT = computed tomography; Discon. = discontinuation; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; MUGA = multiple-gated acquisition (scan); PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; PET = positron emission tomography; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; Treat. = treatment.

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

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window at the investigator's discretion. The Medical Monitor is available to advise as needed.

[c] Treatment must be initiated no later than 7 days after randomization. If initiation of treatment has to be delayed, patient may start treatment at the investigator's discretion. The Medical Monitor is available to advise as needed.

[d] Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) and patients who experience unacceptable toxicity to entinostat will be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Table 6) and will undergo screening assessments to determine eligibility. The Medical Monitor is available to advise as needed. Study-specific details for the Stage 2 treatment regimens are provided in Appendix 12. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[e] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Patients who do not enter Stage 2 will then undergo follow-up assessments. Note that treatment discontinuation assessments will be performed for all patients, regardless of whether they enter Stage 2.

[f] 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.

[g] Assessments to be performed only for patients undergoing Stage 2 screening.

[h] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, 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 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 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.

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

Appendix 8: Study Details Specific to Atezo + Entino Arm (cont.)

[j] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[l] An ECG is to be performed pre-dose on Day 1 of Cycle 3 and then every 3 cycles thereafter. An ECG may be repeated anytime, as clinically indicated.

[m] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[n] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment (Day 1 of Cycle 1).

[o] If screening laboratory assessments were performed within 96 hours prior to dosing, they do not have to be repeated.

[p] Chemistry panel (serum or plasma) includes CPK, sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST. CPK will be performed only on Day 1 of each cycle.

[q] FSH, LH, and estradiol are all required for patients who are <60 years old and in postmenopausal state or who are <60 years old and have had prior ovarian ablation. Only estradiol is required for patients who are <60 years old and are on a LHRH agonist for ovarian suppression.

[r] Required only if an ipatasertib-containing arm is open for enrollment at time of patient screening.

[s] Fasting lipid panel should include cholesterol, HDL, LDL, and triglyceride.

[t] 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.).

[u] At screening, patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.

[v] Viral serology tests are required at Stage 2 screening but are not required at the treatment discontinuation visit. However, patients with a positive quantitative HBV DNA at screening (must be <500 IU/mL per the eligibility criteria) will undergo additional HBV DNA tests on Day 1 of every third cycle (i.e., Cycles 3, 6, 9, etc.), at treatment discontinuation (±7 days), and at 3, 6, 9, and 12 months (±14 days at each timepoint) after treatment discontinuation. Study treatment and procedures may proceed while HBV DNA is being processed, but results should be reviewed by the investigator as soon as they are available. If HBV DNA increases to ≥500 IU/mL, consultation with the Medical Monitor is required prior to continuation of study treatment and consultation with a hepatologist or gastroenterologist with specialty in hepatitis B is recommended.

[w] Includes pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted.

Appendix 8: Study Details Specific to Atezo + Entino Arm (cont.)

[x] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. For patients who show evidence of immune-mediated toxicity, additional samples may be considered.

[y] 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.

[z] 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. It is preferred 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. Refer to Section 4.5.6 for tissue sample requirements.

[aa] Patients will undergo tumor biopsy sample collection during Stage 1, at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled into the mandatory serial biopsy arm will undergo tumor biopsy sample collection, if deemed clinically feasible by the investigator, at 4 weeks (±7 days) from initiation of study treatment. Refer to Section 4.5.6 for tissue sample requirements.

[bb] Patients will undergo optional tumor biopsy sample collection, if deemed clinically feasible by the investigator, 4 weeks (±7 days) after treatment initiation and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[cc] All measurable and evaluable lesions should be assessed and documented at screening (in both Stage 1 and Stage 2). Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with IV contrast; with or without oral contrast) or MRI scans (with IV contrast) of the chest, abdomen, pelvis, and head with one exception: a head scan is not required at Stage 2 screening. In addition, bone scans, PET scans, and/or skeletal survey should be performed at screening to assess bone lesions. Bone lesions identified at baseline should continue to be assessed following the tumor assessment schedule described above. Additional bone scans, PET scans, or skeletal surveys should be performed if clinically indicated. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans (with IV contrast) of the abdomen and pelvis should be performed. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. Refer to Section 4.5.5 for further details on tumor assessments.

[dd] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 24 weeks following treatment initiation, and every 8 weeks (±1 week) from Week 25 to Week 48, and then every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of atezolizumab-treated patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

Appendix 8: Study Details Specific to Atezo + Entino Arm (cont.)

[ee] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[ff] For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of disease progression per RECIST v1.1, loss of clinical benefit, or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided that the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

[gg] 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 10 days prior to initiation of study treatment until the treatment discontinuation visit.

[hh] 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 systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic 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.

[ii] All patients will receive entinostat at a dose of 5 mg orally once a week on Days 1, 8, and 15 of each 21-day cycle. On study days when patients receive both entinostat and atezolizumab, entinostat is to be taken prior to atezolizumab. Entinostat is to be taken on an empty stomach at least 2 hours after a meal and at least 1 hour before the next meal.

[jj] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details).

[kk] The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[ll] 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 study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

[mm] Assessment may be performed within 24 hours prior to dosing during the treatment period.

Table A8-9 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+Entino Arm: Preliminary and Expansion Phases

Visit	Time	Sample
Day 1 of Cycle 1	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Entinostat PK (plasma) • Biomarkers (plasma, serum, PBMC)
	30 (± 10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
	2 – 4 hours after entinostat dose	• Entinostat PK (plasma)
Day 1 of Cycle 2	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Entinostat PK (plasma) • Biomarkers (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 4	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycle 8	Prior to any study treatment infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)

ADA = anti-drug antibody; Atezo + Entino = atezolizumab plus entinostat; PK = pharmacokinetic.

A8–8 REFERENCES

Adeegbe DO, Nishikawa H. Natural and induced T regulatory cells in cancer. Front Immunol 2013;4:190.

Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. Cancer Immunol Immunother 2005;54:307–14.

Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother 2007;56:739–45.

Butte MJ, Keir ME, Phamduy TB. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012;18:6580–7.

Deng R, Bumbaca D, Pastuskovas CV, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti–PD-L1 monoclonal antibody, an immune checkpoint inhibitor. MAbs 2016;8:593–603. doi: 10.1080/19420862.2015.1136043. Epub: 26 February 2016.

Dirix LY, Takacs I, Nikolinakos P, et al. Avelumab (MSB0010718C), an anti–PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase Ib JAVELIN solid tumor trial. Cancer Res 2016;76(Suppl):S1–04.

Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837–46.

Freiser ME, Serafni P, Weed DT. The immune system and head and neck squamous cell carcinoma: from carcinogenesis to new therapeutic opportunities. Immunol Res 2013;57:52–69. doi: 10.1007/s12026-013-8462-3.

Gandhi L, Johnson ML, Opyrchal M, et al. ENCORE-601: phase 1b/2 study of entinostat (ENT) in combination with pembrolizumab (PEMBRO) in patients with non-small cell lung cancer. Presented at the Society for the Immunotherapy of Cancer (SITC) Annual Meeting; November 8–12, 2017; National Harbor, MD, USA.

Hess-Stumpp H, Bracker TU, Henderson D, et al. MS-275, a potent orally available inhibitor of histone deacetylases--the development of an anticancer agent. Int J Biochem Cell Biol 2007;39(7–8):1388–405.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

Johnson ML, Gonzalez R, Opyrchal M, et al. ENCORE 601: a phase II study of entinostat (ENT) in combination with pembrolizumab (PEMBRO) in patients with melanoma. Sepsis 2017;1:8.

Joyce JA, Fearon DT. T cell exclusion, immune privilege, and the tumor microenvironment. Science 2015;348:74–80.

Juergens RA, Wrangle J, Vendetti FP, et al. Combination epigenetic therapy has efficacy in patients with refractory advanced non-small cell lung cancer. Cancer Discov 2011;1:598–607.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annual Rev Immunol 2008;26:677–704.

Kim K, Skora AD, Li Z, et al. Eradication of metastatic mouse cancers resistant to immune checkpoint blockade by suppression of myeloid-derived cells. Proc Natl Acad Sci USA 2014;111:11774–9.

Liu C, Wang Y, Wang C, Feng P, et al. Population alterations of L-arginase- and inducible nitric oxide synthase-expressed CD11b+/CD14−/CD15+/CD33+ myeloid-derived suppressor cells and CD8+ T lymphocytes in patients with advanced-stage non–small cell lung cancer. J Cancer Res Clin Oncol 2010;136:35–45.

Mahoney KM, Rennert PD, Freeman GJ. Combination cancer immunotherapy and new immunomodulatory targets. Nature reviews. Drug Discov 2015;14:561–84.

Marvel D, Gabrilovich DI. Myeloid-derived suppressor cells in the tumor microenvironment: expect the unexpected. J Clin Invest 2015;125:3356–64.

Orillion A, Hashimoto A, Damayanti N, et al. Entinostat neutralizes myeloid-derived suppressor cells and enhances the antitumor effect of PD-1 inhibition in murine models of lung and renal cell carcinoma. Clin Cancer Res 2017;23:5187–201.

Najjar YG, Finke JH. Clinical perspectives on targeting of myeloid derived suppressor cells in the treatment of cancer. Front Oncol 2013;3:49.

Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.

Rugo HS, Rumble RB, Macrae E, et al. Endocrine therapy for hormone receptor-positive metastatic breast cancer: American Society of Clinical Oncology Guideline. J Clin Onocol 2016;34:3069–103.

Shah P, Gau Y, Sabnis G. Histone deacetylase inhibitor entinostat reverses epithelial to mesenchymal transition of breast cancer cells by reversing the repression of E-cadherin. Breast Cancer Res Treat 2014;143:99–111.

Sharma P, Allison JP. The future of immune checkpoint therapy. Science 2015;348:56–61.

Shen Li, Ciesielski M, Ramakrishnan S, et al. Class I histone deacetylase inhibitor entinostat suppresses regulatory T cells and enhances immunotherapies in renal and prostate cancer models. PLoS One 2012;7:e30815.

Solito S, Falisi E, Diaz Montero CM, et al. A human promyelocytic like population is responsible for the immune suppression mediated by myeloid-derived suppressor cells. Blood 2011;118:2254–65.

Tecentriq® (atezolizumab) U.S. prescribing information. South San Francisco (CA): Genentech, 2016.

Tolcher AW. Safety, efficacy, and immune correlates of alternative doses and schedules of entinostat combined with pembrolizumab in patients with advanced solid tumors: results from SNDX-275-0141 phase I trial [abstract]. In: Proceedings of the 109th Annual Meeting of the American Association for Cancer Research (AACR); 2018 Apr 14–18; Chicago, Illinois. Abstract CT179.

Weber JS, Gibney GT, Yu B, et al. Survival, biomarker, and toxicity analysis of nivolumab (NIVO) in patients that progressed on ipilimumab (IPI). J Clin Oncol 2015;33(Suppl);Abstract 9055.

Weed DT, Vella JL, Reis IM, et al. Tadalafil reduces myeloid-derived suppressor cells and regulatory T cells and promotes tumor immunity in patients with head and neck squamous cell carcinoma. Clin Cancer Res 2015;21:39–48.

Wrangle J, Wang W, Koch A, et al. Alterations of immune response of non-small cell lung cancer with azacytidine. Oncotarget 2013;4:2067–79.

Yang J, Riella LV, Chock S. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. J Immunol 2011;187:1113–9.

Zhang HY, Yan KX, Huang Q et al. Target tissue ectoenzyme CD39/CD73-expressing Foxp3+ regulatory T cells in patients with psoriasis. Clin Exp Dermatol 2015; 40:182–91.

Appendix 9
Study Details Specific to Atezo + Fulvestrant Arm

A9–1 TABLE OF CONTENTS

A9–2 BACKGROUND ON ATEZO + FULVESTRANT ARM

A9–2.1 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 cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with dose interruption or treatment, and patients are eligible to continue atezolizumab.

Atezolizumab (Tecentriq®) was first approved in the United Stated for the treatment of patients with locally advanced or metastatic urothelial carcinoma and for the treatment of patients with metastatic non–small cell lung cancer (NSCLC). Marketing Authorization Applications are being submitted globally, and approvals have already been received in a few countries

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

A9–2.2 BACKGROUND ON FULVESTRANT

Fulvestrant is an estrogen receptor (ER) antagonist that binds to the ER, disrupting the signaling pathway and leading to ER degradation. Fulvestrant is approved for the treatment of postmenopausal patients with HR+ HER2-negative breast cancer (HR+ breast cancer) who have disease progression following other anti-estrogen therapy (Faslodex® [fulvestrant] prescribing information). The common adverse events associated with the use of fulvestrant include injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, extremity pain, hot flashes, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, constipation, and increases in liver enzymes (AST, ALT, ALP).

A9–3 RATIONALE FOR ATEZO + FULVESTRANT ARM

A9–3.1 THE PD-L1 PATHWAY

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 downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and 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 (see Atezolizumab Investigator's Brochure for detailed efficacy results).

PD-L1 expression has been observed in HR+ breast cancer tissues. However, few clinically significant responses to single-agent checkpoint inhibitors have been observed in patients with HR+ breast cancer (Dirix et al. 2016; Rugo et al. 2016), highlighting a need for combination therapy to overcome mechanisms of resistance to anti–PD-L1/PD-1 monotherapy. The effects of endocrine therapy (ET) on the tumor microenvironment have not been well characterized to date. This study arm will provide an opportunity to assess this, as well as to evaluate for possible increased efficacy when atezolizumab is added to standard-of-care ET.

A9–3.2 BENEFIT–RISK ASSESSMENT

Patients will receive atezolizumab in combination with fulvestrant (Atezo + Fulvestrant) in order to evaluate the potential synergies of atezolizumab with ET. Fulvestrant is one of several ET regimens approved for the treatment of HR+ breast cancer; therefore these patients will be receiving standard-of-care second-line therapy with this combination

regimen. Furthermore, the tolerable safety profiles for atezolizumab and fulvestrant along with limited overlapping toxicities indicate a low safety risk for patients.

For the evaluation of the impact of the COVID-19 pandemic on the benefit-risk assessment, please refer to Section 1.3.

A9–4 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + FULVESTRANT ARM

A9–4.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 840 mg every 2 weeks (Q2W) (840 mg on Days 1 and 15 of each 28-day cycle). The average concentration following the 840 mg Q2W dosage is expected to be equivalent to that of 1200 mg every 3 weeks (Q3W), the approved dosage for atezolizumab (Tecentriq® U.S. Prescribing Information). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A9–4.2 RATIONALE FOR FULVESTRANT DOSE AND SCHEDULE

In this study, fulvestrant 500 mg will be administered intramuscularly on Days 1 and 15 of Cycle 1. Thereafter, fulvestrant will be administered on Day 1 of each 28-day cycle. This is the current approved fulvestrant dosage for the treatment of HR+ breast cancer.

A9–5 MATERIALS AND METHODS SPECIFIC TO ATEZO + FULVESTRANT ARM

A9–5.1 TREATMENT IN ATEZO + FULVESTRANT ARM

A9–5.1.1 Formulation, Packaging, and Handling

A9–5.1.1.1 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 and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A9–5.1.1.2 Fulvestrant

Fulvestrant will be supplied as 250-mg/mL sterile liquid. For information on the formulation, packaging, and handling of fulvestrant, refer to the local label.

A9–5.1.2 Dosage, Administration, and Compliance

Patients in the Atezo + Fulvestrant arm will receive treatment as outlined in Table A9-1 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) (see Section 3.1.1.1 for details). Treatment must be initiated no later than 7 days after randomization. If initiation of treatment has to be delayed, patient may start treatment at the investigator's discretion. The Medical Monitor is available to advise as needed.

Table A9-1 Treatment Regimen for Atezo + Fulvestrant Arm

Cycle Length	Dose, Route, and Regimen **(drugs listed in order of administration)**
28 days	• Fulvestrant 500 mg by IM injection on Days 1 and 15 of Cycle 1 followed by 500 mg by IM injection on Day 1 of every cycle thereafter • Atezolizumab 840 mg by IV infusion on Days 1 and 15

Atezo = atezolizumab IM = intramuscular.

Refer to Section A9–6.1.4.2 for information on treatment interruptions for patients who experience toxicities. Atezolizumab or fulvestrant treatment interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed. The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Any dose modification of any of the study treatments should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error, along with any associated adverse events, should be reported as described in Section 5.4.3.

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

A9–5.1.2.1 Fulvestrant

Patients will receive fulvestrant at a dose of 500 mg intramuscularly on Days 1 and 15 of Cycle 1, followed by dosing on Day 1 of every cycle thereafter.

Guidelines for dosage modification and treatment interruption or discontinuation because of toxicities are provided in Section A9–6.1.4.2.

A9–5.1.2.2 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg 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 5. Atezolizumab infusions will be administered per the instructions outlined in Table A9-2.

Table A9-2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion of Atezolizumab	Subsequent Infusions of Atezolizumab
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded 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.	• 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 (± 10) minutes after the infusion.

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

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A9–6.1.4.2 and in Appendix 6.

A9–5.1.3 Stage 2 Treatment

Patients who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1.1) will be given the option of receiving atezolizumab in combination with bevacizumab plus one of three ET options (fulvestrant, exemestane, or tamoxifen) on the basis of the physician's choice (Atezo + Bev + ET) during Stage 2 of the study, provided they meet eligibility criteria (see Section 4.1) and a Stage 2 arm is open

for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit and will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator. However, it is recommended that patients begin Stage 2 treatment as soon as possible but no earlier than 2 weeks after the last dose of treatment in Stage 1.

Tumor assessments performed prior to or at the time of disease progression, loss of clinical benefit, or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided that the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

A9–5.2 CONCOMITANT THERAPY FOR ATEZO + FULVESTRANT ARM

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 10 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.

A9–5.2.1 Permitted Therapy for Atezo + Fulvestrant Arm

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

- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section 4.1.2.2).
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- 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 and fulvestrant may be continued during palliative radiotherapy.
- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may

receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) 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 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 continue study treatment at the investigator's discretion. The Medical Monitor is available to advise as needed.
- Anti-convulsant therapy, if required, is administered at a stable dose.
- Bisphosphonates or denosumab
- Megestrol

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

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 5).

A9–5.2.2 Cautionary Therapy for Atezo + Fulvestrant Arm

A9–5.2.2.1 Corticosteroids, *Immunosuppressive Medications,* and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, 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, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator. The Medical Monitor is available to advise as needed.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when

associated with atezolizumab therapy (refer to the Atezolizumab Investigator's Brochure for details).

A9–5.2.2.2 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 A9–5.2.3) may be used during the study at the discretion of the investigator.

A9–5.2.3 Prohibited Therapy for Atezo + Fulvestrant Arm

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

- 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 radiotherapy to the brain under circumstances outlined in Section A9–5.2.1.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.

A9–6 ASSESSMENT OF SAFETY FOR ATEZO + FULVESTRANT ARM

A9–6.1 SAFETY PLAN FOR ATEZO + FULVESTRANT ARM

The anticipated important safety risks are outlined below (see Sections A9–6.1.1, A9–6.1.2, and A9–6.1.3). Guidelines for management of patients who experience specific adverse events are provided in Section A9–6.1.4. These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit-risk balance when managing individual cases.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Fulvestrant will be administered according to institutional practice. 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. Adverse events will be reported as described in Sections 5.2–5.6.

A9–6.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, *facial paresis, myelitis,* meningoencephalitis, myocarditis, *pericardial disorders,* nephritis, myositis, and severe cutaneous adverse reactions. *In addition,* immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis *(HLH)*. Refer to Appendix 6 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A9–6.1.2 Risks Associated with Fulvestrant

Fulvestrant has been associated with risks such as the following: injection site reactions, asthenia, nausea, and increased hepatic enzymes (ALT, AST, ALP). Refer to the local prescribing information for fulvestrant for a detailed description of all anticipated risks for fulvestrant.

A9–6.1.3 Risks Associated with Combination Use of Atezolizumab and Fulvestrant

Currently, there are no identified adverse events with potential overlapping toxicities associated with combination use of atezolizumab and fulvestrant.

A9–6.1.4 Management of Patients Who Experience Specific Adverse Events in Atezo+Fulvestrant Arm

A9–6.1.4.1 Dose Modifications

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

A9–6.1.4.2 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 patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the*

investigator's benefit-risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

In general, the investigator may consider continuing fulvestrant if the observed adverse event is not thought to be fulvestrant-related.

If either atezolizumab or fulvestrant is discontinued, the other drug can be continued if the patient is likely to derive clinical benefit *based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.*

Refer to Section A9–5.1.2 for information on dose interruptions for reasons other than toxicity.

A9–6.1.4.3 Management Guidelines for Adverse Events

Please refer to Appendix 6 and the fulvestrant local prescribing information for guidelines on the management of patients who experience specific adverse events for atezolizumab and fulvestrant, respectively.

A9–6.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + FULVESTRANT ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo + Fulvestrant arm 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 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10 × ULN

- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenzalike illness, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, *optic neuritis*)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥2 cardiac disorders
- Vasculitis
- *Myelitis*
- *Facial paresis*

A9–7 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO + FULVESTRANT ARM

Table A9-3 Schedule of Activities for Atezo + Fulvestrant Arm

Assessment/Procedure	Screening [a]	Treatment Cycles (28-day cycles) [b]				Stage 2 Scrn. [d] or Treat. Discon. [e] ≤30 Days after Last Dose	Follow-Up [e] Every 3 Months
		Cycle 1 [c]		Cycles ≥2			
	–28 to –1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)		
Informed consent	x [f]					x [g]	
Demographic data	x						
Medical history and baseline conditions	x						
Molecular profile of HR+ breast cancer (if available)	x	Whenever updated information becomes available					
Vital signs [h]	x	x	x	x	x	x	
Weight	x	x [ll]		x [ll]		x	
Height	x						
Complete physical examination [i]	x					x	
Limited physical examination [j]		x [ll]		x [ll]			
ECOG Performance Status	x	x [ll]		x [ll]		x	
ECG [k]	x	Perform as clinically indicated				x [g]	
Hematology [l]	x [m]	x [n]	x	x	x	x	
Chemistry [o]	x [m]	x [n]	x	x	x	x	
FSH, LH, and estradiol [p]	x [m]						
Fasting glucose [q]	x [m]						
Fasting lipid panel [q, r]	x [m]						
HbA_{1c} [q]	x [m]						

Appendix 9: Study Details Specific to Atezo + Fulvestrant Arm (cont.)

Assessment/Procedure	Screening [a]	Treatment Cycles (28-day cycles) [b]				Stage 2 Scrn. [d] or Treat. Discon. [e] ≤30 Days after Last Dose	Follow-Up [e]
		Cycle 1 [c]		Cycles ≥2			
	–28 to –1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)		Every 3 Months
Amylase and lipase [q]	x [m]						
Coagulation (INR, aPTT)	x [m]					x [g]	
TSH, free T3 (or total T3), free T4 [s]	x [m]	x [p]				x [g]	
Viral serology	x [m, t]					x [u]	
C-reactive protein	x					x [g]	
LDH	x [m]					x [g]	
Urinalysis [v]	x [m]	Perform as clinically indicated				x [g]	
Serum autoantibody sample [w]	x	Perform if a patient experiences a suspected immune-mediated adverse event					
PK sample		Refer to Table A9-4 below					
ADA sample		Refer to Table A9-4 below					
Samples for biomarkers		Refer to Table A9-4 below					
Blood sample for RBR (optional) [x]		x					
Tumor biopsy	x [y]	x [z]					
Tumor biopsy (optional)		x [aa]					
Tumor response assessments	x [bb]	x [cc, dd, ee]					
Concomitant medications [ff]	x [ff]	x	x	x	x	x	
Adverse events [gg]	x [gg]	x	x	x	x	x [gg]	x [gg]
Fulvestrant administration [hh, ii]		x	x	x			
Atezolizumab administration [ii, jj]		x	x	x	x		
Survival follow-up and anti-cancer							x [kk]

Appendix 9: Study Details Specific to Atezo + Fulvestrant Arm (cont.)

Assessment/Procedure	Screening [a]	Treatment Cycles (28-day cycles) [b]				Stage 2 Scrn. [d] or Treat. Discon. [e] ≤30 Days after Last Dose	Follow-Up [e]
		Cycle 1 [c]		Cycles ≥2			
	–28 to –1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)		Every 3 Months
treatment							

ADA = anti-drug antibody; Atezo + Fulvestrant = atezolizumab plus fulvestrant; CT = computed tomography; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; ET = endocrine therapy; FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LH = luteinizing hormone; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; PET = positron emission tomography; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; Scrn. = screening; Treat. = treatment.

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

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window at the investigator's discretion. The Medical Monitor is available to advise as needed.

[c] Treatment must be initiated no later than 7 days after randomization. If initiation of treatment has to be delayed, patient may start treatment at the investigator's discretion. The Medical Monitor is available to advise as needed.

[d] Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) and patients who experience unacceptable toxicity to fulvestrant will be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Table 6) and will undergo screening assessments to determine eligibility. The Medical Monitor is available to advise as needed. Study-specific details for the Stage 2 treatment regimens are provided in Appendix 12. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[e] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Patients who do not enter Stage 2 will then undergo follow-up assessments. Note that treatment discontinuation assessments will be performed for all patients, regardless of whether they enter Stage 2.

[f] 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.

[g] Assessments to be performed only for patients undergoing Stage 2 screening.

[h] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, 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 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 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.

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

[j] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[l] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[m] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment (Day 1 of Cycle 1).

[n] If screening laboratory assessments were performed within 96 hours prior to dosing, they do not have to be repeated.

[o] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST.

[p] FSH, LH, and estradiol are all required for patients who are <60 years old and in postmenopausal state or who are <60 years old and have had prior ovarian ablation. Only estradiol is required for patients who are <60 years old and are on a LHRH agonist for ovarian suppression.

[q] Required only if an ipatasertib-containing arm is open for enrollment at the time of patient screening.

[r] Fasting lipid panel should include cholesterol, HDL, LDL, and triglyceride.

[s] 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.).

[t] At screening, patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.

[u] Viral serology tests are required at Stage 2 screening but are not required at the treatment discontinuation visit. However, patients with a positive quantitative HBV DNA at screening (must be <500 IU/mL per the eligibility criteria) will undergo additional HBV DNA tests on Day 1 of every third cycle (i.e., Cycles 3, 6, 9, etc.), at treatment discontinuation (±7 days), and at 3, 6, 9, and 12 months (±14 days at each timepoint) after treatment discontinuation. Study treatment and procedures may proceed while HBV DNA is being processed, but results should be reviewed by the investigator as soon as they are available. If HBV DNA increases to ≥500 IU/mL, consultation with the Medical Monitor is

required prior to continuation of study treatment and consultation with a hepatologist or gastroenterologist with specialty in hepatitis B is recommended.

[v] Includes pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted.

[w] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. For patients who show evidence of immune-mediated toxicity, additional samples may be considered.

[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.

[y] 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. It is preferred 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. Refer to Section 4.5.6 for tissue sample requirements.

[z] Patients will undergo tumor biopsy sample collection during Stage 1 at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled into the mandatory serial biopsy arm will undergo tumor biopsy sample collection, if deemed clinically feasible by the investigator, at 4 weeks (±7 days) from initiation of study treatment. Refer to Section 4.5.6 for tissue sample requirements.

[aa] Patients will undergo optional tumor biopsy sample collection, if deemed clinically feasible by the investigator, 4 weeks (±7 days) after treatment initiation and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[bb] All measurable and evaluable lesions should be assessed and documented at screening (in both Stage 1 and Stage 2). Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with IV contrast; with or without oral contrast) or MRI scans (with IV contrast) of the chest, abdomen, pelvis, and head with one exception: a head scan is not required at Stage 2 screening. In addition, bone scans, PET scans, and/or skeletal survey should be performed at screening to assess bone lesions. Bone lesions identified at baseline should continue to be assessed following the tumor assessment schedule described above. Additional bone scans, PET scans, or skeletal surveys should be performed if clinically indicated. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans (with IV contrast) of the abdomen and pelvis should be performed. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. Refer to Section 4.5.5 for further details on tumor assessments.

[cc] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 24 weeks following treatment initiation, and every 8 weeks (±1 week) from Week 25 to Week 48, and then every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of atezolizumab-treated patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue

treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[dd] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[ee] For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided that the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

[ff] 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 10 days prior to initiation of study treatment until the treatment discontinuation visit.

[gg] 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 systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic 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.

[hh] Fulvestrant should be administered intramuscularly into the buttocks slowly (1–2 minutes per injection) as two 5-mL injections, one in each buttock.

[ii] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details).

[jj] The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[kk] 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 study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

[ll] Assessment may be performed within 24 hours prior to dosing during the treatment period.

Table A9-4 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Fulvestrant Arm: Preliminary and Expansion Phases

Visit	Time	Sample
Day 1 of Cycle 1	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum PBMC)
	30 (±10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
Day 15 of Cycle 1	Prior to any study treatment	• Biomarker (plasma, serum)
Day 1 of Cycle 2	Prior to fulvestrant injection	• Fulvestrant PK (plasma)
	Prior to atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to fulvestrant injection	• Fulvestrant PK (plasma)
	Prior to atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 4	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)
Day 1 of Cycle 8	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
120 (±30) days after last dose of atezolizumab [a]	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)

ADA = anti-drug antibody; Atezo + Fulvestrant = atezolizumab plus fulvestrant; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

[a] Does not apply for patients enrolling into Stage 2.

A9–8 REFERENCES

Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. Cancer Immunol Immunother 2005;54:307–14.

Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother 2007;56:739–45.

Butte MJ, Keir ME, Phamduy TB. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012;18:6580–7.

Deng R, Bumbaca D, Pastuskovas CV, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. MAbs 2016;8:593–603.

Dirix LY, Takacs I, Nikolinakos P, et al. Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: A Phase Ib JAVELIN solid tumor trial. Cancer Res 2016;76(Suppl):S1–04.

Faslodex® (fulvestrant) prescribing information. Wilmington (DE): AstraZeneca Pharmaceuticals, 2016.

Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837–46.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annual Rev Immunol 2008;26:677–704.

Nomi C, Sho M, Akahori T, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer, Clin Cancer Res. 2007;13:2151–7.

Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.

Rugo HS, Delord JP, Im SA, et al. Preliminary efficacy and safety of pembrolizumab (MK-3475) in patients with PD-L1-positive, estrogen receptor-positive (ER+)/HER2-negative advanced breast cancer enrolled in KEYNOTE-028. Cancer Res 2016;76(Suppl):S5–07.

Tecentriq® (atezolizumab) U.S. prescribing information. South San Francisco (CA): Genentech, 2016.

Yang J, Riella LV, Chock S. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. J Immunol 2011;187:1113–9.

Appendix 10
Placeholder for Future Arm

The Atezo + Ipat Arm is completed and is now closed; its appendix with study details has been removed. Appendix 10 will serve as a placeholder for a future arm to avoid having to renumber subsequent appendices.

Appendix 11
Study Details Specific to Atezo + Ipat + Fulvestrant Arm

A11–1 TABLE OF CONTENTS

A11–2 BACKGROUND ON ATEZO + IPAT + FULVESTRANT ARM

A11–2.1 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 cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with dose interruption or treatment, and patients are eligible to continue atezolizumab.

Atezolizumab (Tecentriq®) was first approved in the United Stated for the treatment of patients with locally advanced or metastatic urothelial carcinoma and for the treatment of patients with metastatic non–small cell lung cancer (NSCLC). Marketing Authorization Applications are being submitted globally, and approvals have already been received in a few countries.

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

A11–2.2 BACKGROUND ON IPATASERTIB

Ipatasertib (GDC-0068) is a novel, selective, ATP-competitive small molecule inhibitor of all three isoforms of the serine/threonine kinase Akt and is potent in nonclinical models, including tumors with loss of PTEN (PTEN-low, PTEN-null, or PTEN-mutated) or mutations of PIK3CA both in vitro and in vivo. Ipatasertib inhibits the kinase activity of Akt and suppresses the phosphorylation of its direct substrates, including PRAS40, and additional downstream targets, such as S6 ribosomal protein (S6RP), resulting in G1 arrest and/or apoptosis in human cancer cells (Lin et al. 2012).

Ipatasertib shows anti-tumor activity in nonclinical models of multiple tumors, including robust signal-agent activity in xenograft models with PI3K/Akt pathway activation (e.g., via PTEN loss and/or PIK3CA mutation), including breast, prostate, gastric and ovarian cancer models (Genentech data on file and Ipatasertib Investigator's Brochure) as well as in cancer patients.

Ipatasertib is currently being tested as a single agent and in combination with chemotherapy, hormonal agents, or targeted agents in Phase I and Phase II clinical trials.

Ipatasertib has been generally well tolerated, and adverse events have been manageable and reversible. Treatment-related adverse events have included transaminase increased, dehydration, reduced appetite, diarrhea, rash, hyperglycemia, nausea, vomiting, and stomatitis/mucosal inflammation.

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

A11–2.3 BACKGROUND ON FULVESTRANT

Fulvestrant is an estrogen receptor (ER) antagonist that binds to the ER, disrupting the signaling pathway and leading to ER degradation. Fulvestrant is approved for the treatment of postmenopausal patients with HR + HER2-negative breast cancer (HR + breast cancer) who have disease progression following other anti-estrogen therapy (Faslodex® [fulvestrant] prescribing information). The common adverse events associated with the use of fulvestrant include injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, extremity pain, hot flashes, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, constipation, and increases in liver enzymes (AST, ALT, ALP).

A11–3 RATIONALE FOR ATEZO + IPAT + FULVESTRANT ARM

A11–3.1 THE PD-L1 PATHWAY

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 downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and 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 (see Atezolizumab Investigator's Brochure for detailed efficacy results).

PD-L1 expression has been observed in HR+ breast cancer tissues. However, few clinically significant responses to single-agent checkpoint inhibitors have been observed in HR+ breast cancer (Dirix et al. 2016; Rugo et al. 2016), indicating that combination therapy is needed in order to overcome mechanisms of resistance to anti-PD-L1/anti-PD-1 monotherapy.

A11–3.2 PI3K/AKT SIGNALING IN HR+ BREAST CANCER

Akt is the central node of the PI3K-Akt-mammalian target of rapamycin (mTOR) signaling axis and represents a major downstream effector of receptor tyrosine kinases. Activation of the PI3K/Akt pathway results in essential cellular functions including cell survival, growth, and proliferation, which are properties that underlie human cancers. The PI3K/Akt pathway can be activated through loss of the tumor suppressor phosphatase and tensin homolog (PTEN) (Li et al. 1997), through activating mutations and/or amplifications in *PIK3CA* (Bachman et al. 2004), or activating mutations in *AKT1* (Carpten et al. 2007); all these events are frequently observed in HR+ breast cancer.

Up to 70% of breast cancers can have some form of molecular aberration of the PI3K/Akt/mTOR pathway (Cancer Genome Atlas Network 2012). Among the breast cancer subtypes, HR+ breast cancer is associated with the highest prevalence of PI3K pathway activating mutations, making up about 50% of the total HR+ breast cancers (Curtis et al. 2012; Cancer Genome Atlas Network 2012; Wilson et al. 2016). These abnormalities include *PTEN* alterations and *AKT1* and/or *PIK3CA* mutations (Genentech data on meta-analysis of TCGA, METABRIC, and NO17629 studies). Given that the PI3K/Akt pathway in HR+ breast cancer is frequently activated by multiple mechanism, inhibition of Akt represents a compelling and rational potential treatment strategy.

A11–3.3 BENEFIT–RISK ASSESSMENT

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

reduced efficacy of anti-PD1 therapy in melanoma patients. Furthermore, nonclinical studies reveal synergistic anti-tumor responses when combining PI3K-Akt pathway inhibition and PD-L1/PD-1 axis blockade (Peng et al. 2016). In addition, Akt inhibitors may restore and enhance physiological functionalities of T cells in the tumor microenvironment and enhance expansion of tumor-specific lymphocytes with memory cell phenotype (Crompton et al. 2015). Concurrent treatment with ipatasertib may enhance checkpoint inhibitor efficacy by driving development of memory T-cells over effector T-cells, thereby enabling a long-term response in patients (Gubster et al. 2013; Xue et al. 2015).

Fulvestrant is one of several endocrine therapy (ET) regimens for the HR+ breast cancer; therefore these patients will be receiving standard-of-care second-line therapy with this combination regimen. Given that suppression of ER activity (with fulvestrant) may sensitize tumor cells to PI3K/Akt/mTOR inhibition (with ipatasertib) (Bosch et al. 2015), there is additional rationale to test these agents in combination. On the basis of these results—as well as the tolerable safety profiles of atezolizumab, ipatasertib, and fulvestrant—combination treatment with these three agents appears to have promising therapeutic potential in solid tumors such as HR+ breast cancer.

For the evaluation of the impact of the COVID-19 pandemic on the benefit-risk assessment, please refer to Section 1.3.

A11–4 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO+IPAT+FULVESTRANT ARM

A11–4.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 840 mg every 2 weeks (Q2W) (840 mg on Days 1 and 15 of each 28-day cycle). The average concentration following the 840 mg Q2W dosage is expected to be equivalent to that of 1200 mg every 3 weeks (Q3W), the approved dosage for atezolizumab (Tecentriq® U.S. Package Insert). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A11–4.2 RATIONALE FOR IPATASERTIB DOSE AND SCHEDULE

Ipatasertib will be administered orally at a fixed dose of 400 mg once a day (QD) on Days 1–21 of each 28 days cycle. This dose and schedule was selected on the basis of safety data from Arm C of Study PAM4983g, the Phase Ib trial of ipatasertib combined with paclitaxel. In this study, ipatasertib was generally well tolerated when administered at a dose of 400 mg QD on a 21/7 dosing schedule (21 days on and 7 days off), in combination with paclitaxel 90 mg/m^2 administered weekly (3 weeks on and 1 week off). A relative bioavailability study (Study GP29066) has been conducted in healthy volunteers and showed that 400-mg tablet dose of ipatasertib to be used in this study will provide exposures similar to the Phase II 400-mg dose of ipatasertib in the capsule formulation used in Study PAM4983g.

Rationale for PK Sampling

Plasma exposure of ipatasertib and G-037720 (a major metabolite of ipatasertib) will be measured in this study. The remaining PK samples may be used for analysis of other metabolites, method development, or analysis of drug-related markers.

A11–4.3 RATIONALE FOR FULVESTRANT DOSE AND SCHEDULE

In this study, fulvestrant 500 mg will be administered intramuscularly on Days 1 and 15 of Cycle 1. Thereafter, fulvestrant will be administered on Day 1 of each 28-day cycle. This is the current approved fulvestrant dosage for the treatment of HR+ breast cancer.

A11–5 MATERIALS AND METHODS SPECIFIC TO ATEZO + IPAT + FULVESTRANT ARM

A11–5.1 TREATMENT IN ATEZO + IPAT + FULVESTRANT ARM

A11–5.1.1 Formulation, Packaging, and Handling

A11–5.1.1.1 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 and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A11–5.1.1.2 Ipatasertib

Ipatasertib will be supplied as 100-mg tablets packaged in high-density polyethylene bottles for oral administration. For information on the formulation and handling of ipatasertib, see the Ipatasertib Investigator's Brochure.

A11–5.1.1.3 Fulvestrant

Fulvestrant will be supplied as 250-mg/mL sterile liquid. For information on the formulation, packaging, and handling of fulvestrant, refer to the local label.

A11–5.1.2 Dosage, Administration, and Compliance

Patients in the Atezo+Ipat+Fulvestrant arm will receive treatment as outlined in Table A11-1 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) (see Section 3.1.1.1 for details). Treatment must be initiated no later than 7 days after randomization. If initiation of treatment has to be delayed, patient may start treatment at the investigator's discretion. The Medical Monitor is available to advise as needed.

Table A11-1 Treatment Regimen for Atezo+Ipat+Fulvestrant Arm

Cycle Length	Dose, Route, and Regimen **(drugs listed in order of administration)**
28 days	• Ipatasertib 400 mg by mouth once a day on Days 1–21 • Fulvestrant 500 mg by IM injection on Days 1 and 15 of Cycle 1 followed by 500 mg by IM injection on Day 1 of every cycle thereafter • Atezolizumab 840 mg IV infusion on Days 1 and 15

Atezo+Ipat+Fulvestrant = atezolizumab plus ipatasertib plus fulvestrant;
IM=intramuscular.

Refer to Section A11–6.1.5.2 for information on treatment interruptions for patients who experience toxicities. Atezolizumab, ipatasertib, or fulvestrant treatment interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed. The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Any dose modification of any of the study treatments 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 5.4.3.

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

A11–5.1.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Day 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 5. Atezolizumab infusions will be administered per the instructions outlined in Table A11-2.

Table A11-2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion of Atezolizumab	Subsequent Infusions of Atezolizumab
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded 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.	• 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 (±10) minutes after the infusion.

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

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation are provided in Section A11–6.1.5.2 and in Appendix 6.

A11–5.1.2.2 Ipatasertib

Patients will receive ipatasertib at a dose of 400 mg (four 100-mg tablets) orally QD on Days 1–21 of each 28-day cycle. Ipatasertib should be taken approximately the same time each day and no later than 4 hours after the scheduled time. On clinic visit days, patients should take their tablets in the clinic. Ipatasertib may be taken with or without a meal on all days except Day 15 of Cycle 1 of the preliminary phase. On Day 15 of Cycle 1, ipatasertib should be administered with food in the clinic to facilitate time matched PK and glucose measurements post dose and food. Ipatasertib should be swallowed whole with a minimum of 3 ounces (90 mL) of water and should not be

chewed, cut, or crushed. If a dose of ipatasertib is missed (i.e., 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. If any treatment component is interrupted (dose hold), the study cycle day count continues and does not shift. At the discretion of the investigator, if ipatasertib treatment is withheld because of toxicity, the patient is encouraged to make up the missed doses during the 7 days-off week for ipatasertib, so that 21 daily doses in every 28 days is maintained.

Loperamide (2 mg twice a day or 4 mg daily, or per local institutional guidelines) will be administered as prophylaxis for diarrhea in the first cycle. Investigators are encouraged to continue this dosing for the remainder of the study using their discretion based on clinical judgment.

In order to assess the actual intake of ipatasertib and of anti-diarrheal medication use, patients should complete a medication diary each day. Patients will receive the diary on the first day of each cycle, with site staff completing information on any prescribed anti-diarrheal medications, including the recommended dosage and route of administration. Patients should use the diary to record daily ipatasertib dosing and specifically any anti-diarrheal used (prescribed or over-the-counter) taken on that cycle of treatment. The intake of loperamide (or other medication for diarrhea prophylaxis) will be reported in the Concomitant Medications eCRF.

Unless contraindicated, daily oral antihistamine prophylaxis should be used for at least the first cycle. It is suggested that a non-sedating oral antihistamine (such as loratadine, cetirizine, fexofenadine) and longer-acting formulation be used.

Guidelines for dosage modification and treatment interruption or discontinuation because of toxicities are provided in Section A11–6.1.5.2.

A11–5.1.2.3 Fulvestrant

Patients will receive fulvestrant at a dose of 500 mg intramuscularly on Days 1 and 15 of Cycle 1, followed by dosing on Day 1 of every cycle thereafter. Fulvestrant will be administered before the atezolizumab infusion.

A11–5.1.3 Stage 2 Treatment

Patients who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1.1) will be given the option of receiving atezolizumab in combination with bevacizumab plus one of three ET options (fulvestrant, exemestane, or tamoxifen) on the basis of the physician's choice (Atezo + Bev + ET) during Stage 2 of the study, provided they meet eligibility criteria (see Section 4.1) and a Stage 2 arm is open for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit and will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator. However, it is recommended that

patients begin Stage 2 treatment as soon as possible but no earlier than 2 weeks after the last dose of treatment in Stage 1.

Tumor assessments performed prior to or at the time of disease progression, loss of clinical benefit, or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided that the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

A11–5.2 CONCOMITANT THERAPY FOR ATEZO+IPAT+FULVESTRANT ARM

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 10 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.

A11–5.2.1 Permitted Therapy for Atezo+Ipat+Fulvestrant Arm

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

- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section 4.1.2.2).
- 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
- 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 and fulvestrant may be continued during palliative radiotherapy.

  Treatment with ipatasertib should be temporarily held for at least 7 days before and after radiation (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 single-day radiotherapy, this hold may be shorter, if discussed by the investigator with, and approved in advance by, the Medical Monitor.

- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) 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 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 continue on study treatment at the investigator's discretion. The Medical Monitor is available to advise as needed.

- Anti-convulsant therapy, if required, is administered at a stable dose.
- Bisphosphonates or denosumab

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

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 5).

A11–5.2.2 Cautionary Therapy for Atezo+Ipat+Fulvestrant Arm

A11–5.2.2.1 Corticosteroids, *Immunosuppressive Medications,* and Tumor Necrosis Factor-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and tumor necrosis factor alpha (TNF-α) inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator. The Medical Monitor is available to advise as needed.

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

A11–5.2.2.2 Surgery or Radiation

Patients who require radiation or surgery as part of medical treatment in the absence of radiographic disease progression must exercise caution, and ipatasertib 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, ipatasertib may be re-initiated when the patient has sufficiently recovered. For minor surgeries or single-day radiotherapy, this hold may be shorter, if discussed by the investigator with, and approved in advance by, the Medical Monitor.

A11–5.2.2.3 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

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

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

- Strong CYP3A4/5 inhibitors such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and/or grapefruit juice
- Strong CYP3A4/5 inducers such as, but not limited to, rifampin, carbamazepine, rifapentine, phenytoin, phenobarbital, and/or St. John's wort or hyperforin
- Concomitant use of strong and moderate inhibitors of CYP3A (e.g., clarithromycin, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole) should be avoided during ipatasertib treatment because ipatasertib is a sensitive substrate of CYP3A and exposures will be increased in presence of these agents (approximately 7-fold increase in presence of itraconazole in healthy subjects).
- Strong and moderate CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine, and phenobarbital) should be avoided during ipatasertib treatment because they increase the metabolism of ipatasertib. Selection of an alternate concomitant medicinal product with no or minimal potential to induce CYP3A4 should be considered.

- CYP3A4/5 substrates with a narrow therapeutic index such as, but not limited to, alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, ergot alkaloids ergotamine, and/or dihydroergotamine should also be avoided during ipatasertib treatment.

Patients who require short-term use of a strong CYP3A4/5 inhibitor or inducer or use of sensitive CYP3A substrates with a narrow therapeutic window for medical treatment (i.e., an alternative treatment cannot be used) must exercise caution, and ipatasertib should be temporarily held until at least 7 days after the last dose of these drugs. Patients should be closely monitored. Patients are permitted to take moderate inhibitors of CYP3A4 with caution.

Refer to the following information for further guidance on CYP450–drug interactions and a list of common substrates, inhibitors, and inducers:

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

The lists of cautionary medications are not necessarily 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.

A11–5.2.2.4 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section A11–5.2.3) may be used during the study at the discretion of the investigator.

A11–5.2.3 Prohibited Therapy for Atezo+Ipat+Fulvestrant Arm

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

- 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 radiotherapy to the brain under circumstances outlined above in Section A11–5.2.1.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.

- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Quinidine or other anti-arrhythmic agents

  Stable doses of calcium-channel blockers are permitted.

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

A11–5.3 PROHIBITED FOOD FOR ATEZO+IPAT+FULVESTRANT ARM

Grapefruit juice, a potent CYP3A4 enzyme inhibitor, is prohibited during the study and for 30 days after the last dose of ipatasertib.

A11–6 ASSESSMENT OF SAFETY FOR ATEZO+IPAT+FULVESTRANT ARM

A11–6.1 SAFETY PLAN FOR ATEZO+IPAT+FULVESTRANT ARM

The anticipated important safety risks are outlined below (see Sections A11–6.1.1, A11–6.1.2, and A11–6.1.3). Guidelines for management of patients who experience specific adverse events are provided in Section A11–6.1.4. These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit-risk balance when managing individual cases.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Fulvestrant will be administered according to standard institutional practice. 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. Adverse events will be reported as described in Sections 5.2–5.6.

A11–6.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, *facial paresis, myelitis,* meningoencephalitis, myocarditis, *pericardial disorders,* nephritis, myositis, and severe cutaneous adverse reactions. *In addition,* immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis *(HLH)*. Refer to

Appendix 6 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A11–6.1.2 Risks Associated with Ipatasertib

Ipatasertib has been associated with risks such as the following: transaminase increased, dehydration, reduced appetite, nausea, vomiting, diarrhea, stomatitis/mucosal inflammation, asthenia, hyperglycemia, erythema multiforme, and rash.

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

A11–6.1.3 Risks Associated with Fulvestrant

Fulvestrant has been associated with risks such as the following: injection site reactions, asthenia, nausea, and increased hepatic enzymes (ALT, AST, ALP). Refer to the local prescribing information for fulvestrant for a detailed description of all anticipated risks for fulvestrant.

A11–6.1.4 Risks Associated with Combination Use of Atezolizumab+Ipatasertib+Fulvestrant

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

A11–6.1.5 Management of Patients Who Experience Specific Adverse Events in Atezo+Ipat+Fulvestrant Arm

A11–6.1.5.1 Dose Modifications

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

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 A11-3 below. If further dose reduction is indicated after two dose reductions for specified drug-related adverse events, the patient must discontinue ipatasertib but may continue treatment with atezolizumab and fulvestrant at the investigator's discretion.

Table A11-3 Suggested Dose Reductions for Ipatasertib

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

Note: After dose reduction, the dose of ipatasertib may not be re-escalated.

A11–6.1.5.2 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 patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on the investigator's assessment of benefit-risk and documented by the investigator. The Medical Monitor is available to advise as needed. Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's* benefit-risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Ipatasertib treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. *Ipatasertib can be resumed after being withheld for > 28 days if the patient is likely to derive clinical benefit. The decision to re-challenge patients with ipatasertib should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.* If corticosteroids are initiated for treatment of any toxicity, ipatasertib must be held and corticosteroids must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before ipatasertib can be resumed.

In general, the investigator may consider continuing fulvestrant if the observed adverse event is not thought to be fulvestrant-related.

If one or two of the drugs is discontinued, the other drug(s) can be continued if the patient is likely to derive clinical benefit *based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.*

Refer to Section A11–5.1.2 for information on dose interruptions for reasons other than toxicity.

A11–6.1.5.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Appendix 6 and Table A11-4, as outlined below:

- Appendix 6 provides guidelines for the management of patients who experience atezolizumab-associated IRRs and immune-mediated endocrine, pancreatic, neurologic, and meningoencephalitis and ocular events. It is recommended that

atezolizumab be withheld or discontinued per the guidelines in Appendix 6 and that ipatasertib be withheld or discontinued per the guidelines in Table A11-4.

- Table A11-4 provides guidelines for the management of patients who experience the following potential overlapping toxicities: gastrointestinal, dermatologic, hepatic, pulmonary, and hyperglycemia events. It is recommended that study treatments be withheld or discontinued per the guidelines in Table A11-4. For these potential overlapping toxicities, guidelines in Table A11-4 should be followed instead of guidelines in Appendix 6.
- Table A11-4 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 A11-4.

For cases in which management guidelines are not covered in Appendix 6 or Table A11-4, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Please refer to the Fulvestrant local prescribing information for guidelines on the management of patients who experience specific adverse event for fulvestrant.

Table A11-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Ipat + Fulvestrant Arm

Event	Action to Be Taken
IRRs, CRS, and anaphylaxis	• Guidelines for management of IRRs and CRS are provided in Appendix 6. • Withhold ipatasertib. • For anaphylaxis precautions, see Appendix 5. • For severe hypersensitivity reactions, permanently discontinue atezolizumab and ipatasertib.
Gastrointestinal toxicity	
General guidance	• For all patients, dispense loperamide 4 mg once per day as prophylaxis for diarrhea in the first cycle. • After the first cycle, continue this dosing for the remainder of the study as clinically indicated. • All events of diarrhea or colitis should be thoroughly evaluated 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, gastroenterologists should be consulted to rule out the risk of colitis and infection. 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. • 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: <u>Medication</u> — 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 4 mg initial daily dose includes 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 A11-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Ipat + Fulvestrant Arm (cont.)

Event	Action to Be Taken
General guidance (cont.)	— 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 and Gatorade® drinks. — Dose reductions of ipatasertib will be by one level at a time (i.e., 400 to 300 mg; 300 to 200 mg) as outlined in Table A11-3. If Grade ≥2 diarrhea persists following dose reductions of ipatasertib to 200 mg daily and with maximum treatment for diarrhea, ipatasertib should be discontinued. <u>Oral Supplementation</u> — 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. <u>Dietary Modifications</u> — 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.
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 ipatasertib and contact the 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 A11-3) 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.

Table A11-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Ipat + Fulvestrant Arm (cont.)

Event	• Action to Be Taken
Diarrhea, Grade 3	• Withhold ipatasertib and atezolizumab. • 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 the Medical Monitor. [a, b, c] • Interrupt ipatasertib until diarrhea improves to Grade 1 or better. Ipatasertib should be reduced by one dose level (see Table A11-3) when treatment is restarted. • For recurrent Grade 3 diarrhea, reduce ipatasertib dose by one additional dose level (see Table A11-3). • 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.
Diarrhea, Grade 4	• Permanently discontinue atezolizumab and ipatasertib and contact the 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.
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.

Table A11-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Ipat + Fulvestrant Arm (cont.)

Event	Action to Be Taken
Colitis, Grade 2	• Withhold atezolizumab and ipatasertib. • Initiate supportive care and monitor patient closely. • *If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis.* • 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 *upon improvement. If the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • 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 the Medical Monitor. [a, b, c] • If event resolves to Grade 1 or better within 28 days and corticosteroid dose <10 mg oral prednisone or equivalent, 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 *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 the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.* • 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 the Medical Monitor. [a, b, c] • If event resolves to Grade 1 or better within 28 days and corticosteroid dose <10 mg oral prednisone or equivalent, resume ipatasertib with dose reduced by one level. If not, permanently discontinue ipatasertib.

Table A11-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Ipat + Fulvestrant Arm (cont.)

Event	Action to Be Taken
Colitis, Grade 4	• Permanently discontinue atezolizumab and ipatasertib and contact the 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 *corticosteroids equivalent to* 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Endocrine disorders	
Grade 1 hypothyroidism	• Follow atezolizumab-specific guidelines in Appendix 6. • Continue ipatasertib.
Grade 2, 3 or 4 hypothyroidism	• Follow atezolizumab-specific guidelines in Appendix 6. • Continue ipatasertib.
Grade 1 hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Follow atezolizumab-specific guidelines in Appendix 6. • Continue ipatasertib. **TSH < 0.1 mU/L:** • Follow guidelines for *Grade 2* hyperthyroidism.
Grade 2 hyperthyroidism	• Follow atezolizumab-specific guidelines in Appendix 6. • Continue ipatasertib. • For lifethreatening immune-mediated hyperthyroidism, withhold ipatasertib. If event becomes clinically manageable within 28 days, resume ipatasertib with dose reduced by one level. If not, permanently discontinue ipatasertib.
Grade 3 or 4 hyperthyroidism	• *Follow atezolizumab-specific guidelines in* Appendix 6.
Symptomatic adrenal insufficiency, Grade 2, 3, or 4	• Follow guidelines provided in the Atezolizumab Investigator's Brochure. • Withhold ipatasertib; ipatasertib may be resumed when corticosteroids have been tapered to < 10 mg oral prednisone or equivalent.

Table A11-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Ipat + Fulvestrant Arm (cont.)

Event	Action to Be Taken
Hyperglycemia, Any grade	• All events of hyperglycemia should be thoroughly evaluated for more common etiologies other than drug-induced effects. • Investigate for diabetes. If patient has Type 1 diabetes, treat as Grade 3 event. • Workup should include confirmation of fasting blood glucose, urinary glucose and ketones, arterial blood gas, serum bicarbonate, HbA_{1c}, C-peptide levels, anti-islet antibodies, anti-GAD45 antibody. • Hyperglycemia should be treated per institutional guidelines with fluid replacement, insulin, and correction of electrolyte abnormalities.
Hyperglycemia, Grade 1 Fasting glucose value > ULN to 160 mg/dL (8.9 mmol/L)	• Continue atezolizumab and ipatasertib. • The patient should receive education on a diabetic diet and consider home glucose monitoring. • Oral anti-diabetic medications (e.g., metformin) or insulin replacement may be started at the discretion of the investigator, guided by etiology of hyperglycemia.
Hyperglycemia, Grade 2 Fasting glucose value >160–250 mg/dL (>8.9–13.9 mmol/L)	• Withhold atezolizumab and ipatasertib dosing until fasting glucose value resolves to Grade ≤1. (Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines.) • Encourage a diabetic diet and initiate home glucose monitoring. • Start oral anti-diabetic medications (e.g., metformin) or insulin replacement, guided by etiology of hyperglycemia. • If patient is already on an oral anti-diabetic medication, the dose of ipatasertib should be reduced by one dose level (refer to Table A11-3). • 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 A11-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Ipat + Fulvestrant Arm (cont.)

Event	Action to Be Taken
Hyperglycemia, Grade 3 Glucose value 250 to 500 mg/dL (> 13.9–27.8 mmol/L)	• Withhold atezolizumab and ipatasertib dosing until fasting hyperglycemia resolves to Grade ≤ 1 and contact the 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 Grade 3 recurs, the dose of ipatasertib should be reduced by one dose level (see Table A11-3) when treatment is restarted. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hyperglycemia, Grade 4 Glucose value > 500 mg/dL (> 27.8 mmol/L); life-threatening consequences	• Withhold atezolizumab and ipatasertib dosing until fasting glucose value resolves to Grade ≤ 1. • Treat hyperglycemia as per standard of care, noting risk of hypoglycemia if insulin is used. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • Encourage a diabetic diet and initiate home glucose monitoring. • Upon recovery of fasting glucose to Grade ≤ 1, ipatasertib should be reduced by one dose level (Table A11-3) when treatment is restarted. • Resume atezolizumab when symptoms resolve and glucose levels are stable. • If Grade 4 hyperglycemia recurs, permanently discontinue ipatasertib and atezolizumab and contact the Medical Monitor.

Table A11-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Ipat + Fulvestrant Arm (cont.)

Event	Action to Be Taken
Pulmonary events	
General guidance	• All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. • Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab.
Pulmonary event, Grade 1	• Continue atezolizumab and ipatasertib. • 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 *with or without transbronchial biopsy*. • 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 the Medical Monitor. [a, b, c, d] • If event resolves to Grade 1 or better within 28 days and corticosteroid dose < 10 mg oral prednisone or equivalent, resume ipatasertib at current dose. • For recurrent events, treat as a Grade 3 or 4 event.

Table A11-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Ipat + Fulvestrant Arm (cont.)

Event	Action to Be Taken
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and ipatasertib and contact the Medical Monitor. [c, d] • *Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment.* • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL *with or without transbronchial biopsy*. • 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.
Elevations in ALT, AST, and/or bilirubin	
AST/ALT >ULN to ≤3×ULN with total bilirubin ≤2×ULN	• Continue atezolizumab and ipatasertib. • Monitor LFTs until values resolve to within normal limits or to baseline values.
AST/ALT >3×ULN to 5×ULN with total bilirubin >ULN to ≤2×ULN	• Continue atezolizumab and ipatasertib. • Monitor LFTs at least weekly. • Consider patient referral to a hepatologist and liver biopsy. **Suspected immune-mediated events of >5 days' duration:** • Consider withholding atezolizumab and ipatasertib. • Consider initiation of treatment with 1–2 mg/kg/day oral prednisone or equivalent. If corticosteroids are initiated, withhold ipatasertib. • If atezolizumab is withheld and 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 the Medical Monitor. [a, b, c]

Table A11-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Ipat + Fulvestrant Arm (cont.)

Event	Action to Be Taken
AST/ALT > 5 × ULN to < 10 × ULN with total bilirubin > ULN to ≤ 2 × ULN	• Continue atezolizumab and ipatasertib. • Monitor LFTs at least weekly. • Consider patient referral to hepatologist and liver biopsy. **Suspected immune-mediated events:** • Withhold atezolizumab and ipatasertib. • 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 the 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 with total bilirubin > 2 × ULN	• Withhold atezolizumab and ipatasertib. • Monitor LFTs 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 the Medical Monitor. [a, b, c] • If event resolves to AST/ALT ≤ 3 × ULN with total bilirubin ≤ 2 × ULN within 28 days and corticosteroid dose < 10 mg oral prednisone or equivalent, resume ipatasertib with dose reduced by one level. If not, permanently discontinue ipatasertib. • Permanently discontinue atezolizumab and ipatasertib for life-threatening hepatic events and contact the Medical Monitor.

Table A11-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Ipat + Fulvestrant Arm (cont.)

Event	Action to Be Taken
AST/ALT > 10 × ULN	• Permanently discontinue atezolizumab and ipatasertib and contact the Medical Monitor. [c] • Monitor LFTs 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.
Dermatologic toxicity	
General guidance	• Consider having a dermatologist evaluate persistent and/or severe rash or pruritus. • Unless contraindicated, daily oral antihistamine prophylaxis should be used for at least the first cycle. It is suggested that a non-sedating oral antihistamine (such as loratadine, cetirizine, fexofenadine) and longer-acting formulation be used. • Ipatasertib should be permanently discontinued for rash associated with Stevens-Johnson syndrome, toxic epidermal necrolysis, or other suspected severe hypersensitivity or allergic reaction.
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.
Dermatologic event, Grade 2	• Consider referring patient to dermatologist for evaluation and perform a biopsy, if appropriate. • Continue topical corticosteroids and antihistamine administration. • Consider treatment with 10 mg/day oral prednisone or equivalent; treatment with a higher steroid dose may be necessary as clinically indicated. • Ipatasertib: Interrupt ipatasertib treatment until resolution to Grade 1 or better 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 can be continued.

Table A11-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Ipat + Fulvestrant Arm (cont.)

Event	Action to Be Taken
Dermatologic event, Grade 3	• Withhold atezolizumab and ipatasertib. • Refer patient to dermatologist. A biopsy should be performed if appropriate. • If no prior steroid treatment has been initiated, consider treatment with 10 mg/day oral prednisone or equivalent. • If prior oral steroid treatment or no improvement within 48 hours, consider increasing prednisone or equivalent dose to 1–2 mg/kg/day. • Atezolizumab: If event resolves to Grade 1 or better within 12 weeks, resume atezolizumab at a fixed dose. If not, permanently discontinue atezolizumab and contact the Medical Monitor. Only restart atezolizumab (if steroid dose is ≤ 10 mg/day) [a, b, c]. • Ipatasertib: If event resolves to Grade 1 or better or the toxicity is no longer clinically significant, resume ipatasertib at the same dose or dose reduced by one level if considered medically appropriate. Only restart ipatasertib if steroid dose is ≤ 10 mg/day oral prednisone. If not, permanently discontinue ipatasertib. [e]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	• Follow guidelines for atezolizumab in Appendix 6. • Permanently discontinue ipatasertib.
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab and ipatasertib and contact the Medical Monitor. [c, e]
Ipatasertib–related toxicities not described above	
Grade ≥ 3	• Withhold ipatasertib. Continue atezolizumab. • If event resolves to Grade 1 or better within 2 weeks, treatment may resume with ipatasertib at the prior dose level. • If event resolves to Grade 1 or better within 2–4 weeks, the dose of ipatasertib should be reduced by one level per the guidelines in Table A11-3. • Depending on the nature and the severity of the adverse event, if recovery to Grade 1 or better takes > 4 weeks, treatment may resume with the ipatasertib/placebo with dose reduction, or the ipatasertib may be permanently discontinued, at the discretion of the investigator

Table A11-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Ipat + Fulvestrant Arm (cont.)

Event	• Action to Be Taken
Atezolizumab-related toxicities not described above	
Grade ≥ 3	• Follow atezolizumab-specific guidelines in Appendix 6. • Withhold ipatasertib until resolution to Grade 1. • If event resolves to Grade 1 or better within 2 weeks, treatment with ipatasertib may resume at the prior dose level. • If event resolves to Grade 1 or better within 2–4 weeks, the dose of ipatasertib should be reduced by one level per the guidelines in Table A11-3. • Depending on the nature and the severity of the adverse event, if recovery to Grade 1 or better takes >4 weeks, treatment may resume with ipatasertib with dose reduction, or ipatasertib may be permanently discontinued, at the discretion of the investigator.

Atezo + Ipat + Fulvestrant = atezolizumab plus ipatasertib plus fulvestrant; BAL = bronchoscopic alveolar lavage; CRS = cytokine release syndrome; GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; NSAID = non-steroidal anti-inflammatory drug; 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 based on the investigator's benefit-risk assessment and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.*

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re challenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator.*

[d] *In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.*

[e] Resumption of ipatasertib may be considered in patients who are deriving benefit and have fully recovered from the adverse event. *The decision to re challenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator.*

A11–6.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + IPAT + FULVESTRANT ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo + Ipat + Fulvestrant arm 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 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenzalike illness, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, *optic neuritis*)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders
- Vasculitis
- Grade ≥ 3 rash
- Grade ≥ 3 diarrhea or Grade 2 diarrhea that persists for longer than 5 days despite optimal medical management.
- Grade ≥ 3 hyperglycemia
- Grade $\geq$ 3 ALT/AST elevations

- Any grade acute coronary syndrome or myocardial infarction
- Severe cutaneous reactions (e.g., erythema multiforme, Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Autoimmune hemolytic anemia
- *Myelitis*
- *Facial paresis*

A11–7 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO + IPAT + FULVESTRANT ARM

Table A11-5 Schedule of Activities for Atezo + Ipat + Fulvestrant Arm

	Screening [a]	Treatment Cycles (28-day cycles) [b]					Stage 2 Scrn. [d] or Treat. Discon. [e]	Follow-Up
		Cycle 1 [c]			Cycles ≥2			
Assessment/Procedure	–28 to –1	Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)	≤30 Days after Last Dose	Every 3 Months
Informed consent	x [f]							
Demographic data	x							
Medical history and baseline conditions	x							
Molecular profile of HR+ breast cancer (if available)	x	Whenever updated information becomes available						
Vital signs [h]	x	x	x	x	x	x	x	
Weight	x	x [mm]			x [mm]		x	
Height	x							
Complete physical examination [i]	x						x	
Limited physical examination [j]		x [mm]	x		x [mm]			
ECOG Performance Status	x	x [mm]			x [mm]		x	
ECG [k]	x	Perform as clinically indicated					x [g]	
Hematology [l]	x [m]	x [n]		x	x	x	x	
Chemistry [o]	x [m]	x [n]		x	x	x	x	
FSH, LH, and estradiol [p]	x [m]							
Fasting glucose [q]	x [m]	x	x	x	x	x	x	

Appendix 11: Study Details Specific to Atezo + Ipat + Fulvestrant Arm (cont.)

Assessment/Procedure	Screening [a]	Treatment Cycles (28-day cycles) [b]					Stage 2 Scrn. [d] or Treat. Discon. [e]	Follow-Up
		Cycle 1 [c]			Cycles ≥2			
	–28 to –1	Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)	≤30 Days after Last Dose	Every 3 Months
Fasting lipid panel [r]	x [m]	Every 3 cycles from Cycle 3 (Cycles 3, 6, 9, etc.) on Day 1					x	
HbA_{1c}	x [m]	Every 3 cycles from Cycle 3 (Cycles 3, 6, 9, etc.) on Day 1					x	
LDH	x [m]						x [g]	
Amylase and lipase	x [m]	Every 3 cycles from Cycle 3 (Cycles 3, 6, 9, etc.) on Day 1					x	
Coagulation (INR, aPTT)	x [m]						x [g]	
TSH, free T3 (or total T3), free T4 [s]	x [m]	x [s]					x [g]	
Viral serology [t]	x [m]						x [u]	
C-reactive protein	x						x [g]	
Urinalysis [v]	x [m]	Perform as clinically indicated					x [g]	
Serum autoantibody sample [w]	x	Perform if a patient experiences a suspected immune-mediated adverse event						
PK samples		Refer to Table A11-6 and Table A11-7 below						
ADA sample		Refer to Table A11-6 and Table A11-7 below						
Samples for biomarkers		Refer to Table A11-6 and Table A11-7 below						
Blood sample for RBR (optional) [x]		x						
Tumor biopsy	x [y]	x [z]						
Tumor biopsy (optional)		x [aa]						
Tumor response assessments	x [bb]	x [cc, dd, ee]						

Appendix 11: Study Details Specific to Atezo + Ipat + Fulvestrant Arm (cont.)

Assessment/Procedure	Screening [a]	Treatment Cycles (28-day cycles) [b]					Stage 2 Scrn. [d] or Treat. Discon. [e]	Follow-Up
		Cycle 1 [c]			Cycles ≥2			
	–28 to –1	Day 1	Day 8 (±3 days)	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)	≤30 Days after Last Dose	Every 3 Months
Concomitant medications [ff]	x [ff]	x		x	x	x	x	
Adverse events [gg]	x [gg]	x		x	x	x	x [gg]	x [gg]
Dispense ipatasertib [hh, ii]		x			x			
Atezolizumab administration [ii, jj]		x [kk]		x	x	x		
Prophylaxis anti-diarrheal (4 mg QD loperamide or equivalent for the first cycle. If loose watery stools occur, take additional 2 mg after each loose watery stool, and up to 16 mg per day)		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 Table A11-3; anti-diarrheal treatment should also be resumed with loperamide prophylaxis as needed.						
Fulvestrant administration [ii, kk]		x		x	x			
Survival follow-up and anti-cancer treatment								x [ll]

ADA = anti-drug antibody; Atezo + Ipat = atezolizumab plus ipatasertib; CT = computed tomography; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; ET = endocrine therapy; FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LH = luteinizing hormone; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; PET = positron emission tomography; QD = once a day; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; Scrn. = screening; Treat. = treatment.

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

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

Appendix 11: Study Details Specific to Atezo + Ipat + Fulvestrant Arm (cont.)

[b] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window at the investigator's discretion. The Medical Monitor is available to advise as needed.

[c] Treatment must be initiated no later than 7 days after randomization. If initiation of treatment has to be delayed, patient may start treatment at the investigator's discretion. The Medical Monitor is available to advise as needed.

[d] Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) and patients who experience unacceptable toxicity to ipatasertib or fulvestrant will be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Table 6) and will undergo screening assessments to determine eligibility. The Medical Monitor is available to advise as needed. Study-specific details for the Stage 2 treatment regimens are provided in Appendix 12. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[e] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Patients who do not enter Stage 2 will then undergo follow-up assessments. Note that treatment discontinuation assessments will be performed for all patients, regardless of whether they enter Stage 2.

[f] 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.

[g] Assessments to be performed only for patients undergoing Stage 2 screening.

[h] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, 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 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 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.

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

[j] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[l] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[m] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment (Day 1 of Cycle 1).

[n] If screening laboratory assessments were performed within 96 hours prior to dosing, they do not have to be repeated.

[o] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST. Day 15 of Cycle 1 has several glucose measurements (see Table A11-6).

[p] FSH, LH, and estradiol are all required for patients who are <60 years old and in postmenopausal state or who are <60 years old and have had prior ovarian ablation. Only estradiol is required for patients who are <60 years old and are on a LHRH agonist for ovarian suppression.

[q] Fasting glucose on Days 1, 8, and 15 of Cycle 1; Days 1 and 15 of Cycle 2; and Day 1 of every cycle thereafter.

[r] Fasting lipid panel should include cholesterol, HDL, LDL, and triglyceride.

[s] 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.).

[t] At screening, patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.

[u] Viral serology tests are required at Stage 2 screening but are not required at the treatment discontinuation visit. However, patients with a positive quantitative HBV DNA at screening (must be <500 IU/mL per the eligibility criteria) will undergo additional HBV DNA tests on Day 1 of every third cycle (i.e., Cycles 3, 6, 9, etc.), at treatment discontinuation (±7 days), and at 3, 6, 9, and 12 months (±14 days at each timepoint) after treatment discontinuation. Study treatment and procedures may proceed while HBV DNA is being processed, but results should be reviewed by the investigator as soon as they are available. If HBV DNA increases to ≥500 IU/mL, consultation with the Medical Monitor is required prior to continuation of study treatment and consultation with a hepatologist or gastroenterologist with specialty in hepatitis B is recommended.

[v] Includes pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted.

[w] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. For patients who show evidence of immune-mediated toxicity, additional samples may be considered.

[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.

[y] 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. It is preferred 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. Refer to Section 4.5.6 for tissue sample requirements.

Appendix 11: Study Details Specific to Atezo + Ipat + Fulvestrant Arm (cont.)

[z] Patients will undergo tumor biopsy sample collection during Stage 1, at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details), if deemed clinically feasible by the investigator. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. Patients enrolled into the mandatory serial biopsy arm will undergo tumor biopsy sample collection, if deemed clinically feasible by the investigator, at 4 weeks (±7 days) from initiation of study treatment. Refer to Section 4.5.6 for tissue sample requirements.

[aa] Patients will undergo optional tumor biopsy sample collection, if deemed clinically feasible by the investigator, 4 weeks (±7 days) after treatment initiation and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[bb] All measurable and evaluable lesions should be assessed and documented at screening (in both Stage 1 and Stage 2). Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with IV contrast; with or without oral contrast) or MRI scans (with IV contrast) of the chest, abdomen, pelvis, and head with one exception: a head scan is not required at Stage 2 screening. In addition, bone scans, PET scans, and/or skeletal survey should be performed at screening to assess bone lesions. Bone lesions identified at baseline should continue to be assessed following the tumor assessment schedule described above. Additional bone scans, PET scans, or skeletal surveys should be performed if clinically indicated. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans (with IV contrast) of the abdomen and pelvis should be performed. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. Refer to Section 4.5.5 for further details on tumor assessments.

[cc] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 24 weeks following treatment initiation, and every 8 weeks (±1 week) from Week 25 to Week 48, and then every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of atezolizumab-treated patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[dd] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[ee] For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided that the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

[ff] 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 10 days prior to initiation of study treatment until the treatment discontinuation visit.

Appendix 11: Study Details Specific to Atezo + Ipat + Fulvestrant Arm (cont.)

[gg] 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 systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic 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.

[hh] All patients will receive ipatasertib orally once a day on Days 1–21 of each 28-day cycle. At least 7 days off ipatasertib are required prior to starting a new treatment cycle. Ipatasertib should be taken approximately the same time each day and no later than 4 hours after the scheduled time. On clinic visit days, patients should take their tablets in the clinic.

[ii] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details).

[jj] The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[kk] Fulvestrant should be administered intramuscularly into the buttocks slowly (1–2 minutes per injection) as two 5-mL injections, one in each buttock.

[ll] 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 study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

[mm] Assessment may be performed within 24 hours prior to dosing during the treatment period.

Table A11-6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Ipat + Fulvestrant Arm: Preliminary Phase

Visit	Time	Sample
Day 1 of Cycle 1	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
	30 (±10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
Day 15 of Cycle 1	Prior to ipatasertib dose	• Ipatasertib PK (plasma)[a] • Biomarkers (plasma, serum)
	1 hour after ipatasertib dose	• Ipatasertib PK (plasma)[a] • Blood glucose
	2 hours after ipatasertib dose	• Ipatasertib PK (plasma)[a] • Blood glucose
	4 hours after ipatasertib dose	• Ipatasertib PK (plasma)[a] • Blood glucose
	6 hours after ipatasertib dose	• Ipatasertib PK (plasma)[a] • Blood glucose
Day 1 of Cycle 2	Prior to fulvestrant injection	• Fulvestrant PK (plasma)
	Prior to atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to fulvestrant injection	• Fulvestrant PK (plasma)
	Prior to atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 15 of Cycle 3	1–3 hours after ipatasertib dose	• Ipatasertib PK (plasma)[a]
Day 1 of Cycle 4	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycle 8	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)

Table A11-6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Ipat + Fulvestrant Arm: Preliminary Phase (cont.)

Visit	Time	Sample
Treatment discontinuation visit (≤30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
120 (±30) days after last dose of atezolizumab [b]	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)

ADA = anti-drug antibody; Atezo + Ipat + Fulvestrant = atezolizumab plus ipatasertib plus fulvestrant; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

[a] Ipatasertib PK samples may further be used to assay for G-037720 PK as appropriate.

[b] Does not apply for patients enrolling into Stage 2.

Table A11-7 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Ipat + Fulvestrant Arm: Expansion Phase

Visit	Time	• Sample
Day 1 of Cycle 1	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
	30 (±10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
Day 15 of Cycle 1	Prior to ipatasertib dose	• Ipatasertib PK (plasma) [a] • Biomarkers (plasma, serum)
	1–3 hours after ipatasertib dose	• Ipatasertib PK (plasma) [a]
Day 1 of Cycle 2	Prior to fulvestrant injection	• Fulvestrant PK (plasma)
	Prior to atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to fulvestrant injection	• Fulvestrant PK (plasma)
	Prior to atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 15 of Cycle 3	1–3 hours after ipatasertib dose	• Ipatasertib PK (plasma) [a]
Day 1 of Cycle 4	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycle 8	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
120 (±30) days after last dose of atezolizumab [a]	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)

ADA = anti-drug antibody; Atezo + Ipat + Fulvestrant = atezolizumab plus ipatasertib plus fulvestrant; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

[a] Ipatasertib PK samples may further be used to assay for G-037720 PK as appropriate.

[b] Does not apply for patients enrolling into Stage 2.

A11–8 REFERENCES

Bachman KE, Argani P, Samuels Y, et al. The *PIK3CA* gene is mutated with high frequency in human breast cancers. Cancer Biol Ther 2004;3:772–5.

Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. Cancer Immunol Immunother 2005;54:307–14.

Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother 2007;56:739–45.

Bosch A, Li Z, Bergamaschi A, et al. PI3K inhibition results in enhanced estrogen receptor function and dependence in hormone receptor-positive breast cancer. Sci Transl Med. 2015;7:283ra51.

Butte MJ, Keir ME, Phamduy TB. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature 2012;490:61–70.

Carpten JD, Faber AL, Horn C, et al. A transforming mutation in the pleckstrin homology domain of AKT1 in cancer. Nature 2007;448:439–44.

Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012;18:6580–7.

Crompton JG, Sukumar M, Roychoudhuri R, et al. Akt inhibition enhances expansion of potent tumor-specific lymphocytes with memory cell characteristics. Cancer Research 2015;75:296–305.

Curtis C, Shah SP, Chin SF, et al. The genomic and transcriptomic architecture of 2,000 breast tumors reveals novel subgroups. Nature 2012;486:346–52.

Deng R, Bumbaca D, Pastuskovas CV, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. MAbs 2016;8:593–603.

Dirix LY, Takacs I, Nikolinakos P, et al. Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: A Phase Ib JAVELIN solid tumor trial. Cancer Res 2016;76(Suppl):S1–04.

Faslodex® (fulvestrant) prescribing information. Wilmington (DE): AstraZeneca Pharmaceuticals, 2016

Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837–46.

Gubser PM, Bantug GR, Razik L, et al. Rapid effector function of memory CD8+ T cells requires an immediate-early glycolytic switch. Nat Immunol 2013;14:1064–72.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annual Rev Immunol 2008;26:677–704.

Li J, Yen C, Liaw D, et al. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. Science 1997;275:1943–7.

Lin K, Lin J, Wu WI, et al. An ATP-site on-off switch that restricts phosphatase accessibility of Akt. Sci Signal 2012;5:ra37.

Peng W, Chen JQ, Liu C, et al. Loss of PTEN promotes resistance to T cell-mediated immunotherapy. Cancer Discov 2016;6:202–16.

Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.

Rugo HS, Delord JP, Im SA, et al. Preliminary efficacy and safety of pembrolizumab (MK-3475) in patients with PD-L1-positive, estrogen receptor-positive (ER+)/HER2-negative advanced breast cancer enrolled in KEYNOTE-028. Cancer Res 2016;76(Suppl):S5–07.

Tecentriq® (atezolizumab) U.S. prescribing information. South San Francisco (CA): Genentech, 2016.

Wilson TR, Yu J, Lu X, et al. The molecular landscape of high-risk early breast cancer: comprehensive biomarker analysis of a phase III adjuvant population. NPJ Breast Cancer 2016;2:16022.

Xue G, Zippelius A, Wicki A, et al. Integrated Akt/PKB signaling in immunomodulation and its potential role in cancer immunotherapy. J Natl Cancer Inst 2015;107:1–10.

Yang J, Riella LV, Chock S. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. J Immunol 2011;187:1113–9.

Appendix 12
Study Details Specific to Atezo + Bev + ET Arm (Stage 2)

A12–1 TABLE OF CONTENTS

A12–2 BACKGROUND ON ATEZO + BEV+ET ARM

A12–2.1 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 cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with dose interruption or treatment, and patients are eligible to continue atezolizumab.

Atezolizumab (Tecentriq®) was first approved in the United Stated for the treatment of patients with locally advanced or metastatic urothelial carcinoma and for the treatment of patients with metastatic non–small cell lung cancer (NSCLC). Marketing Authorization Applications are being submitted globally, and approvals have already been received in a few countries.

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

A12–2.2 BACKGROUND ON BEVACIZUMAB

Vascular endothelial growth factor (VEGF) is the most important pro-angiogenic factor and a key regulator of physiological angiogenesis. It is also implicated in pathological angiogenesis such as that associated with tumor growth. Increased levels of VEGF have been found in many tumors examined to date, including breast cancer tumors where overexpression is associated with a poorer prognosis (Eppenberger et al. 1998; Gasparini 2000).

Bevacizumab is a recombinant humanized monoclonal antibody that recognizes all isoforms of VEGF. It may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor microenvironment. Additional anti-tumor activity may be on tumor vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced chemotherapy delivery to tumor cells (Jain 2001).

Bevacizumab is approved in over 40 countries worldwide for the first-line treatment of metastatic colorectal cancer (CRC) in combination with chemotherapy, as second-line CRC treatment, and first-line treatment of advanced NSCLC, metastatic breast cancer, advanced renal cell carcinoma (RCC), ovarian cancer, and glioblastoma.

Bevacizumab is currently being tested in combination with atezolizumab in Phase I and Phase II clinical trials. Bevacizumab has been generally well tolerated, and adverse events have been manageable.

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

A12–2.3 BACKGROUND ON FULVESTRANT

Fulvestrant is an estrogen receptor (ER) antagonist that binds to the ER, disrupting the signaling pathway and leading to ER degradation. Fulvestrant is approved for the treatment of postmenopausal patients with HR+ HER2-negative breast cancer (HR + breast cancer) who have disease progression following other anti-estrogen therapy (Faslodex® [fulvestrant] prescribing information). The common adverse events associated with the use of fulvestrant include injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, extremity pain, hot flashes, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, constipation, and increases in liver enzymes (AST, ALT, ALP). In randomized studies that compared fulvestrant with anastrozole, similar rates of common adverse events were reported, with the exception of injection-site pain.

A12–2.4 BACKGROUND ON EXEMESTANE

Aromatase is a rate-limiting enzyme involved in estrogen production, converting androstenedione and estrone into estrogen via aromatization. Exemestane is one of various aromatase inhibitors (AI) approved for the treatment of postmenopausal women. Although premenopausal women produce too much aromatase for single agent activity, AIs including exemestane may be used in these patients when administered in combination with ovarian suppressors.

Unlike anastrozole and letrozole, which temporarily inhibits aromatase activity, exemestane is a known irreversible AI.

A12–2.5 BACKGROUND ON TAMOXIFEN

Tamoxifen binds directly to estrogen receptor and is a known selective estrogen receptor modulator with both agonist and antagonist roles. Tamoxifen is considered a standard of care for premenopausal breast cancer and has been used for more than 30 years to treat HR + breast cancer.

A12–3 RATIONALE FOR ATEZO + BEV + ET ARM

A12–3.1 THE PD-L1 PATHWAY

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 downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and 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, RCC, melanoma, CRC, head and neck cancer, gastric cancer, breast cancer, and sarcoma (see Atezolizumab Investigator's Brochure for detailed efficacy results).

PD-L1 expression has been observed in HR + breast cancer tissues. However, no clinically significant response to single-agent checkpoint inhibitors has been observed in HR + breast cancer (Dirix et al. 2016; Rugo et al. 2016).

A12–3.2 BEVACIZUMAB AS AN IMMUNOMODULATOR

Bevacizumab is a recombinant, humanized therapeutic antibody directed against VEGF. In addition to promoting tumor angiogenesis, there is increasing evidence that VEGF

plays a role in cancer immune evasion through several different mechanisms. For example, experiments with activated endothelial cells suggested that in the tumor microenvironment, VEGF may reduce lymphocyte adhesion to vessel walls, thus contributing to decreased immune cell recruitment to the tumor site (Bouzin et al. 2007). Some immunosuppressive activities of VEGF can be reversed by inhibition of VEGF signaling. Accordingly, mice exposed to pathophysiological levels of VEGF exhibited impaired dendritic cell function, which could be restored by blockade of VEGF receptor 2 (Huang et al. 2010).

In a murine melanoma model, the VEGF blockade synergized with adoptive immunotherapy as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010). Synergistic effects have also been observed in a clinical study combining an immunomodulatory antibody (anti-cytotoxic T lymphocyte-associated antigen 4 [anti-CTLA-4]; ipilimumab) and bevacizumab: Hodi et al. (2010) described increased T-cell trafficking in post-treatment biopsies, as well as marked increased in central memory cells in peripheral blood in the majority of patients.

A12–3.3 BENEFIT–RISK ASSESSMENT

As described in Section A12–3.2, bevacizumab has immunomodulatory properties that include increased T-cell trafficking into tumors and the reduction of suppressive cytokines and infiltrating regulatory T cells. Meta-analysis of data pooled from three separate HER2-negative metastatic breast cancer Phase III trials (E2100, AVADO, RIBBON-1) demonstrate an improved response rate and progression-free survival when combined with chemotherapy, although overall survival was not significantly affected (Miles et al. 2013). These data, in combination with nonclinical and clinical data for bevacizumab plus immune checkpoint inhibition (i.e., ipilimumab), suggest a potential added benefit for combining bevacizumab and atezolizumab. Therefore, combining bevacizumab with blockade of the PD-L1/PD-1 pathway with atezolizumab may result in an enhanced protective anti-tumor immune response. Furthermore, the addition of endocrine therapy (ET) to bevacizumab and atezolizumab will ensure that these patients continue to receive standard of care therapy, supporting the study of this treatment combination for patients with HR + breast cancer.

For the evaluation of the impact of the COVID-19 pandemic on the benefit-risk assessment, please refer to Section 1.3.

A12–4 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO + BEV + ET ARM

A12–4.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 840 mg every 2 weeks (Q2W) (840 mg on Days 1 and 15 of each 28-day cycle) or a fixed dose of 1200 mg Q3W (1200 mg on Day 1 of each 21-day cycle) based on the selection of ET that will be administered in combination with atezolizumab and bevacizumab; refer to Table A12-1, Table A12-2, and Table A12-3). The average concentration following the 840 mg Q2W dosage is expected to be equivalent to that of 1200 mg every 3 weeks (Q3W), the approved dosage for atezolizumab (Tecentriq® U.S. Prescribing Information). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A12–4.2 RATIONALE FOR BEVACIZUMAB DOSE AND SCHEDULE

Bevacizumab will be administered intravenously at a fixed dose of 10 mg/kg Q2W (10 mg/kg on Days 1 and 15 of each 28-day cycle) or a fixed dose of 15 mg/kg every 3 weeks (Q3W) (15 mg/kg on Day 1 of each 21-day cycle) based on the selection of ET that will be administered in combination with atezolizumab and bevacizumab; refer to Table A12-1, Table A12-2, and Table A12-3. This dose and schedule were selected on the basis of both nonclinical studies and available clinical data and are the doses recommended for use for indications in which bevacizumab is approved. Furthermore, these doses have been previously tested in combination with atezolizumab demonstrating tolerability without exacerbation of bevacizumab or atezolizumab-associated adverse events (Refer to the Bevacizumab and Atezolizumab Investigator's Brochures for further details).

A12–4.3 RATIONALE FOR FULVESTRANT DOSE AND SCHEDULE

In this study, fulvestrant 500 mg will be administered intramuscularly on Days 1 and 15 of Cycle 1. Thereafter, fulvestrant will be administered on Day 1 of each 28-day cycle. This is the current approved fulvestrant dosage for the treatment of HR+ breast cancer. If a patient has already received treatment with fulvestrant during Stage 1 and the last fulvestrant administration is within 6 weeks of Cycle 1 Day 1 of Stage 2, the Cycle 1 Day 15 fulvestrant administration should be omitted.

A12–4.4 RATIONALE FOR EXEMESTANE DOSE AND SCHEDULE

In this study, exemestane 25 mg will be administered orally once a day (QD) for each 21-day cycle. This is the current approved exemestane dosage for the treatment breast cancer.

A12–4.5 RATIONALE FOR TAMOXIFEN DOSE AND SCHEDULE

In this study, tamoxifen 20 mg will be administered orally QD for each 21-day cycle. This is the current approved tamoxifen dosage for the treatment breast cancer.

A12–5 MATERIALS AND METHODS SPECIFIC TO ATEZO+BEV+ET ARM

A12–5.1 TREATMENT IN ATEZO+BEV+ET ARM

A12–5.1.1 Formulation, Packaging, and Handling

A12–5.1.1.1 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 and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A12–5.1.1.2 Bevacizumab

The bevacizumab drug product will be supplied by the Sponsor as a sterile liquid in single-use 400-mg preservative-free glass vials to deliver 4 mL or 16 mL bevacizumab (25 mg/mL). The vial contains approximately 4 mL or 16 mL of bevacizumab solution.

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

A12–5.1.1.3 Fulvestrant

Fulvestrant will be supplied as 250-mg/mL sterile liquid. For information on the formulation, packaging, and handling of fulvestrant, refer to the local label.

A12–5.1.1.4 Exemestane

Exemestane will be supplied as 25-mg tablets for oral administration. For information on the formulation, packaging, and handling of exemestane, refer to the local label.

A12–5.1.1.5 Tamoxifen

Tamoxifen will be supplied as 10-mg or 20-mg tablets for oral administration. For information on the formulation, packaging, and handling of tamoxifen, refer to the local label.

A12–5.1.2 Dosage, Administration, and Compliance

Patients in the atezolizumab plus bevacizumab plus ET (Atezo + Bev + ET) arm will receive treatment as outlined in Table A12-1 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) (see Section 3.1.1.1 for details).

Table A12-1 Treatment Regimen for Atezo + Bev + Fulvestrant

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• Fulvestrant 500 mg IM injection on Days 1 and 15 of Cycle 1 followed by 500 mg IM injection on Day 1 of every cycle thereafter [a] • Atezolizumab 840 mg by IV infusion on Days 1 and 15 • Bevacizumab 10 mg /kg by IV infusion on Days 1 and 15

Atezo + Bev + Fulvestrant = atezolizumab plus bevacizumab plus fulvestrant; IM = intramuscular.

[a] If a patient has already received treatment with fulvestrant during Stage 1 and the last fulvestrant administration is within 6 weeks of Cycle 1 Day 1 of Stage 2, the Cycle 1 Day 15 fulvestrant administration should be omitted.

Table A12-2 Treatment Regimen for Atezo + Bev + Exemestane

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Exemestane 25 mg by mouth once a day • Atezolizumab 1200 mg by IV infusion on Day 1 • Bevacizumab 15 mg/kg by IV infusion on Day 1

Atezo + Bev + Exemestane = atezolizumab plus bevacizumab plus exemestane.

Table A12-3 Treatment Regimen for Atezo + Bev + Tamoxifen

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	• Tamoxifen 20 mg by mouth once a day • Atezolizumab 1200 mg by IV infusion on Day 1 • Bevacizumab 15 mg/kg by IV infusion on Day 1

Atezo + Bev + Tamoxifen = atezolizumab plus bevacizumab plus tamoxifen.

Refer to Section A12–6.1.7.2 for information on treatment interruptions for patients who experience toxicities. Atezolizumab, bevacizumab, or ET treatment interruptions for

reasons other than toxicity (e.g., surgical procedures) may be allowed. The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Any dose modification of any of the study treatments 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 5.4.3.

No safety data related to overdosing of atezolizumab, bevacizumab, or fulvestrant are available to date. For information on overdosing of exemestane or tamoxifen, refer to the local prescribing information for each agent.

A12–5.1.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Day 1 and 15 of each 28-day cycle or at a fixed dose of 1200 mg on Day 1 of each 21-day cycle, depending on the selection of ET (refer to Table A12-1, Table A12-2, and Table A12-3).

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 5. Atezolizumab infusions will be administered per the instructions outlined in Table A12-4.

Table A12-4 Administration of First and Subsequent Atezolizumab Infusions

First Infusion of Atezolizumab	Subsequent Infusions of Atezolizumab
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded 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.	• 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 (± 10) minutes after the infusion.

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

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation because of toxicities are provided in Section A12–6.1.7.2 and in Appendix 6.

A12–5.1.2.2 Bevacizumab

Bevacizumab will be administered by IV infusion at a fixed dose of 10 mg/kg on Day 1 and 15 of each 28-day cycle or at a fixed dose of 15 mg/kg on Day 1 of each 21-day cycle depending on the selection of ET (see Table A12-1, Table A12-2, and Table A12-3).

Administration of bevacizumab 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 5. Bevacizumab infusions will be administered per the instructions outlined in Table A12-5.

Guidelines for dosage modification and treatment interruption or discontinuation because of toxicities are provided in Section A12–6.1.7.2.

Table A12-5 Administration of First and Subsequent Bevacizumab Infusions

First Infusion of Bevacizumab	Subsequent Infusions of Bevacizumab
• No premedication is permitted. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. • Bevacizumab should be infused over 90 (± 15) minutes. • Vital signs should be at the end of infusion and 2 (± 1) hours after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.	• If the patient 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. • Bevacizumab should be infused over 60 (± 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 90 (± 15) minutes if the patient experienced an infusion-related reaction with the previous infusion. If the 60-minute infusion was well tolerated, bevacizumab may be infused over 30 (± 15) minutes thereafter. • Vital signs should be at the end of infusion and 2 (± 1) hours after the infusion.

A12–5.1.2.3 Fulvestrant

Patients will receive fulvestrant at a dose of 500 mg intramuscularly on Days 1 and 15 of Cycle 1, followed by dosing on Day 1 of every 28-day cycle thereafter.

A12–5.1.2.4 Exemestane

Patients will receive exemestane at a dose of 25 mg (one 25-mg tablet) orally QD for each 21-day cycle. Exemestane should be taken approximately the same time each day and no later than 4 hours after the scheduled time. Exemestane must be taken after a meal. Exemestane should be swallowed whole with a minimum of 3 ounces (90 mL) of water and should not be chewed, cut, or crushed. If a dose of exemestane is missed (i.e., 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.

A12–5.1.2.5 Tamoxifen

Patients will receive tamoxifen at a dose of 20 mg orally once a day (QD) for each 21-day cycle.

Tamoxifen should be taken approximately the same time each day and no later than 4 hours after the scheduled time. Tamoxifen may be taken with or without a meal. Tamoxifen should be swallowed whole with a minimum of 3 ounces (90 mL) of water and should not be chewed, cut, or crushed. If a dose of tamoxifen is missed (i.e., 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.

A12–5.2 CONCOMITANT THERAPY FOR ATEZO + BEV + ET ARM

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 10 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.

A12–5.2.1 Permitted Therapy for Atezo + Bev + ET Arm

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

- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section 4.1.2.2).
- 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
- 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 Atezo + Bev + ET may be continued during palliative radiotherapy.
- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may

receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) 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 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 continue on study treatment at the investigator's discretion. The Medical Monitor is available to advise as needed.
- Anti-convulsant therapy, if required, is administered at a stable dose.

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

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 5).

A12–5.2.2 Cautionary Therapy for Atezo + Bev + ET Arm

A12–5.2.2.1 Corticosteroids, *Immunosuppressive Medications,* and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, 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, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator. The Medical Monitor is available to advise as needed.

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

A12–5.2.2.2 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

Strong and moderate CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine, and phenobarbital) should be avoided during exemestane and tamoxifen treatment because they increase the metabolism of exemestane. Strong inducers of CYP3A4 should be avoided, or selection of an alternate concomitant medicinal product with no or minimal potential to induce CYP3A4 should be considered. In addition, strong CYP2D6 inhibitors (e.g., celecoxib, methadone) should be avoided during tamoxifen treatment. Weak to moderate CYP2D6 inhibitors (e.g., risperidone, venlafaxine) should be used with caution during tamoxifen treatment.

A12–5.2.2.3 Bisphosphonates

Osteonecrosis of the jaw has been reported in patients receiving bevacizumab, mainly in combination with bisphosphonates. Thus, caution must be exercised in using bevacizumab in patients receiving concomitant bisphosphonates.

The lists of cautionary medications are not necessarily comprehensive. The investigator should consult the prescribing information when determining whether a concomitant medication can be safety administered with study treatment. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

A12–5.2.2.4 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer (see Section A12–5.2.3) may be used during the study at the discretion of the investigator.

A12–5.2.3 Prohibited Therapy for Atezo + Bev + ET Arm

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

- 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 radiotherapy to the brain under circumstances outlined above in Section A12–5.2.1.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.

- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Antithrombotic treatment with aspirin (> 325 mg/day) or clopidogrel (> 75 mg/day) is prohibited.

A12–6 ASSESSMENT OF SAFETY FOR ATEZO + BEV + ET ARM

A12–6.1 SAFETY PLAN FOR ATEZO + BEV + ET ARM

The anticipated important safety risks are outlined below (see Sections A12–6.1.1 through A12–6.1.6). Guidelines for management of patients who experience specific adverse events are provided in Section A12–6.1.7. These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit-risk balance when managing individual cases.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. Fulvestrant, exemestane, and tamoxifen will be administered according to standard institutional practice. Administration of atezolizumab and bevacizumab 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. Adverse events will be reported as described in Sections 5.2–5.6.

A12–6.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, *facial paresis, myelitis,* meningoencephalitis, myocarditis, *pericardial disorders,* nephritis, myositis, and severe cutaneous adverse reactions. *In addition,* immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis *(HLH)*. Refer to Appendix 6 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A12–6.1.2 Risks Associated with Bevacizumab

Bevacizumab has been associated with risks such as the following: GI perforations, fistulae, hemorrhage, hypertension, posterior reversible encephalopathy syndrome (PRES), arterial and venous thromboembolic events, congestive heart failure (CHF), other cardiac disorders, neutropenia and infection, wound-healing complications, proteinuria, hypersensitivity or IRRs, osteonecrosis of the jaw, ovarian failure, and pulmonary hypertension. Refer to Section 6 of the Bevacizumab Investigator's Brochure for a detailed description of all anticipated risks for bevacizumab.

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

Perforations and Fistulae

Guidelines for management of patients who develop a perforation or fistula are provided in Table A12-6.

Gastrointestinal Perforation and Fistula. Bevacizumab has been associated with serious cases of GI perforation in patients with metastatic CRC, and a few reports of gallbladder perforation have been reported from the postmarketing experience. Presentation of these events has varied in type and severity, ranging from free air seen only on the plain abdominal X-ray, which resolved without treatment, to a colonic perforation with abdominal abscess and fatal outcome. In some cases, the underlying intra-abdominal inflammation was present, either from gastric ulcer disease, tumor necrosis, diverticulitis, or chemotherapy-associated colitis. A causal association of an intra-abdominal inflammatory process and GI perforation to treatment with bevacizumab has not been established. However, caution should be exercised when treating patients with intra-abdominal inflammatory process with bevacizumab. Patients treated with bevacizumab for persistent, recurrent, or metastatic cervical cancer may be at increased risk of fistulae between the vagina and any part of the GI tract. Fatal outcomes have been reported in cases of GI perforations.

Bevacizumab use has been associated with serious cases of fistula, including events resulting in death. Fistulae within the GI tract are common in patients with metastatic CRC and ovarian cancer, but are uncommon or rare in other indications. Patients who develop GI–vaginal fistulae may also have bowel obstructions and may require surgical intervention as well as diverting ostomies.

Non-Gastrointestinal Fistula. Bevacizumab use has been associated with serious cases of non-GI fistula, including events resulting in death. Patients may be at increased risk for the development of non-GI fistulae when treated with bevacizumab. Other fistulae (e.g., bronchopleural, tracheoesophageal, urogenital, biliary) have been reported uncommonly in bevacizumab clinical trials patients and in postmarketing reports.

Hemorrhage

In clinical trials, an increased incidence of bleeding events has been observed in patients treated with bevacizumab compared with control. The hemorrhagic events observed in bevacizumab studies were predominantly tumor-associated hemorrhage and minor mucocutaneous hemorrhage. Patients with untreated CNS metastases were routinely excluded from clinical trials with bevacizumab, on the basis of imaging procedures or signs and symptoms. Therefore, the risk of CNS hemorrhage in such patients has not been prospectively evaluated in randomized clinical studies. Patients should be monitored for signs and symptoms of CNS bleeding.

Guidelines for management of patients who develop a hemorrhage are provided in Table A12-6.

Hypertension

An increased incidence of hypertension has been observed in patients treated with bevacizumab. Clinical safety data suggest the incidence of hypertension is likely to be dose dependent. Preexisting hypertension should be adequately controlled before starting bevacizumab treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating therapy. In most cases, hypertension is controlled adequately by standard anti-hypertensive treatment. Very rare cases of hypertensive encephalopathy have been reported, some of which were fatal. Blood pressure must be assessed before each bevacizumab administration.

Guidelines for management of patients who develop hypertension are provided in Table A12-6.

Posterior Reversible Encephalopathy Syndrome

There have been rare reports of patients treated with bevacizumab developing signs and symptoms that are consistent with PRES, a rare neurological disorder (also known as reversible posterior leukoencephalopathy syndrome). PRES can present with the following signs and symptoms (among others): seizures, headache, altered mental status, or visual disturbance or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by magnetic resonance imaging (MRI) of the brain. In patients developing PRES, treatment of specific symptoms, including control of hypertension, is recommended. The safety of re-initiating bevacizumab therapy in patients previously experiencing PRES is not known. Adequate brain imaging through use of MRI must be performed as a follow-up measurement for patients with PRES.

Guidelines for management of patients who develop PRES are provided in Table A12-6.

Thromboembolism

Guidelines for management of patients who develop a thromboembolism are provided in Table A12-6.

Arterial Thromboembolism. In clinical trials, the incidence of arterial thromboembolism reactions, including cerebrovascular accidents, transient ischemic attack, and myocardial infarction, was higher in patients receiving bevacizumab in combination with chemotherapy compared with those receiving chemotherapy alone. Patients receiving bevacizumab plus chemotherapy with a history of arterial thromboembolism, diabetes, or age >65 years have an increased risk of developing arterial thromboembolic events during bevacizumab therapy. Caution should be taken when treating these patients with bevacizumab.

Venous Thromboembolism. Patients may be at risk of developing venous thromboembolic reactions, including pulmonary embolism, while receiving bevacizumab. An increased risk of venous thromboembolic events and bleeding has been observed in bevacizumab-treated patients receiving anticoagulation therapy after an initial venous thromboembolic event. Patients with venous thromboembolisms should be managed and monitored with appropriate medical therapy.

Congestive Heart Failure

Events consistent with CHF have been reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction to symptomatic CHF requiring treatment or hospitalization. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, has received prior radiotherapy to the left chest wall, or had other risk factors for CHF. Caution should be exercised when administering bevacizumab to patients with clinically significant cardiovascular disease, such as preexisting coronary artery disease, concomitant cardiotoxic therapy, or CHF.

Guidelines for management of patients who develop CHF are provided in Table A12-6.

Other Cardiac Disorders

Cardiac disorders, including arrhythmias, have been seen in clinical trials using bevacizumab in combination with 5-FU and leucovorin or bevacizumab in combination with capecitabine and oxaliplatin. However, for the vast majority of cases, the patient's history included preexisting underlying cardiovascular diseases, concomitant treatment with potentially arrhythmogenic medications, or severe intercurrent illnesses.

Neutropenia and Infection

Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some

myelotoxic chemotherapy regimens plus bevacizumab compared with chemotherapy alone.

Guidelines for management of patients who develop neutropenia are provided in Table A12-6.

Wound-Healing Complications

Bevacizumab may adversely affect the wound-healing process. Serious wound-healing complications with a fatal outcome have been reported. Bevacizumab therapy should not be initiated in patients who have had major surgery within the previous 28 days or patients with a surgical wound that has not fully healed. Bevacizumab therapy should be withheld for a minimum of 28 days prior to major elective surgery. Emergency surgery should be performed as appropriate without delay after a careful benefit–risk assessment.

Necrotizing fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab, usually secondary to wound-healing complications, GI perforation, or fistula formation.

Guidelines for management of patients who develop necrotizing fasciitis or wound dehiscence are provided in Table A12-6.

Proteinuria

In clinical studies, the incidence of proteinuria was higher in patients receiving bevacizumab in combination with chemotherapy compared with those receiving chemotherapy alone. Proteinuria reported in patients receiving bevacizumab has ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome. Nephrotic syndrome was seen in up to 1.4% of treated patients. Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. Patients with proteinuria will be excluded from bevacizumab-containing arms.

Guidelines for management of patients who develop proteinuria are provided in Table A12-6.

Hypersensitivity or Infusion-Related Reactions

Patients may be at risk of developing hypersensitivity or IRRs to bevacizumab. Patients will be closely monitored during and following administration of bevacizumab. Systematic premedication is not warranted.

Guidelines for management of patients who develop hypersensitivity reactions or IRRs are provided in Table A12-6.

Osteonecrosis of the Jaw

Osteonecrosis of the jaw has been reported in patients receiving bevacizumab, mainly in combination with bisphosphonates in the postmarketing setting. The pathogenesis of the osteonecrosis is unclear. Caution must be exercised in using bevacizumab in patients receiving concomitant bisphosphonates.

Pulmonary Hypertension

Pulmonary hypertension has been seen in patients treated with bevacizumab, primarily in the postmarketing setting. Patients at risk included those with preexisting cardiac disease, pulmonary disease, thromboembolic disease, metastasis to the lungs, or use of other medications associated with pulmonary hypertension.

Guidelines for management of patients who develop hypertension are provided in Table A12-6.

A12–6.1.3 Risks Associated with Fulvestrant

Fulvestrant has been associated with risks such as the following: injection site reactions, asthenia, nausea, and increased hepatic enzymes (ALT, AST, ALP). Refer to the local prescribing information for fulvestrant for a detailed description of all anticipated risks for fulvestrant.

A12–6.1.4 Risks Associated with Exemestane

Exemestane has been associated with risks such as the following: hot flashes, arthralgia, and fatigue. Refer to the local prescribing information for exemestane for a detailed description of all anticipated risks for exemestane.

A12–6.1.5 Risks Associated with Tamoxifen

Tamoxifen has been associated with risks such as the following: stroke, pulmonary embolism, and uterine malignancies. Refer to the local prescribing information for tamoxifen for a detailed description of all anticipated risks for tamoxifen.

A12–6.1.6 Risks Associated with Combination Use of Atezo+Bev+ET

Refer to the Atezolizumab and Bevacizumab Investigator's Brochures and local prescribing information for a detailed description of all anticipated risks.

A12–6.1.7 Management of Patients Who Experience Specific Adverse Events in Atezo+Bev+ET Arm

A12–6.1.7.1 Dose Modifications

There will be no dose modifications for atezolizumab, bevacizumab, fulvestrant, exemestane, or tamoxifen in this study.

A12–6.1.7.2 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 patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on investigator's benefit-risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.
Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's* benefit-risk *assessment* and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Temporary suspension of bevacizumab must occur if a patient experiences a serious adverse event or a Grade 3 or 4 non-serious adverse event assessed by the investigator as related to bevacizumab. If the event resolves to Grade ≤1, bevacizumab may be restarted at the same dose level. If bevacizumab is delayed due to toxicity for >42 days beyond when the next dose should have been given, the patient must be permanently discontinued from bevacizumab. Bevacizumab can be resumed after being withheld for >12 weeks if the patient is likely to derive clinical benefit. *The decision to re-challenge patients with bevacizumab should be based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.*

In general, the investigator may consider continuing fulvestrant, exemestane, and tamoxifen if the observed adverse event is not thought to be ET-related.

If one or two of the drugs is discontinued, the other drug(s) can be continued if the patient is likely to derive clinical benefit *based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.*

Refer to Section A12–5.1.2 for information on dose interruptions for reasons other than toxicity.

A12–6.1.7.3 Management Guidelines for Adverse Events

Please refer to the local prescribing information for fulvestrant, exemestane, and tamoxifen for guidelines on the management of patients who experience specific adverse events each ET.

Guidelines for the management of patients who experience specific adverse events are provided in Appendix 6 and Table A12-6, as outlined below:

- Appendix 6 provides guidelines for the management of patients who experience atezolizumab-associated IRRs and immune-mediated pulmonary, hepatic, gastrointestinal, endocrine, ocular, pancreatic, dermatologic, neurologic, and meningoencephalitis events. It is recommended that atezolizumab be withheld or discontinued per the guidelines in Appendix 6.
- Table A12-6 provides guidelines for the management of patients who experience adverse events associated with bevacizumab. It is recommended that bevacizumab be withheld or discontinued per the guidelines in Table A12-6.
- For cases in which management guidelines are not covered in Table A12-6 or Appendix 6 for atezolizumab, patients should be managed and treatments should be withheld or discontinued as deemed appropriate by the investigator according to best medical judgment.

Bevacizumab-Specific General Guidelines

- Temporary suspension of bevacizumab must occur if a patient experiences a serious adverse event or a Grade 3 or 4 nonserious adverse event assessed by the investigator as related to bevacizumab. If the event resolves to Grade ≤ 1, bevacizumab may be restarted at the same dose level.
- Surgery

  The appropriate interval between the last dose of bevacizumab and major surgery is unknown. Because bevacizumab has a half-life of approximately 21 days, elective surgery should be delayed whenever possible, but if necessary, bevacizumab should be withheld for ≥ 28 days prior to the procedure. Re-initiation of bevacizumab following surgery should not occur for ≥ 28 days and until wounds have fully healed. Re-initiation of bevacizumab after surgery requires documented approval from the Medical Monitor.
- Infusion-Associated Events

  Infusion of bevacizumab should be interrupted in patients who develop dyspnea or clinically significant hypotension. Patients who experience a National Cancer Institute Common Terminology Criteria for Adverse Events Grade 3 or 4 allergic reaction/hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment. If possible, a sample for anti-drug antibody assessment will be collected at the time of discontinuation.

  Bevacizumab infusion should be slowed to ≤ 50% or interrupted for patients who experience any infusion-associated symptoms not specified above. If the

  infusion is interrupted, it may be resumed at ≤ 50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in

50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.

Table A12-6 Guidelines for Management of Patients Who Experience Bevacizumab-Specific Adverse Events

Event	Action to Be Taken
Posterior reversible encephalopathy syndrome	Permanently discontinue bevacizumab.
GI perforation and fistula	
GI perforation, any grade	Permanently discontinue bevacizumab.
Tracheoesophageal fistula, any grade	Permanently discontinue bevacizumab.
Non-tracheoesophageal fistula, Grade 2 or 3	Withhold bevacizumab until resolution to Grade 1 or better.
Non-tracheoesophageal fistula, Grade 4	Permanently discontinue bevacizumab.
Non-GI internal fistula	Consider permanent discontinuation of bevacizumab.
Hypertension	
Medically significant hypertension not adequately controlled with antihypertensive therapy	Permanently discontinue bevacizumab.
Hypertensive crisis	Permanently discontinue bevacizumab.
Hypertensive encephalopathy	Permanently discontinue bevacizumab.
Congestive heart failure, Grade ≥3	Permanently discontinue bevacizumab.
Proteinuria	
Grade 1 (1+ proteinuria; urinary protein <1.0 g/24 hr)	No bevacizumab dose modification.
Grade 2 (2+ proteinuria; urinary protein 1.0–3.4 g/24 hr)	For 2+ dipstick: may administer bevacizumab without dose modification and collect 24-hr urine prior to subsequent bevacizumab administration. For 3+ dipstick: must obtain 24-hr urine prior to administering bevacizumab. Withhold bevacizumab for urinary protein ≥2 g/24 hr. Resume bevacizumab when proteinuria is <2 g/24 hr.
Grade 3 (urinary protein ≥3.5 g/24 hr)	Withhold bevacizumab. Resume bevacizumab when proteinuria is <2 g/24 hr.
Nephrotic syndrome	Permanently discontinue bevacizumab.

Table A12-6 Guidelines for Management of Patients Who Experience Bevacizumab-Specific Adverse Events (cont.)

Event	Action to Be Taken
Thrombosis/embolism	
Venous thrombosis, Grade 3	Withhold bevacizumab until patient is on a stable dose of anticoagulation for ≥ 2 weeks. [a]
Recurrent venous thrombosis, Grade ≥ 3	Permanently discontinue bevacizumab.
Venous thrombosis, Grade 4	Permanently discontinue bevacizumab.
Arterial thrombosis/embolism, any grade	Permanently discontinue bevacizumab.
Hemorrhage	
Grade ≥ 2 hemoptysis (≥ 2.5 mL of bright red blood per episode)	Withhold or permanently discontinue bevacizumab.
Grade 3 or 4 bleeding	Permanently discontinue bevacizumab.
Bleeding in patients on full-dose anticoagulant therapy	Permanently discontinue bevacizumab. [b]
CNS bleeding, any grade	Permanently discontinue bevacizumab.
Major surgery or wound-healing complication	Withhold bevacizumab until the wound is fully healed. If the wound does not fully heal despite withholding treatment, permanently discontinue bevacizumab.
Hypersensitivity/allergic reactions	Permanently discontinue bevacizumab.
Infusion-associated events	See above "Bevacizumab-Specific General Guidelines"
Febrile neutropenia, Grade 4 [c]	Withhold bevacizumab until resolution to Grade 1.
Thrombocytopenia, Grade 4 [c]	Withhold bevacizumab until resolution to Grade 1.

GI = gastrointestinal; NCI CTCAE v4.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0; ULN = upper limit of normal.

Note: All grades are per NCI CTCAE v4.0.

[a] Patients on heparin treatment should have an aPTT between 1.5 – 2.5 × ULN (or patient value before starting heparin treatment). Patients on coumarin derivatives should have an INR between 2.0 and 3.0 assessed in two consecutive measurements 1 – 4 days apart. Patients on full-dose low-molecular-weight heparins should receive the appropriate dose based on the weight of the patient according to package insert.

[b] Follow guidelines of the treating institution. Standard procedures such as antagonization with protamine or vitamin K and infusion of vitamin K–dependent factors should be considered dependent on the severity of the bleeding.

[c] Bevacizumab should be temporarily withheld in the event of Grade 4 febrile neutropenia and/or Grade 4 thrombocytopenia (regardless of the relationship to treatment), because these conditions are predisposing factors for an increased bleeding tendency.

A12–6.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + BEV + ET ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo + Bev + ET arm 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 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $> 10 \times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenzalike illness, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, *optic neuritis*)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders
- Vasculitis
- Grade ≥ 3 hypertension
- Grade ≥ 3 proteinuria
- Any grade GI perforation, abscess, or fistula

Appendix 12: Study Details Specific to Atezo + Bev + ET Arm (cont.)

- Grade ≥2 non-GI fistula or abscess
- Grade ≥3 wound-healing complication
- Hemorrhage

  Any grade CNS bleeding

  Grade ≥2 hemoptysis

  Other Grade ≥3 hemorrhagic event
- Any grade arterial thromboembolic event
- Grade ≥3 venous thromboembolic event
- Any grade posterior reversible encephalopathy syndrome
- Grade ≥3 congestive heart failure/left ventricular systolic dysfunction
- *Myelitis*
- *Facial paresis*

A12–7 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+BEV+ET ARM

Table A12-7 Schedule of Activities for Atezo+Bev+Fulvestrant

Assessment/Procedure	Screening [a]	Treatment Cycles (28-day cycles) [b]				Treat. Discon. [c]	Follow-Up
		Cycle 1		Cycles ≥2			
	–28 to –1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)	≤30 Days after Last Dose	Every 3 Months
Informed consent	x [d]						
Molecular profile of HR+ breast cancer (if available)	x	Whenever updated information becomes available					
Vital signs [e]	x [f]	x	x	x	x	x	
Weight	x [f]	x [hh]		x [hh]		x	
Complete physical examination [g]	x [f]					x	
Limited physical examination [h]		x [hh]		x [hh]			
ECOG Performance Status	x [f]	x [hh]		x [hh]		x	
ECG [i]	x	Perform as clinically indicated.					
Hematology [j]	x [k]	x [l]	x	x	x	x	
Chemistry [m]	x [k]	x [l]	x	x	x	x	
Coagulation (INR, aPTT)	x [k]	Perform as clinically indicated.				x	
TSH, free T3 (or total T3), free T4 [n]	x [k]	x [n]				x	
Viral serology [o]	x [k]					x [p]	
C-reactive protein	x						
LDH	x [f, k]						
Urinalysis [q]	x [k]	x [r]		x [s]		x	

Appendix 12: Study Details Specific to Atezo + Bev + ET Arm (cont.)

Assessment/Procedure	Screening [a]	Treatment Cycles (28-day cycles) [b]				Treat. Discon. [c]	Follow-Up
		Cycle 1		Cycles ≥2			
	–28 to –1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)	≤30 Days after Last Dose	Every 3 Months
Serum autoantibody sample [t]	x	Perform if a patient experiences a suspected immune-mediated adverse event					
PK samples		Refer to Table A12-9 below					
ADA sample		Refer to Table A12-9 below					
Samples for biomarkers		Refer to Table A12-9 below					
Blood sample for RBR (optional) [u]		x					
Tumor biopsy	x [f]						
Tumor biopsy (optional)		x [v]					
Tumor response assessments	x [f, w]	x [x, y]					
Concomitant medications [z]	x [f, z]	x	x	x	x	x	
Adverse events [aa]	x [f, aa]	x	x	x	x	x [aa]	x [aa]
Fulvestrant administration [bb, cc]		x	x [dd]	x			
Atezolizumab administration [cc, ee]		x	x	x	x		
Bevacizumab administration [cc, ff]		x	x	x	x		
Survival follow-up and anti-cancer treatment							x [gg]

Appendix 12: Study Details Specific to Atezo + Bev + ET Arm (cont.)

ADA = anti-drug antibody; Atezo + Bev + fulvestrant = atezolizumab plus bevacizumab plus fulvestrant; CT = computed tomography; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; ET = endocrine therapy; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; PET = positron emission tomography; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; Treat. = treatment.

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

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window at the investigator's discretion. The Medical Monitor is available to advise as needed.

[c] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed by the investigator (see Section 3.1.1.1 for details) may be used as the treatment discontinuation visit.

[d] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

[e] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, 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 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 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.

[f] Assessments performed at end of treatment for Stage 1 may serve as baseline assessments for Stage 2, provided that these assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1) (with the exception of the tumor biopsy sample). Patients who had a tumor biopsy collected within 3 months prior to the initiation of Stage 2 treatment do not need to provide an additional biopsy sample.

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

[h] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

Appendix 12: Study Details Specific to Atezo + Bev + ET Arm (cont.)

[j] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[k] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment (Cycle 1, Day 1).

[l] If screening laboratory assessments were performed within 96 hours prior to dosing, they do not have to be repeated.

[m] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST.

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

[o] At screening, patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.

[p] Viral serology tests are required at Stage 2 screening but are not required at the treatment discontinuation visit. However, patients with a positive quantitative HBV DNA at screening (must be $<$500 IU/mL per the eligibility criteria) will undergo additional HBV DNA tests on Day 1 of every third cycle (i.e., Cycles 3, 6, 9, etc.), at treatment discontinuation ($\pm$7 days), and at 3, 6, 9, and 12 months ($\pm$14 days at each timepoint) after treatment discontinuation. Study treatment and procedures may proceed while HBV DNA is being processed, but results should be reviewed by the investigator as soon as they are available. If HBV DNA increases to $\geq$500 IU/mL, consultation with the Medical Monitor is required prior to continuation of study treatment and consultation with a hepatologist or gastroenterologist with specialty in hepatitis B is recommended.

[q] Includes pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted. All patients with $\geq$2+ protein on dipstick urinalysis must undergo a 24-hour urine collection for protein during screening.

[r] Baseline urinalysis to be performed only if screening urinalysis is not performed within 7 days prior to initiation of study treatment. Patients with $\geq$2+ protein on dipstick urinalysis must undergo a 24-hour urine collection and demonstrate $<$1.0 g of protein in 24 hours.

[s] Urinalysis may be performed up to 72 hours prior to Day 1 of each cycle, as results must be available prior to treatment administration. Patients with Grade 2 proteinuria must undergo a 24-hour urine collection prior to the subsequent bevacizumab infusion. Patients with Grade 3 proteinuria must undergo a 24-hour urine collection prior to the current bevacizumab infusion. Refer to Table A12-6 for details on management of proteinuria.

[t] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. For patients who show evidence of immune-mediated toxicity, additional samples may be considered.

[u] 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.

Appendix 12: Study Details Specific to Atezo + Bev + ET Arm (cont.)

[v] Patients will undergo optional tumor biopsy sample collection, if deemed clinically feasible by the investigator, 4 weeks (±7 days) after treatment initiation and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[w] All measurable and evaluable lesions should be assessed and documented at screening (in both Stage 1 and Stage 2). Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with IV contrast; with or without oral contrast) or MRI scans (with IV contrast) of the chest, abdomen, pelvis, and head with one exception: a head scan is not required at Stage 2 screening. In addition, bone scans, PET scans, and/or skeletal survey should be performed at screening to assess bone lesions. Bone lesions identified at baseline should continue to be assessed following the tumor assessment schedule described above. Additional bone scans, PET scans, or skeletal surveys should be performed if clinically indicated. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans (with IV contrast) of the abdomen and pelvis should be performed. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. Refer to Section 4.5.5 for further details on tumor assessments.

[x] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 24 weeks following treatment initiation, and every 8 weeks (±1 week) from Week 25 to Week 48, and then every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of atezolizumab-treated patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[y] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[z] 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 10 days prior to initiation of study treatment until the treatment discontinuation visit.

[aa] 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 systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic 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.

Appendix 12: Study Details Specific to Atezo + Bev + ET Arm (cont.)

[bb] Fulvestrant should be administered intramuscularly into the buttocks slowly (1–2 minutes per injection) as two 5-mL injections, one in each buttock.

[cc] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details).

[dd] If a patient has already received treatment with fulvestrant during Stage 1 and the last fulvestrant administration is within 6 weeks of Cycle 1 Day 1 of Stage 2, the Cycle 1 Day 15 fulvestrant administration should be omitted.

[ee] The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[ff] The initial dose of bevacizumab will be delivered over 90 (± 15) minutes. If the first bevacizumab infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 60 (± 10) minutes. If the 60 (± 10) minute infusion was tolerated without infusion-associated adverse events, the third infusion may be delivered over 30 (± 15) minutes. If the 30-minute bevacizumab infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. Note: Patients who received bevacizumab as part of a prior treatment regimen may receive bevacizumab at the highest previously tolerate rate of infusion.

[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 study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

[hh] Assessment may be performed within 24 hours prior to dosing during the treatment period.

Table A12-8 Schedule of Activities for Atezo + Bev + Exemestane or Tamoxifen

Assessment/Procedure	Screening [a]	Treatment Cycles (21-day cycles) [b]		Treat. Discon. [c]	Follow-Up
		Cycle 1	Cycles ≥2		
	–28 to –1	Day 1	Day 1 (±3 days)	≤30 Days after Last Dose	Every 3 Months
Informed consent	x [d]				
Molecular profile of HR+ breast cancer (if available)	x	Whenever updated information becomes available			
Vital signs [e]	x [f]	x	x	x	
Weight	x [f]	x [gg]	x [gg]	x	
Complete physical examination [g]	x [f]			x	
Limited physical examination [h]		x [gg]	x [gg]		
ECOG Performance Status	x [f]	x [gg]	x [gg]	x	
ECG [i]	x	Perform as clinically indicated			
Hematology [j]	x [k]	x	x	x	
Chemistry [m]	x [k]	x [m]	x	x	
Coagulation (INR, aPTT)	x [k]	Perform as clinically indicated		x	
TSH, free T3 (or total T3), free T4 [n]	x [k]	x [n]		x	
Viral serology [o]	x [k]			x [p]	
C-reactive protein	x				
LDH	x				
Urinalysis [q]	x [k]	x [r]	x [s]	x	
Serum autoantibody sample [t]	x	Perform if a patient experiences a suspected immune-mediated adverse event			

Appendix 12: Study Details Specific to Atezo + Bev + ET Arm (cont.)

Assessment/Procedure	Screening [a]	Treatment Cycles (21-day cycles) [b]		Treat. Discon. [c]	Follow-Up
		Cycle 1	Cycles ≥2		
	–28 to –1	Day 1	Day 1 (±3 days)	≤30 Days after Last Dose	Every 3 Months
PK samples		Refer to Table A12-10 below			
ADA sample		Refer to Table A12-10 below			
Samples for biomarkers		Refer to Table A12-10 below			
Blood sample for RBR (optional) [u]		x			
Tumor biopsy	x [f]				
Tumor biopsy (optional)		x [v]			
Tumor response assessments	x [f, w]	x [x, y]			
Concomitant medications [z]	x [f, z]	x	x	x	
Adverse events [aa]	x [f, aa]	x	x	x [aa]	x [aa]
Exemestane or tamoxifen dispensation [bb, cc]		x	x		
Atezolizumab administration [cc, dd]		x	x		
Bevacizumab administration [cc, ee]		x	x		
Survival follow-up and anti-cancer treatment					x [ff]

ADA = anti-drug antibody; Atezo + Bev + Exemestane or Tamoxifen = atezolizumab plus bevacizumab plus exemestane or tamoxifen; CT = computed tomography; Discon. = discontinuation; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; ET = endocrine therapy; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; PET = positron emission tomography; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; Treat. = treatment.

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

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

Appendix 12: Study Details Specific to Atezo + Bev + ET Arm (cont.)

[b] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window at the investigator's discretion. The Medical Monitor is available to advise as needed.

[c] Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed by the investigator (see Section 3.1.1.1 for details) may be used as the treatment discontinuation visit.

[d] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

[e] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, 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 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 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.

[f] Assessments performed at end of treatment for Stage 1 may serve as baseline assessments for Stage 2, provided that these are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1) (with the exception of the tumor biopsy sample). Patients who had a tumor biopsy collected within 3 months prior to the initiation of Stage 2 treatment do not need to provide an additional biopsy sample.

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

[h] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[j] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[k] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment (Cycle 1, Day 1).

[l] If screening laboratory assessments were performed within 96 hours prior to dosing, they do not have to be repeated.

[m] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST.

[n] TSH, free T3 (or total T3 for sites where free T3 is not performed), and free T4 will be assessed at screening and on Day 1 of Cycle 1 and every fourth cycle thereafter (i.e., Cycles 5, 9, 13, etc.).

[o] At screening, patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.

[p] Viral serology tests are required at Stage 2 screening but are not required at the treatment discontinuation visit. However, patients with a positive quantitative HBV DNA at screening (must be <500 IU/mL per the eligibility criteria) will undergo additional HBV DNA tests on Day 1 of every third cycle (i.e., Cycles 3, 6, 9, etc.), at treatment discontinuation (±7 days), and at 3, 6, 9, and 12 months (±14 days at each timepoint) after treatment discontinuation. Study treatment and procedures may proceed while HBV DNA is being processed, but results should be reviewed by the investigator as soon as they are available. If HBV DNA increases to ≥500 IU/mL, consultation with the Medical Monitor is required prior to continuation of study treatment and consultation with a hepatologist or gastroenterologist with specialty in hepatitis B is recommended.

[q] Includes pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted. All patients with ≥2+ protein on dipstick must undergo a 24-hour urine collection for protein.

[r] Baseline urinalysis to be performed only if screening urinalysis is not performed within 7 days prior to initiation of study treatment. Patients with ≥2+ protein on dipstick urinalysis must undergo a 24-hour urine collection and demonstrate <1.0 g of protein in 24 hours.

[s] Urinalysis may be performed up to 72 hours prior to Day 1 of each cycle, as results must be available prior to treatment administration. Patients with Grade 2 proteinuria must undergo a 24-hour urine collection prior to the subsequent bevacizumab infusion. Patients with Grade 3 proteinuria must undergo a 24-hour urine collection prior to the current bevacizumab infusion. Refer to Table A12-6 for details on management of proteinuria.

[t] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. For patients who show evidence of immune-mediated toxicity, additional samples may be considered.

[u] 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.

[v] Patients will undergo optional tumor biopsy sample collection, if deemed clinically feasible by the investigator, 4 weeks (±7 days) after treatment initiation and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

Appendix 12: Study Details Specific to Atezo + Bev + ET Arm (cont.)

[w] All measurable and evaluable lesions should be assessed and documented at screening (in both Stage 1 and Stage 2). Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with IV contrast; with or without oral contrast) or MRI scans (with IV contrast) of the chest, abdomen, pelvis, and head with one exception: a head scan is not required at Stage 2 screening. In addition, bone scans, PET scans, and/or skeletal survey should be performed at screening to assess bone lesions. Bone lesions identified at baseline should continue to be assessed following the tumor assessment schedule described above. Additional bone scans, PET scans, or skeletal surveys should be performed if clinically indicated. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans (with IV contrast) of the abdomen and pelvis should be performed. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. Refer to Section 4.5.5 for further details on tumor assessments.

[x] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 24 weeks following treatment initiation, and every 8 weeks (±1 week) from Week 25 to Week 48, and then every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of atezolizumab-treated patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[y] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[z] 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 10 days prior to initiation of study treatment until the treatment discontinuation visit.

[aa] 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 systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic 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.

[bb] All patients will receive either exemestane at a dose of 25 mg orally once a day or tamoxifen 20 mg orally once a day. ET should be taken approximately the same time each day and no later than 4 hours after the scheduled time. On clinic visit days, patients should take their tablets in the clinic.

Appendix 12: Study Details Specific to Atezo + Bev + ET Arm (cont.)

[cc] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details).

[dd] The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[ee] The initial dose of bevacizumab will be delivered over 90 (± 15) minutes. If the first bevacizumab infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over 60 (± 10) minutes. If the 60 (± 10) minute infusion was tolerated without infusion-associated adverse events, the third infusion may be delivered over 30 (± 15) minutes. If the 30-minute bevacizumab infusion is well tolerated, all subsequent infusions may be delivered over 30 (± 10) minutes. Note: Patients who received bevacizumab as part of a prior treatment regimen may receive bevacizumab at the highest previously tolerate rate of infusion.

[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 study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

[gg] Assessment may be performed within 24 hours prior to dosing during the treatment period.

Table A12-9 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Bev + Fulvestrant

Visit	Time	Sample
Day 1 of Cycle 1	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Bevacizumab PK (serum) • Bevacizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
	30 (± 10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
	30 (± 10) minutes after bevacizumab infusion	• Bevacizumab PK (serum)
Day 15 of Cycle 1	Prior to infusion	• Biomarkers (plasma, serum)
Day 1 of Cycle 2	Prior to fulvestrant injection	• Fulvestrant PK (plasma)
	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to fulvestrant injection	• Fulvestrant PK (plasma)
	Prior to atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Bevacizumab PK (serum) • Bevacizumab ADA (serum)
	30 (± 10) minutes after bevacizumab infusion	• Bevacizumab PK (serum)
Day 1 of Cycle 4	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycle 8	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)

Table A12–9 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Bev + Fulvestrant (cont.)

Visit	Time	Sample
Treatment discontinuation visit (≤30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Bevacizumab PK (serum) • Bevacizumab ADA (serum) • Biomarkers (plasma, serum)
120 (±30) days after last dose of atezolizumab	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Bevacizumab PK (serum) • Bevacizumab ADA (serum)

ADA = anti-drug antibody; Atezo + Bev + Fulvestrant = atezolizumab plus bevacizumab plus fulvestrant; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic.

Table A12-10 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Bev + Exemestane or Tamoxifen

Visit	Time	Sample
Day 1 of Cycle 1	Prior to first atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Bevacizumab PK (serum) • Bevacizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
	30 (±10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
	30 (±10) minutes after bevacizumab infusion	• Bevacizumab PK (serum)
Day 1 of Cycle 2	Prior to exemestane or tamoxifen dose	• Exemestane or tamoxifen PK (plasma)
	Prior to atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Bevacizumab PK (serum) • Bevacizumab ADA (serum)
	30 (±10) minutes after bevacizumab infusion	• Bevacizumab PK (serum)
Day 1 of Cycle 4	Prior to atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycle 8	Prior to atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to atezolizumab infusion	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)

Table A12-10 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo + Bev + Exemestane or Tamoxifen (cont.)

Visit	Time	Sample
Treatment discontinuation visit (≤30 days after last dose)[a]	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Bevacizumab PK (serum) • Bevacizumab ADA (serum) • Biomarkers (plasma, serum)
120 (±30) days after last dose of atezolizumab	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Bevacizumab PK (serum) • Bevacizumab ADA (serum)

ADA = anti-drug antibody; Atezo + Bev + exemestane or tamoxifen = atezolizumab plus bevacizumab plus exemestane or tamoxifen; PK = pharmacokinetic.

A12–8 REFERENCES

Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. Cancer Immunol Immunother 2005;54:307–14.

Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother 2007;56:739–45.

Bouzin C, Brouet A, De Vriese J, et al. Lymphocyte-endothelium interactions: identification of caveolin-1 and nitric oxie as control point of endothelial cell anergy. J Immunol 2007;178:1505–11.

Butte MJ, Keir ME, Phamduy TB. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012;18:6580–7.

Deng R, Bumbaca D, Pastuskovas CV, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. MAbs 2016;8:593–603.

Dirix LY, Takacs I, Nikolinakos P, et al. Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: A Phase Ib JAVELIN solid tumor trial. Cancer Res 2016;76(Suppl):S1–04.

Eppenberger U, Kueng W, Schlaeppi J-M, et al. Markers of tumor angiogenesis and proteolysis independently define high- and low-risk subsets of node-negative breast cancer patients. J Clin Oncol 1998;16:3129–36.

Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837–46.

Gasparini G. Prognostic value of vascular endothelial growth factor in breast cancer. Oncologist 2000;5:37–44.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

Huang H, Bhat A, Woodnutt G, et al. Targeting the ANGPT-TIE2 pathway in malignancy. Nat Rev Cancer 2010;10:575–85.

Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. Nat Med 2001;7:987–9.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annual Rev Immunol 2008;26:677–704.

Lyman GH, Bohlke K, Khorana AA, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology; Clinical Practice Guideline Update 2014. J Clin Oncol. 2015;33:654–6.

Miles DW, Dieras V, Cortes J, et al. First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analysis of data from 2447 patients. Annals of Oncology 2013;24:2773–80.

Nagaraj S, Gabrilovich DI. Tumor escape mechanism governed by myeloid-derived suppressor cells. Cancer Res 2008;68:2561–3.

Naito Y, Saito K, Shiiba K, et al. CD8 + T cells infiltrated within cancer cell nests as a prognostic factor in human colorectal cancer. Cancer Res 1998;58:3491–4.

Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.

Rugo HS, Delord JP, Im SA, et al. Preliminary efficacy and safety of pembrolizumab (MK-3475) in patients with PD-L1-positive, estrogen receptor-positive (ER +)/HER2-negative advanced breast cancer enrolled in KEYNOTE-028. Cancer Res 2016;76(Suppl):S5–07.

Sato E, Olson SH, Ahn J, et al. Intraepithelial CD8+ tumor-infiltrating lymphocytes and a high CD8+/regulatory T cell ratio are associated with favorable prognosis in ovarian cancer. Proc Natl Acad Sci U S A 2005;102:18538–43.

Shrimali RK, Yu Z, Theoret MR, et al. Antiangiogenic agents can increase lymphocyte infiltration into tumor and enhance the effectiveness of adoptive immunotherapy for cancer. Cancer Res 2010;70:6172–80.

Tecentriq® (atezolizumab) U.S. prescribing information. South San Francisco (CA): Genentech, 2016.

Yang J, Riella LV, Chock S. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. J Immunol 2011;187:1113–9.

Zhang L, Conejo-Garcia JR, Katsaros D, et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. N Engl J Med 2003;348:203–13.

Appendix 13
Study Details Specific to Atezo + Abema + Fulvestrant Arm

A13–1 TABLE OF CONTENTS

A13–2 BACKGROUND ON ATEZO + ABEMA + FULVESTRANT ARM

A13–2.1 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 cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab has been generally well tolerated. Adverse events with potentially immune-mediated causes consistent with an immunotherapeutic agent, including rash, influenza-like illness, endocrinopathies, hepatitis or transaminitis, pneumonitis, colitis, and myasthenia gravis, have been observed (see Atezolizumab Investigator's Brochure for detailed safety results). To date, these events have been manageable with dose interruption or treatment, and patients are eligible to continue atezolizumab.

Atezolizumab (Tecentriq®) was first approved in the United Stated for the treatment of patients with locally advanced or metastatic urothelial carcinoma and for the treatment of patients with metastatic non–small cell lung cancer (NSCLC). Marketing Authorization Applications are being submitted globally, and approvals have already been received in a few countries.

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

A13–2.2 BACKGROUND ON ABEMACICLIB

The cyclin-dependent kinases (CDKs) play an important role in regulating cell-cycle progression. The interaction of cyclin D with CDK4 and CDK6 promotes phosphorylation of the Rb protein, cell proliferation, and tumor growth. Multiple oncogenic signals in hormone receptor–positive (HR+) breast cancer converge to promote expression of cyclin D1 and activation of CDK4 and CDK6 to drive breast cancer proliferation. CDK4/6 inhibition prevents Rb phosphorylation, blocking progression from G1 into S phase of the cell cycle, leading to suppression of tumor growth. Three CDK4/6 inhibitors have been approved in HR+, HER2-negative advanced or metastatic breast cancer: palbociclib, ribociclib, and abemaciclib.

Abemaciclib is an oral small molecule inhibitor of CDK4 and CDK6 and was most active against cyclin D1/CDK4 in enzymatic assays. Abemaciclib in combination with endocrine therapy has been approved both in the first line (with aromatase inhibitor) and second-line settings (with fulvestrant) for postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer. It is the only CDK4/6 inhibitor that has been approved as a monotherapy in HR+, HER2-negative advanced or metastatic breast cancer patients with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting. The approvals of abemaciclib are primarily based on multiple Phase II and III studies: MONARCH 1, MONARCH 2, and MONARCH 3. The most common side effects include diarrhea, neutropenia, nausea, abdominal pain, infections, fatigue, anemia, leukopenia, decreased appetite, vomiting, headache, alopecia, thrombocytopenia, and pneumonitis/interstitial lung disease. Refer to the Abemaciclib Investigator's Brochure for a detailed description of anticipated safety risks for abemaciclib.

A13–2.3 BACKGROUND ON FULVESTRANT

Fulvestrant is an estrogen receptor (ER) antagonist that binds to the ER, disrupting the signaling pathway and leading to ER degradation. Fulvestrant is approved for the treatment of postmenopausal patients with HR+ HER2-negative breast cancer (HR+ breast cancer) who have disease progression following other anti-estrogen therapy (Faslodex® [fulvestrant] prescribing information). The common adverse events associated with the use of fulvestrant include injection site pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, extremity pain, hot flashes, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea, constipation, and increases in liver enzymes (AST, ALT, ALP).

A13–3 RATIONALE FOR ATEZO+ABEMA+FULVESTRANT ARM

A13–3.1 THE PD-L1 PATHWAY

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 downregulates immune responses through binding to its two receptors, PD-1 and B7-1. PD-1 is an inhibitory receptor expressed on T cells following T-cell activation, and 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 (see Atezolizumab Investigator's Brochure for detailed efficacy results).

PD-L1 expression has been observed in HR+ breast cancer tissues. However, few clinically significant responses to single-agent checkpoint inhibitors have been observed in HR+ breast cancer (Dirix et al. 2016; Rugo et al. 2016), indicating that combination therapy is needed in order to overcome mechanisms of resistance to anti–PD-L1/anti-PD-1 monotherapy.

A13–3.2 RATIONALE FOR COMBINING ATEZOLIZUMAB WITH ABEMACICLIB AND FULVESTRANT

While checkpoint inhibitors have shown great success in the treatment of inflamed tumor types (e.g., melanoma and NSCLC), they are less efficacious in the treatment of non-inflamed tumors. HR+ breast cancer is considered less immunogenic. Moreover, it has also been reported that a high number of T-regulatory cells (Tregs) in the tumor predicts a poor clinical outcome in patients with breast cancer (Bates et al. 2006). In order to provide improved anti-tumor immunity in patients with HR+ breast cancer, combination therapy approaches are needed to overcome the immune suppression.

Recent data from nonclinical models have shown that CDK4/6 inhibitors not only induced tumor cell cycle arrest but also promoted anti-tumor immunity (Goel et al. 2017). Specifically, treatment with CDK4/6 inhibitors increased the functional capability of tumor cells to present antigen and reduced the population of immunosuppressive Tregs by suppression of their proliferation (Goel et al. 2017; Zhang et al. 2018). Moreover, combination treatment of CDK4/6 inhibitor with an anti–PD-L1 antibody induced significant tumor regression in multiple animal models.

A similar hypothesis that treatment with a CDK4/6 inhibitor could potentiate the susceptibility to checkpoint inhibitor is currently being tested clinically in the JPCE study (NCT02779751). The JCPE study is an ongoing, Phase I, open-label, multicenter study that includes an arm to evaluate the combination of abemaciclib and pembrolizumab in HR+, HER2-negative metastatic breast cancer. Twenty-eight patients were treated with abemaciclib at a dose of 150 mg twice a day and pembrolizumab 200 mg IV on Day 1 of every 21-day cycle. At the 24 week analysis, the combination treatment demonstrated a confirmed ORR of 28.6% compared with an ORR of 10.6% in MONARCH1. The combination demonstrated a manageable safety profile, and no new safety signals were

reported at the 24 week analysis. The JPCE study has demonstrated a preliminary efficacy signal for the combination of a CDK4/6 inhibitor with checkpoint inhibition, and the results also support the combinability and use of full-dose abemaciclib with a checkpoint inhibitor (Tolaney et al. 2018).

Emerging clinical data also suggest synergy when combining anti-estrogen therapy with CDK4/6 inhibitors. For example, data from the MONARCH-2 study has demonstrated that both ORR and PFS were significantly improved when combining abemaciclib with fulvestrant in patients previously treated with endocrine therapy (Sledge et al. 2017).

One outstanding question is whether there is any role for the continuation of CDK4/6 inhibition beyond progression on these agents and whether to combine with endocrine therapy and immune check point inhibition. Currently, there are very little nonclinical data available to address this question. Despite understanding of the CDK4/6 pathway, identification of molecular biomarkers that predict response or resistance to CDK4/6 inhibitors is not clear. The intact Rb pathway is indispensable in mediating anti-tumor responses to CDK4/6 inhibitors. Tumors that have acquired resistance to CDK4/6 inhibitors showed new RB1 mutations that are predicted to confer loss of function (Condorelli et al. 2018). However, analysis from large randomized trials has not revealed a clear association between RB levels and benefit from CDK4/6 inhibitors (Finn et al. 2017, Turner 2018). Gene expression analysis from PALOMA3 indicated that higher expression of cyclin E was associated with relative resistance to palbociclib. However, this result was not upheld in the analysis of the larger first-line study PALOMA-2 (Finn et al. 2017, Turner 2018).

To date, the question of CDK4/6 inhibitor use beyond progression is being tested in several ongoing clinical trials. Some of these trials maintain the CDK4/6 inhibitor while changing the endocrine agent, and others change the CDK4/6 inhibitor used. For example, MAINTAIN (NCT026320450) is a randomized Phase II study of patients who have progressed on an aromatase inhibitor plus a CDK4/6 inhibitor (either palbociclib or ribociclib) to either fulvestrant alone or fulvestrant with ribociclib. PACE (NCT03147287) is a randomized Phase II study evaluating the activity of fulvestrant alone, fulvestrant and palbociclib, or the triplet combination of fulvestrant, palbociclib, and avelumab in patients who had previously stopped responding to prior palbociclib and endocrine therapy. TRINITI-1 (NCT02732119) is a Phase I/II study evaluating the anti-tumor activity of exemestane, everolimus, and ribociclib following progression on a CDK4/6 inhibitor. Preliminary clinical data from TRINITI-1 demonstrated encouraging clinical benefit and tolerability of this combination following progression on a CDK4/6 inhibitor. Among 42 patients evaluable for efficacy, 6 had prior chemotherapy, 13 had ≥ 2 prior lines of therapy (median, 1 line), and 13 were on therapy on 15 December 2017. At Week 24, 17 patients (40.5%) had clinical benefit by local assessment; the overall response rate was 7.1% (n = 3; all had partial response at Week 24). Median PFS was 8.8 months (95% CI, 1.9 months to not evaluable) (Moulder et al. 2018).

A similar hypothesis is being tested in this study with combination treatment with atezolizumab, abemaciclib, and fulvestrant, which could induce a synergistic anti-tumor

response in patients beyond progression of CDK4/6 inhibitor, driving improved clinical outcomes.

A13–3.3 BENEFIT–RISK ASSESSMENT

PD-L1 expression has been observed in HR+ HER2-negative breast cancer tissue. However, clinically significant response to single-agent checkpoint inhibitor therapy is limited in patients with HR+ breast cancer (Dirix et al. 2016; Rugo et al. 2016), indicating that combination therapy is needed in order to overcome mechanisms of resistance to anti–PD-L1/anti–PD-1 monotherapy. One potential mechanism for converting otherwise resistant cancers is

modulation of the immune system by means of CDK4/6 inhibition to increase tumor antigen presentation and suppress immunosuppressive Tregs. The combined nonclinical and clinical data for abemaciclib plus checkpoint inhibitor suggest a potential added benefit. The JPCE study has shown tolerability of combining full-dose abemaciclib with check point inhibitor without new safety signal.

Fulvestrant is approved for the treatment of HR+ breast cancer. Therefore, patients will receive standard-of-care therapy with this combination regimen. Furthermore, the tolerable safety profiles for fulvestrant plus abemaciclib, and fulvestrant plus atezolizumab indicate a low safety risk for patients.

Considering the high therapeutic need for tolerable and effective treatment in HR+ metastatic breast cancer, the compelling immunologic rationale for the combination of atezolizumab and abemaciclib, and the anticipated safety profile of the combination, the benefit–risk assessment favors moving forward with the evaluation of atezolizumab, abemaciclib, and fulvestrant in the second- or third-line locally advanced or metastatic HR+ HER2-negative breast cancer.

For the evaluation of the impact of the COVID-19 pandemic on the benefit-risk assessment, please refer to Section 1.3.

A13–4 RATIONALE FOR DOSE AND SCHEDULE FOR ATEZO+ABEMA+FULVESTRANT ARM

A13–4.1 RATIONALE FOR ATEZOLIZUMAB DOSE AND SCHEDULE

Atezolizumab will be administered at a fixed dose of 840 mg every 2 weeks (Q2W) (840 mg on Days 1 and 15 of each 28-day cycle). The average concentration following the 840 mg Q2W dosage is expected to be equivalent to that of 1200 mg every 3 weeks (Q3W), the approved dosage for atezolizumab (Tecentriq® U.S. Prescribing Information). Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study PCD4989g, the maximum tolerated dose of atezolizumab was not reached and no dose-limiting toxicities were observed at any dose. The fixed dose of 1200 mg Q3W (equivalent to an average body weight–based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies (Deng et al. 2016) and available

clinical pharmacokinetic, efficacy, and safety data (refer to the Atezolizumab Investigator's Brochure for details).

A13–4.2 RATIONALE FOR ABEMACICLIB DOSE AND SCHEDULE

Abemaciclib will be administered at a starting dose of 150 mg twice daily, and it is provided as 50-mg capsules. Abemaciclib should be taken twice daily (with at least 6-hour separating doses) at the same time each day with a glass of water. Patients should be instructed to swallow capsules whole and not open, chew, or crush. This is the current approved abemaciclib dosage in combination with fulvestrant for the treatment of HR+ breast cancer.

A13–4.3 RATIONALE FOR FULVESTRANT DOSE AND SCHEDULE

In this study, fulvestrant 500 mg will be administered intramuscularly on Days 1 and 15 of Cycle 1. Thereafter, fulvestrant will be administered on Day 1 of each 28-day cycle. This is the current approved fulvestrant dosage for the treatment of HR+ breast cancer.

A13–5 MATERIALS AND METHODS SPECIFIC TO ATEZO+ABEMA+FULVESTRANT ARM

A13–5.1 TREATMENT IN ATEZO+ABEMA+FULVESTRANT ARM

A13–5.1.1 Formulation, Packaging, and Handling

A13–5.1.1.1 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 and handling of atezolizumab, see the pharmacy manual and the Atezolizumab Investigator's Brochure.

A13–5.1.1.2 Abemaciclib

Abemaciclib will be supplied as 50-mg tablets for oral administration. For information on the formulation and handling of abemaciclib, see the pharmacy manual and the Abemaciclib Investigator's Brochure.

A13–5.1.1.3 Fulvestrant

Fulvestrant will be supplied as 250-mg/mL sterile liquid. For information on the formulation, packaging, and handling of fulvestrant, refer to the local label.

A13–5.1.2 Dosage, Administration, and Compliance

Patients in the Atezo+Abema+Fulvestrant arm will receive treatment as outlined in Table A13-1 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) (see Section 3.1.1.1 for details). Treatment must be initiated

no later than 7 days after randomization. If initiation of treatment has to be delayed, patient may start treatment at the investigator's discretion. The Medical Monitor is available to advise as needed.

Table A13-1 Treatment Regimen for Atezo + Abema + Fulvestrant Arm

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
28 days	• Abemaciclib 150 mg by mouth twice daily during each 28-day cycle • Fulvestrant 500 mg by IM injection on Days 1 and 15 of Cycle 1 followed by 500 mg by IM injection on Day 1 of every cycle thereafter • Atezolizumab 840 mg by IV infusion on Days 1 and 15

Atezo + Abema + Fulvestrant = atezolizumab plus abemaciclib plus fulvestrant;
IM = intramuscular.

Refer to Section A13–6.1.5.2 for information on treatment interruptions for patients who experience toxicities. Atezolizumab, abemaciclib, or fulvestrant treatment interruptions for reasons other than toxicity (e.g., surgical procedures) may be allowed. The acceptable length of treatment interruption must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Any dose modification of any of the study treatments 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 5.4.3.

No safety data related to overdosing of atezolizumab, abemaciclib, or fulvestrant are available.

A13–5.1.2.1 Atezolizumab

Atezolizumab will be administered by IV infusion at a fixed dose of 840 mg on Day 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 5. Atezolizumab infusions will be administered per the instructions outlined in Table A13-2.

Table A13-2 Administration of First and Subsequent Atezolizumab Infusions

First Infusion of Atezolizumab	Subsequent Infusions of Atezolizumab
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded 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.	• 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 (± 10) minutes after the infusion.

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

Guidelines for medical management of infusion-related reactions (IRRs) are provided in Appendix 6.

No dose modification for atezolizumab is allowed. Guidelines for treatment interruption or discontinuation are provided in Section A13–6.1.5.2 and in Appendix 6.

A13–5.1.2.2 Abemaciclib

Patients will receive abemaciclib at a dose of 150 mg orally twice daily during each 28-day cycle. Doses should be spaced approximately 12 hours apart, with a minimum of 6 hours between doses. Abemaciclib should be taken with or without food at approximately the same times each day with a glass of water. Abemaciclib tablets should not be opened, crushed, or chewed and should be swallowed whole. On clinic visit days that require PK collection of study drugs, patients should take their tablets in the clinic. Missed doses can be taken immediately when patient realizes dose was missed. The patient should wait at least 6 hours before taking the next scheduled dose. Vomited doses will not be made up; the patient should resume abemaciclib dosing with the next scheduled dose.

In order to assess the actual intake of abemaciclib use, patients should complete a medication diary each day. Patients will receive the diary on the first day of each cycle. Patients should use the diary to record daily abemaciclib dosing.

Guidelines for dosage modification and treatment interruption or discontinuation because of toxicities are provided in Section A13–6.1.5.2.

A13–5.1.3 Stage 2 Treatment

Patients who experience loss of clinical benefit as determined by the investigator (as described in Section 3.1.1.1) will be given the option of receiving atezolizumab in combination with bevacizumab plus one of three ET options (fulvestrant, exemestane, or tamoxifen) on the basis of the physician's choice (Atezo+Bev+ET) during Stage 2 of the study, provided they meet eligibility criteria (see Section 4.1.1.3) and a Stage 2 arm is open for enrollment. Stage 2 treatment must begin within 3 months after the patient has experienced loss of clinical benefit and will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator. However, it is recommended that patients begin Stage 2 treatment as soon as possible but no earlier than 2 weeks after the last dose of treatment in Stage 1.

Tumor assessments performed prior to or at the time of disease progression, loss of clinical benefit, or unacceptable toxicity during Stage 1 may serve as baseline assessments for Stage 2, provided that the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1). Stage 2 treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator.

A13–5.2 CONCOMITANT THERAPY FOR ATEZO+ABEMA+FULVESTRANT ARM

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 10 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.

A13–5.2.1 Permitted Therapy for Atezo+Abema+Fulvestrant Arm

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

- Prophylactic or therapeutic anticoagulation therapy (such as warfarin at a stable dose or low-molecular-weight heparin)
- Vaccinations (such as influenza, COVID-19)

  Live, attenuated vaccines are not permitted (see Section 4.1.2.2).
- Mineralocorticoids (e.g., fludrocortisone)

- Inhaled corticosteroids administered for chronic obstructive pulmonary disease or asthma
- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency
- 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 and fulvestrant may be continued during palliative radiotherapy.

  Limited data are available with abemaciclib and radiotherapy. Thus, caution should be exercised with co-administering abemaciclib with radiotherapy. Treatment with abemaciclib should be temporarily held for 14 days after radiation. If the dose is myeloablative, abemaciclib should be temporarily withheld for 28 days. The patient may continue abemaciclib treatment after treatment holding has been completed and the patient has sufficiently recovered.
- Radiotherapy to the brain as outlined below:

  Patients whose extracranial tumor burden is stable or responding to study treatment and who are subsequently found to have three or fewer brain metastases may receive radiotherapy to the brain (either stereotactic radiosurgery or whole-brain radiation therapy) 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 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 continue study treatment at the investigator's discretion. The Medical Monitor is available to advise as needed.
– Anti-convulsant therapy, if required, is administered at a stable dose.

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

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

as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists; see Appendix 5).

A13–5.2.2 Cautionary Therapy for Atezo + Abema + Fulvestrant Arm

A13–5.2.2.1 Corticosteroids, *Immunosuppressive Medications,* and Tumor Necrosis Factor–α Inhibitors

Systemic corticosteroids, immunosuppressive medications, 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, immunosuppressive medications, or TNF-α inhibitors would be routinely administered, alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator. The Medical Monitor is available to advise as needed.

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

A13–5.2.2.2 Medications Given with Precaution due to Effects Related to Cytochrome P450 Enzymes

Abemaciclib is predominantly cleared by oxidative metabolism via CYP3A. Clinical drug interaction studies with a CYP3A inhibitor and CYP3A inducer significantly altered the PK of abemaciclib and its circulating major metabolites. Therefore, the following treatments are not recommended throughout the duration of the active treatment phase. Alternative therapies should be considered whenever possible. If one of the following treatments is deemed necessary, consultation and agreement with the Medical Monitor is required prior to treatment initiation.

CYP3A Inducers

Avoid concomitant use of CYP3A inducers and consider alternative agents.

CYP3A Inhibitors

Avoid concomitant use of strong CYP3A inhibitors (e.g., voriconazole) and use caution with co-administered moderate (e.g., ciprofloxacin) or weak (e.g., ranitidine) CYP3A inhibitors. If coadministration with a strong CYP3A inhibitor is unavoidable, reduce the abemaciclib dose to 100 mg twice daily or, in the case of ketoconazole, reduce the abemaciclib dose to 50 mg twice daily. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the abemaciclib dose to 50 mg twice daily. If a CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3–5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor.

A13–5.2.2.3 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 A13–5.2.3) may be used during the study at the discretion of the investigator.

A13–5.2.3 Prohibited Therapy for Atezo+Abema + Fulvestrant Arm

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

- 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 radiotherapy to the brain under circumstances outlined above in Section A13–5.2.1.
- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 28 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 4 weeks prior to initiation of study treatment, during treatment with atezolizumab, and for 5 months after the last dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and interleukin-2) are prohibited within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Megestrol acetate administered as an appetite stimulant after initiation of study treatment

A13–5.3 PROHIBITED FOOD FOR ATEZO+ABEMA+FULVESTRANT ARM

Grapefruit or grapefruit juice, a potent CYP3A4 enzyme inhibitor, is prohibited during the study and for 5 days after the last dose of abemaciclib.

A13–6 ASSESSMENT OF SAFETY FOR ATEZO+ABEMA+FULVESTRANT ARM

A13–6.1 SAFETY PLAN FOR ATEZO+ABEMA+FULVESTRANT ARM

The anticipated important safety risks are outlined below (see Sections A13–6.1.1, A13–6.1.2, and A13–6.1.3). Guidelines for management of patients who experience specific adverse events are provided in Section A13–6.1.4. These guidelines are intended to inform rather than supersede an investigator's clinical judgment and assessment of the benefit-risk balance when managing individual cases.

Measures will be taken to ensure the safety of patients participating in this study, including the use of stringent inclusion and exclusion criteria and close monitoring of patients during the study. 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. Adverse events will be reported as described in Sections 5.2–5.6.

A13–6.1.1 Risks Associated with Atezolizumab

Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, *facial paresis, myelitis,* meningoencephalitis, myocarditis, *pericardial disorders,* nephritis, myositis, and severe cutaneous adverse reactions. *In addition,* immune-mediated reactions may involve any organ system and lead to hemophagocytic lymphohistiocytosis *(HLH)*. Refer to Appendix 6 of the protocol and Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

A13–6.1.2 Risks Associated with Abemaciclib

Abemaciclib has been associated with risks such as the following: neutropenia, infections, diarrhea, hepatic events, venous thromboembolic events, and interstitial lung disease (ILD) or pneumonitis.

Venous thromboembolic events (VTE) were reported in patients receiving abemaciclib plus fulvestrant or aromatase inhibitors in breast cancer studies. Monitor patients for signs and symptoms of DVT and PE. If a patient experiences a VTE during treatment with abemaciclib, the patient should be treated as clinically indicated. It is recommended to temporarily stop abemaciclib while anticoagulation is initiated. After approximately 2 weeks of anticoagulation, the investigator may decide to restart abemaciclib based on his/her clinical judgment that it is appropriate for the patient to resume dosing. For life-threatening (Grade 4) VTEs, it is recommended not to restarted abemaciclib until there is evidence of resolution of the VTE and a discussion with the Medical Monitor

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

A13–6.1.3 Risks Associated with Fulvestrant

Fulvestrant has been associated with risks such as the following: injection site reactions, asthenia, nausea, and increased hepatic enzymes (ALT, AST, ALP). Refer to the local prescribing information for fulvestrant for a detailed description of all anticipated risks for fulvestrant.

A13–6.1.4 Risks Associated with Combination Use of Atezolizumab + Abemaciclib + Fulvestrant

The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab, abemaciclib, and fulvestrant: pneumonitis, diarrhea, pericardial disorders, and hepatic events.

A13–6.1.5 Management of Patients Who Experience Specific Adverse Events in Atezo + Abema + Fulvestrant Arm

A13–6.1.5.1 Dose Modifications

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

Dose level reduction for abemaciclib should be made in 50-mg increments. For example, if starting dose of abemaciclib is 150 mg twice daily, dose reduction 1 would be 100 mg twice daily, dose reduction 2 would be 50 mg twice daily as outlined in Table A13-3 below. If further dose reduction is indicated after two dose reductions for specified drug-related adverse events, the patient must discontinue abemaciclib but may continue treatment with atezolizumab and fulvestrant at the investigator's discretion.

Table A13-3 Suggested Dose Reductions for Abemaciclib

Dose Level	Abemaciclib
Starting dose	150 mg
First dose reduction	100 mg
Second dose reduction	50 mg
Third dose reduction	Discontinue

Note: For patients requiring a dose reduction of abemaciclib, any re-escalation to a prior dose level is permitted only after consultation with the Medical Monitor.

A13–6.1.5.2 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 patient is likely to derive clinical benefit. The decision to re-challenge patients with atezolizumab should be based on investigator's benefit-risk *assessment* and documented by the investigator. The Medical Monitor is available to advise as needed.
Atezolizumab treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption must be based on *the investigator's* benefit-risk *assessment* and in alignment with the protocol requirements for

the duration of treatment and documented by the investigator. The Medical Monitor is available to advise as needed.

Abemaciclib treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If abemaciclib is withheld for >28 days, the patient should be considered for discontinuation from abemaciclib. Abemaciclib treatment can be resumed after being withheld for >28 days *if the patient is likely to derive clinical benefit. The decision to re-challenge patients with abemaciclib should be based on the investigator's assessment of benefit-risk and documented by the investigator. The Medical Monitor is available to advise as needed.*

In general, the investigator may consider continuing fulvestrant if the observed adverse event is not thought to be fulvestrant-related.

If one or two of the drugs is discontinued, the other drug(s) can be continued if the patient is likely to derive clinical benefit *based on the investigator's benefit-risk assessment and documented by the investigator. The Medical Monitor is available to advise as needed.*

Refer to Section A13–5.1.2 for information on dose interruptions for reasons other than toxicity.

A13–6.1.5.3 Management Guidelines for Adverse Events

Guidelines for the management of patients who experience specific adverse events are provided in Appendix 6 and Table A13-4, as outlined below:

- Appendix 6 provides guidelines for the management of patients who experience atezolizumab-associated IRRs and immune-mediated endocrine, pancreatic, neurologic, and meningoencephalitis and ocular events. It is recommended that atezolizumab be withheld or discontinued per the guidelines in Appendix 6 and that abemaciclib be withheld or discontinued per the guidelines in Table A13-4.
- Table A13–4 provides guidelines for the management of patients who experience the following potential overlapping toxicities: diarrhea, hepatic events, and pneumonitis. It is recommended that study treatments be withheld or discontinued per the guidelines in Table A13–4. For these potential overlapping toxicities, guidelines in Table A13–4 should be followed instead of guidelines in Appendix 6.
- Table A13–4 provides guidelines for the management of patients who experience adverse events associated with abemaciclib. It is recommended that atezolizumab and/or abemaciclib be withheld or discontinued per the guidelines in Table A13–4.

For cases in which management guidelines are not covered in Appendix 6 or Table A13–4, patients should be managed and treatments should be withheld or

discontinued as deemed appropriate by the investigator according to best medical judgment.

Please refer to the Fulvestrant local prescribing information for guidelines on the management of patients who experience specific adverse event for fulvestrant.

Table A13-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Abema + Fulvestrant Arm

Event	Action to Be Taken
IRRs, CRS, and anaphylaxis	• Guidelines for management of IRRs and CRS are provided in Appendix 6. • For anaphylaxis precautions, see Appendix 5. • For severe hypersensitivity reactions, permanently discontinue atezolizumab and abemaciclib.
Pulmonary events, including interstitial lung disease or pneumonitis	
General guidance	• 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. • Investigations may include imaging, such as high-resolution computed tomography, BAL, and biopsy as clinically indicated.
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Continue abemaciclib with no dose reduction. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Continue abemaciclib with no dose reduction. • If event persists or recurs despite maximal supportive measures and does not return to Grade 1 or better within 7 days, withhold abemaciclib. If event resolves to Grade 1 or better while withholding abemaciclib, resume abemaciclib at next lower dose. • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL *with or without transbronchial biopsy*. • 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 the Medical Monitor. [c, d] • For recurrent events after management above, treat as a Grade 3 or 4 event.

Table A13-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Abema + Fulvestrant Arm (cont.)

Event	Action to Be Taken
Pulmonary events, including interstitial lung disease or pneumonitis (cont.)	
Pulmonary event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c, d] • *Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment.* • Permanently discontinue abemaciclib. • Bronchoscopy or BAL *with or without transbronchial biopsy* is recommended. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Gastrointestinal toxicity	
General Guidance	• All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. • At enrollment, patients should receive instructions on the prompt management of diarrhea. In the event of diarrhea, supportive care measures should be initiated as early as possible. These include the following: • At the first sign of loose stools, the patient should initiate antidiarrheal therapy (e.g., loperamide) and notify the investigator for further instructions and appropriate followup. • Patients should also be encouraged to drink fluids (e.g., 8 to 10 glasses of clear liquids per day). • Site personnel should assess response within 24 hours. • In cases of significant diarrhea (Grade 2 through 4) that has not responded to interventions as outlined below, if the investigator is considering the addition of steroids to treat potential colitis, the sponsor strongly recommends an endoscopic procedure to document colitis prior to initiating steroids. • In severe cases of diarrhea, the measuring of neutrophil counts and body temperature should be considered. • If diarrhea is severe (requiring IV rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones must be prescribed.

Table A13-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Abema + Fulvestrant Arm (cont.)

Event	• Action to Be Taken
Gastrointestinal toxicity (cont.)	
General Guidance (cont.)	• Patients with severe diarrhea or any grade of diarrhea associated with severe nausea or vomiting should be carefully monitored and given IV fluid (IV hydration) and electrolyte replacement. • For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Continue abemaciclib with no dose modification. • Initiate symptomatic treatment (e.g., loperamide). • Endoscopy is recommended if symptoms persist for > 7 days despite provision of maximal supportive care. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • If event does not resolve within 24 hours to Grade 1 or better, withhold abemaciclib. • Initiate symptomatic treatment (e.g., loperamide). • *If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis.* • Patient referral to GI specialist is recommended if symptoms persists for > 7 days despite maximal supportive care. • For recurrent events or events that persist > 5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. *If the 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 the Medical Monitor. [c]

Table A13-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Abema + Fulvestrant Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea or colitis, Grade 2 (cont.)	• If event resolves to Grade 1 or better while withholding abemaciclib, resume abemaciclib with no dose reduction. • For Grade 2 event that recurs after resuming the same dose of abemaciclib despite maximal supportive measures, withhold abemaciclib until event resolves to Grade 1 or better and resume abemaciclib at next lower dose.
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Withhold abemaciclib until event resolves to Grade 1 or better. • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with *corticosteroids equivalent to* 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. *If event 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 the Medical Monitor. [c] • If event resolves to Grade 1 or better while withholding abemaciclib, resume abemaciclib at next lower dose.

Table A13-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Abema + Fulvestrant Arm (cont.)

Event	Action to Be Taken
Gastrointestinal toxicity (cont.)	
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Withhold abemaciclib until event resolves to Grade 1 or better. • Refer patient to GI specialist for evaluation and *confirmatory* biopsy. • Initiate treatment with *corticosteroids equivalent to* 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event 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. • If event resolves to Grade 1 or better while withholding abemaciclib, resume abemaciclib at next lower dose.
Hepatic events	
General Guidance	• Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately and reviewed before administration of the next dose of study drug. • For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.
Hepatic event, Grade 1	• Continue atezolizumab. • Continue abemaciclib with no dose reduction. • Monitor LFTs until values resolve to within normal limits.

Table A13-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Abema + Fulvestrant Arm (cont.)

Event	Action to Be Taken
Hepatic events (cont.)	
Hepatic event, Grade 2	• Continue abemaciclib with no dose reduction. • For persistent or recurrent Grade 2 event within the next 8 weeks, withhold abemaciclib. If event resolves to Grade 1 or better, resume abemaciclib at next lower dose. All events: • Monitor LFTs more frequently until return to baseline values. • Events of > 5 days' duration: • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact the Medical Monitor. [c]
Hepatic event, Grade 3	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • For Grade 3, withhold abemaciclib. • For Grade 3 ALT and with total bilirubin >2 × ULN, in the absence of cholestasis, permanently discontinue abemaciclib. [e] • Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. • If event resolves to Grade 1 or better while withholding abemaciclib, resume abemaciclib at next lower dose. If event does not resolve to Grade 1 or better, permanently discontinue abemaciclib and contact the Medical Monitor.

Table A13-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Abema + Fulvestrant Arm (cont.)

Event	Action to Be Taken
Hepatic event, Grade 4	• Permanently discontinue atezolizumab and contact the Medical Monitor. [c] • Permanently discontinue abemaciclib. [e] • Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Hematologic toxicities	
General Guidance	• Monitor complete blood counts prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.
Grade 1 or 2	• Continue abemaciclib with no dose modification. • Continue atezolizumab.
Grade 3	• Withhold abemaciclib until event resolves to Grade 2 or better. • Continue atezolizumab. • If event resolves to Grade 2 or better, resume abemaciclib with no dose reduction. • For Grade 3 thrombocytopenia, consider withholding atezolizumab until event improves and Medical Monitor agrees that atezolizumab should be continued.
Grade 3 (recurrent) or Grade 4	• Withhold abemaciclib until event resolves to Grade 2 or better. • If event resolves to Grade 2 or better, resume abemaciclib at next lower dose level. • Consider withholding atezolizumab. If event improves and Medical Monitor agrees that atezolizumab should be continued, resume atezolizumab.
Patient requires administration of a blood cell growth factor	• Withhold abemaciclib for at least 48 hours after the last dose of blood cell growth factor and until event resolves to Grade 2 or better. • If event resolves to Grade 2 or better while withholding abemaciclib, resume abemaciclib at next lower dose level unless the dose was already reduced for the toxicity that led to the use of the growth factor.

Table A13-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Abema + Fulvestrant Arm (cont.)

Event	Action to Be Taken
Atezolizumab-related toxicities not described above	
Grade 1 or 2	• Follow atezolizumab-specific guidelines in Appendix 6. • Continue abemaciclib with no dose modification.
Grade 3 or 4	• Follow atezolizumab-specific guidelines in Appendix 6. • Withhold abemaciclib until event resolves to Grade 1 or better. • If event resolves to Grade 1 or better while withholding abemaciclib, resume abemaciclib at next lower dose. If event does not resolve to Grade 1 or better, permanently discontinue abemaciclib and contact the Medical Monitor. [c]
Abemaciclib-related toxicities not described above	
Grade 1 or 2	• Continue atezolizumab. • Continue abemaciclib with no dose modification.
Grade 3 or 4 and persistent or recurrent Grade 2 events that do not resolve with maximal supportive measures within 7 days to baseline or Grade 1	• Atezolizumab may be continued only after consultation with the Medical Monitor. • Withhold abemaciclib until event resolves to baseline or Grade 1 or better. • If event resolves to baseline or Grade 1 or better while withholding abemaciclib, resume abemaciclib at next lower dose.

Table A13-4 Guidelines for Management of Patients Who Experience Specific Adverse Events in Atezo + Abema + Fulvestrant Arm (cont.)

BAL = bronchoscopic alveolar lavage; CRS = cytokine release syndrome; GI = gastrointestinal; IRR = infusion-related reaction; LFT = liver function test; ULN = upper limit of normal.

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

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

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. *The decision to re-challenge patients with atezolizumab should be based on the investigator's benefit-risk assessment and documented by the investigator.*

[d] *In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.*

[e] If a patient experiences elevated ALT 5 × ULN and elevated total bilirubin 2 × ULN, or ALT 8 × ULN, liver tests, including ALT, AST, total bilirubin, direct bilirubin, GGT, and CPK, should be repeated within 3 to 5 days to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator as described in the Abemaciclib Investigator's Brochure.

A13–6.2 ADVERSE EVENTS OF SPECIAL INTEREST FOR ATEZO + ABEMA+ FULVESTRANT ARM (IMMEDIATELY REPORTABLE TO THE SPONSOR)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for the Atezo + Abema+ Fulvestrant arm 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 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10 × ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, IRRs, cytokine release syndrome, influenzalike illness, HLH, and MAS
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, *optic neuritis*)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders
- Vasculitis
- Grade ≥ 3 neutropenia
- Grade ≥ 3 diarrhea
- Grade ≥ 3 blood creatinine increase
- Grade ≥ 3 venous thromboembolic event
- *Myelitis*
- *Facial paresis*

A13–7 SCHEDULES OF ACTIVITIES AND SAMPLE COLLECTION FOR ATEZO+ABEMA+FULVESTRANT ARM

Table A13-5 Schedule of Activities for Atezo+Abema+Fulvestrant Arm

Assessment/Procedure	Screening [a]	Treatment Cycles (28-day cycles) [b]				Stage 2 Scrn. [d] or Treat. Discon. [e]	Follow-Up
		Cycle 1 [c]		Cycles ≥2			
	–28 to –1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)	≤30 Days after Last Dose	Every 3 Months
Informed consent	x [f]					x [g]	
Demographic data	x						
Medical history and baseline conditions	x						
Molecular profile of HR+ breast cancer (if available)	x	Whenever updated information becomes available					
Vital signs [h]	x	x	x	x	x	x	
Weight	x	x [kk]		x [kk]		x	
Height	x						
Complete physical examination [i]	x					x	
Limited physical examination [j]		x [kk]		x [kk]			
ECOG Performance Status	x	x [kk]		x [kk]		x	
ECG [k]	x	Perform as clinically indicated				x [g]	
Hematology [l]	x [m]	x [n]	x	x	x	x	
Chemistry [o]	x [m]	x [n]	x	x	x	x	
FSH, LH, and estradiol [p]	x [m]						
LDH	x [m]					x [g]	
Coagulation (INR, aPTT)	x [m]					x [g]	

Appendix 13: Study Details Specific to Atezo + Abema + Fulvestrant Arm (cont.)

Assessment/Procedure	Screening [a]	Treatment Cycles (28-day cycles) [b]				Stage 2 Scrn. [d] or Treat. Discon. [e]	Follow-Up
		Cycle 1 [c]		Cycles ≥2			
	–28 to –1	Day 1	Day 15 (±3 days)	Day 1 (±3 days)	Day 15 (±3 days)	≤30 Days after Last Dose	Every 3 Months
TSH, free T3 (or total T3), free T4 [q]	x [m]	x [q]				x [g]	
Viral serology [r]	x [m]					x [r]	
C-reactive protein	x					x [g]	
Urinalysis [t]	x [m]	Perform as clinically indicated				x [g]	
Serum autoantibody sample [u]	x	Perform if a patient experiences a suspected immune-mediated adverse event					
PK samples		Refer to Table A13-6 below					
ADA sample		Refer to Table A13-6 below					
Samples for biomarkers		Refer to Table A13-6 below					
Blood sample for RBR (optional) [v]		x					
Tumor biopsy	x [v]	x [x]					
Tumor biopsy (optional)		x [y]					
Tumor response assessments	x [z]	x [aa, bb, cc]					
Concomitant medications [dd]	x [dd]	x	x	x	x	x	
Adverse events [ee]	x [ee]	x	x	x	x	x [ee]	x [ee]
Dispense abemaciclib [ff, gg]		x		x			
Fulvestrant administration [gg, hh]		x	x	x			
Atezolizumab administration [gg, ii]		x	x	x	x		
Survival follow-up and anti-cancer treatment							x [ii]

Appendix 13: Study Details Specific to Atezo + Abema + Fulvestrant Arm (cont.)

ADA = anti-drug antibody; Atezo + Abema + Fulvestrant = atezolizumab plus abemaciclib plus fulvestrant; CT = computed tomography; Discon. = discontinuation;; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; ET = endocrine therapy; FSH = follicle-stimulating hormone; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LH = luteinizing hormone; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetic; PET = positron emission tomography; QD = once a day; RBR = Research Biosample Repository; RECIST = Response Evaluation Criteria in Solid Tumors; Scrn. = screening; Treat. = treatment.

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

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] If a visit is precluded because of a holiday, vacation, or other circumstance, it can occur outside of the specified window at the investigator's discretion. The Medical Monitor is available to advise as needed.

[c] Treatment must be initiated no later than 7 days after randomization. If initiation of treatment has to be delayed, patient may start treatment at the investigator's discretion. The Medical Monitor is available to advise as needed.

[d] Patients who experience loss of clinical benefit as determined by the investigator (see Section 3.1.1 for details) and patients who experience unacceptable toxicity to abemaciclib will be given the option of receiving a different treatment combination during Stage 2 of the study (as outlined in Table 6) and will undergo screening assessments to determine eligibility. The Medical Monitor is available to advise as needed. Study-specific details for the Stage 2 treatment regimens are provided in Appendix 12. Written informed consent must be obtained before performing screening evaluations for Stage 2.

[e] Patients will return to the clinic for a Stage 2 screening or treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which loss of clinical benefit is confirmed may be used as the Stage 2 screening or treatment discontinuation visit. Patients who do not enter Stage 2 will then undergo follow-up assessments. Note that treatment discontinuation assessments will be performed for all patients, regardless of whether they enter Stage 2.

[f] 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.

[g] Assessments to be performed only for patients undergoing Stage 2 screening.

[h] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, pulse oximetry, 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 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 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.

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

Appendix 13: Study Details Specific to Atezo + Abema + Fulvestrant Arm (cont.)

[j] Perform a limited, symptom-directed examination at specified timepoints and as clinically indicated at other timepoints. Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. Patients should be resting in a supine position for at least 10 minutes prior to ECG recording.

[l] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[m] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment (Day 1 of Cycle 1).

[n] If screening laboratory assessments were performed within 96 hours prior to dosing, they do not have to be repeated.

[o] Chemistry panel (serum or plasma) includes sodium, potassium, magnesium, chloride, bicarbonate or carbon dioxide, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST.

[p] FSH, LH, and estradiol are all required for patients who are <60 years old and in postmenopausal state or who are <60 years old and have had prior ovarian ablation. Only estradiol is required for patients who are <60 years old and are on a LHRH agonist for ovarian suppression.

[q] 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.).

[r] At screening, patients without a prior positive HIV test result will undergo an HIV test, unless not permitted per local regulations. Patients will also be tested for HBsAg, total HBcAb, and HCV antibody. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test must also be performed to determine if the patient has an HBV infection. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.

[s] Viral serology tests are required at Stage 2 screening but are not required at the treatment discontinuation visit. However, patients with a positive quantitative HBV DNA at screening (must be <500 IU/mL per the eligibility criteria) will undergo additional HBV DNA tests on Day 1 of every third cycle (i.e., Cycles 3, 6, 9, etc.), at treatment discontinuation (±7 days), and at 3, 6, 9, and 12 months (±14 days at each timepoint) after treatment discontinuation. Study treatment and procedures may proceed while HBV DNA is being processed, but results should be reviewed by the investigator as soon as they are available. If HBV DNA increases to ≥500 IU/mL, consultation with the Medical Monitor is required prior to continuation of study treatment and consultation with a hepatologist or gastroenterologist with specialty in hepatitis B is recommended.

[t] Includes pH, specific gravity, glucose, protein, ketones, and blood); dipstick permitted.

[u] Autoantibody analysis includes anti-nuclear antibody, anti–double-stranded DNA, circulating anti-neutrophil cytoplasmic antibody, and perinuclear anti-neutrophil cytoplasmic antibody. For patients who show evidence of immune-mediated toxicity, additional samples may be considered.

[v] 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.

Appendix 13: Study Details Specific to Atezo + Abema + Fulvestrant Arm (cont.)

[w] 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. It is preferred 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. Refer to Section 4.5.6 for tissue sample requirements.

[x] Patients will undergo tumor biopsy sample collection during Stage 1, at the time of unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details), if deemed clinically feasible by the investigator. For patients enrolled into the mandatory serial biopsy arm, patients will undergo tumor biopsy sample collection, if deemed clinically feasible by the investigator, at 4 weeks (±7 days) from initiation of study treatment. Biopsies should be performed within 40 days after determination of unacceptable toxicity or loss of clinical benefit, or prior to the next anti-cancer therapy, whichever is sooner. See Section 4.5.6 for tissue sample requirements.

[y] Patients will undergo optional tumor biopsy sample collection, if deemed clinically feasible by the investigator, 4 weeks (±7 days) after treatment initiation and may undergo additional on-treatment biopsies at any other time at the investigator's discretion.

[z] All measurable and evaluable lesions should be assessed and documented at screening (in both Stage 1 and Stage 2). Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening. Screening assessments must include CT scans (with IV contrast; with or without oral contrast) or MRI scans (with IV contrast) of the chest, abdomen, pelvis, and head with one exception: a head scan is not required at Stage 2 screening. In addition, bone scans, PET scans, and/or skeletal survey should be performed at screening to assess bone lesions. Bone lesions identified at baseline should continue to be assessed following the tumor assessment schedule described above. Additional bone scans, PET scans, or skeletal surveys should be performed if clinically indicated. A spiral CT scan of the chest may be obtained but is not a requirement. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans (with IV contrast) of the abdomen and pelvis should be performed. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. Refer to Section 4.5.5 for further details on tumor assessments.

[aa] Patients will undergo tumor assessments at baseline, every 6 weeks (±1 week) for the first 24 weeks following treatment initiation, and every 8 weeks (±1 week) from Week 25 to Week 48, then every 12 weeks (±2 weeks) thereafter, regardless of dose delays, until radiographic disease progression according to RECIST v1.1, except in the case of atezolizumab-treated patients who continue treatment after radiographic disease progression; such patients will undergo tumor assessments every 6 weeks (±1 week) until loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details). Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit, even if they start new non–protocol-specified anti-cancer therapy.

[bb] All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[cc] For patients who receive treatment during Stage 2, tumor assessments performed prior to or at the time of loss of clinical benefit during Stage 1 may serve as baseline assessments for Stage 2, provided that the tumor assessments are performed within 28 days prior to initiation of Stage 2 treatment (i.e., Day 1 of Cycle 1).

Appendix 13: Study Details Specific to Atezo + Abema + Fulvestrant Arm (cont.)

[dd] 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 10 days prior to initiation of study treatment until the treatment discontinuation visit.

[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 systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 135 days after the last dose of study treatment or until initiation of new systemic 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] All patients will receive abemaciclib orally twice daily on each 28-day cycle. Doses should be spaced approximately 12 hours apart, with a minimum of 6 hours between doses. On clinic visit days that require PK collection of study drugs, patients should take their tablets in the clinic.

[gg] Treatment will continue until unacceptable toxicity or loss of clinical benefit as determined by the investigator (see Section 3.1.1.1 for details).

[hh] Fulvestrant should be administered intramuscularly into the buttocks slowly (1–2 minutes per injection) as two 5-mL injections, one in each buttock.

[ii] The initial dose of atezolizumab will be delivered over 60 (±15) minutes. Subsequent infusions will be delivered over 30 (±10) minutes if the previous infusion was tolerated without infusion-associated adverse events, or 60 (±15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion.

[jj] 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. For an experimental arm in which all patients discontinued treatment and passed the safety follow-up window, as well as approximately 80% of patients discontinued the study, the Sponsor may conclude the arm (the remaining ~20% of patients will be discontinued from the study).

[kk] Assessment may be performed within 24 hours prior to dosing during the treatment period.

Table A13-6 Schedule of Pharmacokinetic, Immunogenicity, and Biomarker Samples for Atezo+Abema+Fulvestrant Arm:

Visit	Time	Sample
Day 1 of Cycle 1	Prior to any study treatment	• Abemaciclib PK (plasma) • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum PBMC)
	30 (±10) minutes after atezolizumab infusion	• Atezolizumab PK (serum)
	4-8 hours after the first dose of abemaciclib	• Abemaciclib PK (plasma)
Day 15 of Cycle 1	Prior to any study treatment	• Abemaciclib PK (plasma) • Biomarker (plasma, serum)
Day 1 of Cycle 2	Prior to any study treatment	• Abemaciclib PK (plasma) • Fulvestrant PK (plasma) • Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum, PBMC)
Day 1 of Cycle 3	Prior to any study treatment	• Abemaciclib PK (plasma) • Fulvestrant PK (serum) • Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Day 1 of Cycle 4	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)
Day 1 of Cycle 8	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarker (plasma, serum)
Day 1 of Cycles 12 and 16	Prior to any study treatment	• Atezolizumab PK (serum) • Atezolizumab ADA (serum)
Treatment discontinuation visit (≤30 days after last dose)	At visit	• Atezolizumab PK (serum) • Atezolizumab ADA (serum) • Biomarkers (plasma, serum)

ADA=anti-drug antibody; Atezo+Abema+Fulvestrant=atezolizumab plus abemaciclib plus fulvestrant; PBMC=peripheral blood mononuclear cell; PK=pharmacokinetic.

A13–8 REFERENCES

Bates GJ, Fox SB, Han C, et al. Quantification of regulatory T cells enables the identification of high-risk breast cancer patients and those at risk of late relapse. J Clin Oncol 2006;24:5373–80.

Blank C, Gajewski TF, Mackensen A. Interaction of PD-L1 on tumor cells with PD-1 on tumor-specific T cells as a mechanism of immune evasion: implications for tumor immunotherapy. Cancer Immunol Immunother 2005;54:307–14.

Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother 2007;56:739–45.

Butte MJ, Keir ME, Phamduy TB. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

Chen DS, Irving BA, Hodi FS. Molecular pathways: next-generation immunotherapy—inhibiting programmed death-ligand 1 and programmed death-1. Clin Cancer Res 2012;18:6580–7.

Condorelli R, Spring L, O'Shaughnessy J, et al. Polyclonal RB1 mutations and acquired resistance to CDK4/6 inhibitors in patients with metastatic breast cancer. Annals of Oncology 2018;29:640–5.

Deng R, Bumbaca D, Pastuskovas CV, et al. Preclinical pharmacokinetics, pharmacodynamics, tissue distribution, and tumor penetration of anti-PD-L1 monoclonal antibody, an immune checkpoint inhibitor. MAbs 2016;8:593–603.

Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+, HER2– metastatic breast cancer. Clin Cancer Res 2017;23:5218–24.

Dirix LY, Takacs I, Nikolinakos P, et al. Avelumab (MSB0010718C), an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: A Phase Ib JAVELIN solid tumor trial. Cancer Res 2016;76(Suppl):S1–04.

Faslodex® (fulvestrant) prescribing information. Wilmington (DE): AstraZeneca Pharmaceuticals, 2016

Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837–46.

Finn RS, Liu Y, Martin M, et al. Comprehensive gene expression biomarker analysis of CDK4/6 and endocrine pathways from the PALOMA-2 study [abstract]. In: San Antonio Breast Cancer Symposium;2018.Abstract P2-09-10.

Goel S, DeCristo MJ, Watt AC, et al. CDK4/6 inhibition triggers anti-tumor immunity. Nature 2017;548:471–5.

Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. J Clin Onc 2017;doi: 10.1200/JCO.2017.75.6155.Epub: 2 October 2017.

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.

Keir ME, Butte MJ, Freeman GJ, et al. PD-1 and its ligands in tolerance and immunity. Annual Rev Immunol 2008;26:677–704.

Moulder S, Karuturi M, Yardley DA, et al. Ribociclib in combination with everolimus and exemestane in men and postmenopausal women with HR+/HER2– advanced breast cancer after progression on a CDK4/6 inhibitor: efficacy and safety results from phase II of the TRINITI-1 study [abstract]. In: American Association for Cancer Research;2018:Abstract CT107.

Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.

Rugo HS, Delord JP, Im SA, et al. Preliminary efficacy and safety of pembrolizumab (MK-3475) in patients with PD-L1-positive, estrogen receptor-positive (ER+)/HER2-negative advanced breast cancer enrolled in KEYNOTE-028. Cancer Res 2016;76(Suppl):S5–07.

Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2– advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol 2017;35:2875–84.

Tecentriq® (atezolizumab) U.S. prescribing information. South San Francisco (CA): Genentech, 2016.

Tolaney SM, Kabos P, Dickler MN, et al. Updated efficacy, safety, and PD-L1 status of patients with HR+, HER2– metastatic breast cancer administered abemaciclib plus pemroblizumab. J Clin Oncol 2018;doi:10.1200/JCO.2018.36.15_suppl.1059.

Turner NC. Cyclin E1 (CCNE1) expression associates with benefit from palbociclib in metastatic breast cancer (MBC) in the PALOMA3 trial [abstract]. In: American Association for Cancer Research;2018.

Yang J, Riella LV, Chock S. The novel costimulatory programmed death ligand 1/B7.1 pathway is functional in inhibiting alloimmune responses in vivo. J Immunol 2011;187:1113–9.

Zhang J, Bu X, Wang H, et al. Cyclin D-CDK4 kinase destabilizes PD-L1 via cullin 3-SPOP to control cancer immune surveillance. Nature 2018;553:91–5.

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